BASIC SCIENCE

208. STEM CELL FACTOR EXPRESSION IS INCREASED IN THE SKIN OF PATIENTS WITH SYSTEMIC SCLEROSIS AND PROMOTES PROLIFERATION AND MIGRATION OF FIBROBLASTS IN VITRO

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Background: SSc is an autoimmune disease characterized by progressive fibrosis of the skin and internal organs. Development of an activated population of fibroblasts and myofibroblasts in lesional tissue is likely to be central to pathogenesis. In this study, we identify stem cell factor (SCF) as a potential driving factor in this process and future therapeutic target. SCF is a cytokine which acts via c-Kit a tyrosine kinase receptor. In a phosphorylation array analysis of migrating fibroblasts c-Kit was found to be upregulated. Our aim was to examine the role of SCF in the migration and proliferation of fibroblasts in SSC and healthy controls.

Methods: Primary skin fibroblast lines were cultured in vitro with varying concentrations of SCF, or neutralizing antibodies directed against its receptor c-Kit or SCF itself. Proliferation was assessed using the WST-1 assay and by direct cell counting. Migration was assessed using the scratch wound assay and area of wound invasion measured following treatment with either SCF or anti-Kit antibodies. The expression and quantity of SCF and c-Kit by SSc (n = 6) and control skin (n = 6) fibroblasts was assessed by western blotting. Epidermal equivalents also harvested from healthy (n = 5) and SSc (n = 9) skin using the blister technique. SCF gene expression was assessed using quantitative PCR (qPCR).

Results: SCF expression was enhanced in SSc epidermis samples by qPCR as compared with healthy controls (566 vs 336 copy numbers respectively). In the Western of fibroblasts, both c-Kit and SCF were strongly present in SSc skin derived fibroblasts and hardly detectable in healthy controls (normalized band intensity 2.14 vs 0.03 for c-Kit and 1.81 vs 0.07 in SSc vs normal skin respectively P < 0.002 in both). Human recombinant SCF (rSCF) promoted the migration of normal human fibroblasts. At both 24 and 48 h, cells treated with rSCF showed a much greater percentage wound coverage compared as treated with media only-with greatest migration at the rSCF concentration of 2.5 ng/ml (wound invasion 86% compared with 52% at 48 h P < 0.002). Conversely, treatment with antibody to c-Kit resulted in a reduction of wound invasion (19% compared with 62% P < 0.04). Addition of rSCF to normal fibroblast cell induced proliferation as measured by the WST-1 assay (13% increase, not statistically significant). Conversely, adding anti-Kit or anti-SCF neutralizing antibodies to cell culture medium resulted in reduction of proliferation (30% reduction, P = 0.066 and 20% reduction P < 0.020 respectively).

Conclusions: SCF is found at higher levels in the skin of SSc subjects compared with controls. We have demonstrated that in vitro, SCF promotes proliferation and migration of fibroblasts and that its blockade using specific antibodies results in reduction in both these processes. SCF appears to be a potential therapeutic target for future treatment in SSc.

Disclosures: The authors have declared no conflicts of interest.

209. FROM HEALTH TO AUTOIMMUNITY: EFFECTS OF PTPN22 R620W AND SMOKING ON CD4+ T-CELL SIGNALLING AND CYTOKINE PRODUCTION

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Background: A single nucleotide polymorphism (SNP) in the tyrosine phosphatase gene PTPN22 (R620W) and smoking have been shown in epidemiological studies to interact to confer an increased risk of RA. The molecular basis for this interaction is unknown but PTPN22/Lyp regulates signalling through immune cell receptors. Lyp is expressed in T lymphocytes, which are important in adaptive immunity, but aberrant T-cell receptor (TCR) signalling may promote autoimmunity. Here we investigated how PTPN22 R620W and smoking affect Lyp activity, TCR signalling and function, to determine possible mechanisms by which the allelic variant could interact with smoking to promote disease.

Methods: A cohort of healthy controls (n = 82) were genotyped for the PTPN22 R620W SNP, CD4+ T cells were isolated from control (GG) and heterozygous/variant (AG) subjects and exposed to cigarette smoke extract (CSE). The phosphatase activity of Lyp and phosphor- ylation status of the Lyp substrate Lck were assessed. The effects downstream from Lyp were determined by measurement of proliferation and cytokine production.

Results: The R620W allele (A) was highly expressed in healthy controls (AG = 26%, AA = 1%, GG = 71%), and 17 heterozygous/variant individuals were identified. The amount of Lyp protein was significantly decreased in variant T cells (GG = 1.2 ng ± 0.3/1.0 x 10^6 cells, AG = 0.7 ng ± 0.1/1.0 x 10^6 cells, P < 0.05, n = 6), but there was no significant difference in phosphatase activity. The decreased amount of Lyp variant protein had a higher specific activity resulting in no overall change in Lyp activity. There was no difference in phosphor- ylation of the Lyp substrate Lck on tyrosines 394 or 505. Proliferation of control and variant T cells was equivalent, and unaffected by CSE. Cytokine profiles were significantly different, with variant Lyp T cells producing more IFNγ (GG = 22.2 pg/ml ± 60, AG = 40 pg/ml ± 64, P < 0.002, n = 4) and TNFs (GG = 237 pg/ml ± 28, AG = 308 pg/ ml ± 9, P < 0.05, n = 4) compared with controls. Production of TNFα was decreased by CSE treatment in both cell types, with variant Lyp T cells being more sensitive to CSE. Low concentrations of CSE had no effect on IFNγ production by variant T cells; however control T cells increased secretion, and thus produced comparable amounts of IFNγ to variant T cells (GG = 312 pg/ml ± 77, AG = 340 pg/ml ± 46, n = 4). Secretion of IL-4, IL-10 and IL-17 were not significantly different in control and variant T cells, or following CSE treatment.

Conclusions: The PTPN22 R620W allelic variant was common in the cohort tested, and its expression results in decreased Lyp protein, but increased phosphatase activity in CD4+ T cells. Although phosphor- ylation of the Lyp substrate Lck was unchanged, the PTPN22 R620W variant resulted in increased production of inflammatory cytokines. This also occurred after exposure to CSE, suggesting R620W and smoke may synergise to promote inflammatory T cells.

Disclosures: The authors have declared no conflicts of interest.
Moreover, in both AS and RA patients, the frequencies of effector and naïve Treg were decreased (effector Treg: NC = 0.73 ± 0.07%, AS = 0.48 ± 0.07%, P < 0.05; naïve Treg, NC = 1.10% ± 0.15%, AS = 0.18% ± 0.33%, P < 0.01). The identification of Treg subsets by Foxp3+ expression requires intracellular staining and cell permeabilization, making the isolation of live Treg cells and their functional analysis impossible. CD25 expression has previously been used for purification of live Treg for functional studies, but is also not optimal since CD25bright, CD25dim, and CD25− populations are not clearly defined. Therefore we have investigated the use of CD39 to define subsets of Foxp3+ Treg cells, and find that CD4+CD25−CD39−CD45RO− cells are effector Treg, whilst naïve Treg are defined as CD4+CD25−CD39+CD45RO+. Activated Foxp3+ effector cells are CD4+CD25+CD39−CD45RO−.

Conclusions: The frequencies of both effector Treg and naïve Treg are lower in autoimmune disease compared with healthy controls recruited to date have been analysed. GPA and SLE patients only the frequency of effector Treg was restored. CD39 expression can be used to identify Treg subsets, and will facilitate future functional studies of Treg in health and disease.

Disclosures: The authors have declared no conflicts of interest.

211. ALTERATIONS IN CIRCULATING T FOLLICULAR HELPER CELLS AND T REGULATORY CELLS IN AUTOINMUNE TREATMENTS TREATED WITH B-CELL DEPLETION THERAPY: RITUXIMAB

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Background: Granulomatosis with polyangiitis (GPA) and SLE are autoimmune diseases which develop due to failure of immune self-tolerance. T follicular helper cells reside in lymphoid tissues within the germinal centres and are a minor subset of CD4+ T cells in peripheral blood. They have been associated with autoimmunity in animal models, where they are thought to reduce the threshold for B-cell survival. In contrast, T regulatory cells can be induced to suppress autoimmune responses.

Methods: In GPA and SLE there is a decrease in the T regulatory (Treg) cell population and an increase in the circulating T follicular helper (cTFH) cell population during active disease. B-cell depletion therapy may correct disease-associated changes of cTFH and TREG frequencies in autoimmune disease patients who have a positive clinical response.

Results: Mean age of GPA patients = 51 years (38–67), GPA patients = 42 years old (18–64) and healthy controls = 42 years (25–65), GPA pre-rituximab mean BVAS = 18, 1 month post-rituximab = 7 [P = 0.002], 3 months post-rituximab = 3.5 [P = 0.01], SLE mean total BILAG score pre-rituximab = 29, 1 month post-rituximab = 19 [P = 0.003], 3 months post-rituximab = 12 [P = 0.003]. cTFH%CD4+ lymphocytes in healthy controls mean = 0.21% (s.d. 0.12), GPA pre-rituximab = 0.54% (s.d. 0.28) [P = 0.0037] and SLE pre-rituximab = 0.61% (s.d. 0.37) [P = 0.03]. The frequency of cTFH cells is decreased at intervals post-rituximab with GPA 3 months post-rituximab mean = 0.25% (s.d. 0.05) [P = 0.04] and SLE 3 months post-rituximab mean = 0.32% (s.d. 0.28) [P = 0.02]. Mean TREG%CD4+ lymphocytes in healthy controls = 8.42% (s.d. 2.3), GPA pre-rituximab = 5.42% (s.d. 2.92) [P = 0.023] and SLE pre-rituximab = 7.79% (s.d. 3.37) [P = 0.31]. The frequency of regulatory T cells is increased at intervals post-rituximab with GPA 3 months post-rituximab mean = 10.8% (s.d. 3.54) [P = 0.05] and SLE 3 months post-rituximab = 12.92% (s.d. 3.9) [P = 0.046].

Conclusions: We have shown that frequencies of cTFH are higher and TREG are lower in autoimmune disease compared with healthy controls; however, these frequencies are restored to normality following treatment with rituximab. A high ratio of cTFH:TREG cells may highlight clinical disease activity or relapse of autoimmune disease.

Disclosures: D.D., Roche, GlaxoSmithKline—Consultation Fees. All other authors have declared no conflicts of interest.

212. DIRECT VISUALIZATION OF HLA-B27 FORMS IN LINEAR AND SPONDYLOARTHROPATHY TISSUES

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Background: The strong association of the human leucocyte antigen HLA-B27 (B27) with the SpAs, particularly with AS, was discovered more than four decades ago, yet the role of B27 plays in disease remains unclear. Our research group discovered that B27 free heavy chains (B27 HC) can form dimers (B272) and/or non-classical B27 molecules (NC-B27), which can bind innate immune receptors in non-conventional way, compared with other MHC class I molecules. We therefore investigated the pathogenic role for these forms of B27 in AS.

Methods: We used a novel HD6 antibody, generated against B272, and established conventional HLA-C and ME1 antibodies to examine surface expression of NC-B27 in AS patient and healthy control primary cells and transduced cell lines using flow cytometry, confocal microscopy and immunoprecipitation techniques.

Results: Confocal microscopy experiments revealed that NC-B27 can form clusters at the cell surface of B27-transduced cells. Immunoprecipitation data demonstrated that NC-B27 are present at the surface of the B27-positive cells more abundantly in a higher molecular weight form (~80kDa) compared with the monomeric form (~45kDa). Moreover, low pH treatment of cells can further induce both forms of B27. HD6 did not stain monocyte-derived dendritic cells (moDCs) from AS patients or healthy controls, irrespective of moDC maturation state. However, LPS treated AS moDCs expressed higher levels of HC10-reactive molecules than those from healthy controls. HD6 and HC10 staining can be induced in AS moDCs by low pH treatment.

Conclusions: Confocal microscopy data brought additional insight into the segregation patterns of classical and non-classical B27 molecules at the cell surface. We showed by flow cytometry and immunoprecipitation that HC-B27 expression on AS moDCs is significantly increased compared with healthy controls. Furthermore, we showed that low pH treatment can induce HD6 and HC10 staining on the B27 positive cells.

Disclosures: The authors have declared no conflicts of interest.

213. DIFFERENTIAL GENERATION OF CC CHEMOKINES AT MICROVASCULAR ENDOTHelial CELLS OF BLOOD AND LYMPHATIC VESSELS UNDER INFLAMMATORY CONDITIONS

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Background: Synovial inflammation in RA is directly associated with inflammatory cell migration across microvascular endothelial cells (ECs). This migration is dependent on the generation of chemokines which are involved in the localization, recruitment and activation of leucocytes in response to inflammatory stimuli. Earlier work established the presence of CCL7, CCL14 and CCL16 at RA synovial endothelial cells. However, it was not known if these chemokines are presented by the synovial ECs following their generation by infiltrating cells, or resident fibroblasts/macrophages, or if they are expressed directly by endothelial cells themselves. The purpose of this study was to elucidate if these chemokines are generated by cultured EC monolayers under inflammatory and non-inflammatory conditions and to compare their generation in ECs from blood and lymphatic vessels.

Methods: Bone marrow endothelial cells (HBMECs) and lung lymphatic human microvascular endothelial cells (HMVEC-Ly) were cultured to confluence and inflammatory conditions were simulated by activating with 100 ng/ml TNF-α (HBMECs) or 100 ng/ml TNF-α and 100 ng/ml IFN-γ (HMVEC-Ly). Cells were fixed using ice cold 1:1 acetone:methanol for 15 min. Following this immunofluorescence microscopy was used to establish the presence of the chemokines CCL7, CCL14 and CCL16 chemokines. Cell software was used to assess the average intensity for the staining of each chemokine.

Results: The intensity of staining for the chemokines on both activated and unactivated cell monolayers was assessed at 3 areas in 3 fields of view for 3 individual monolayers (n = 3).
The staining intensity is given in arbitrary units. Unactivated HBMEC: CCL7 = 40.8, CCL14 = 30, CCL16 = 19.75. Activated HBMEC: CCL7 = 57.4, CCL14 = 44, CCL16 = 43.

Percentage change following activation:
CCL7: +40.7%, CCL14: +46.7%, CCL16: +117.7%
Unactivated HMVEC-Ly: CCL7: +43, CCL14: +13, CCL16: +27.4
Activated HMVEC-Ly: CCL7: +16.3, CCL14: +15.5, CCL16: +43.1

Percentage change following activation:
CCL7: +62.1%, CCL14: +1.5%, CCL16: +58.1%

Conclusions: This study provides new information about the generation of CCL7, CCL14 and CCL16 by ECs under inflammatory conditions. The level of these chemokines increased on blood ECs under inflammatory conditions. However, CCL7 showed a reduction in level in lymphatic ECs under inflammatory conditions compared with non-inflammatory conditions. This indicates a role for CCL7 in lymphatic EC recruitment persistence in RA and disregulation of lymphatic EC chemokine expression. Further work will include functional analysis of CCL7 to ascertain the degree to which leucocyte recruitment and/or persistence is affected by their altered expression under these differing conditions.

Disclosures: The authors have declared no conflicts of interest.

214. HUNTING THE LIGAND FOR ORPHAN RECEPTOR GPR15/BOB WHOSE EXPRESSION IS UP-REGULATED IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory condition of the joints in which the accumulation of leucocytes in the synovial membrane results in development of inflammation, joint destruction and pain. Chemokines and their receptors play a central role in this process. GPR15/BOB is a member of the chemokine receptor family whose ligand is unknown. We previously found expression of GPR15/BOB mRNA to be up-regulated in RA compared with non-RA synovial tissue with the receptor expressed on macrophages. GPR15/BOB was observed on leucocytes in peripheral blood, where expression was up-regulated on monocytes and neutrophils in RA patients in comparison with healthy controls. Identification of a ligand for GPR15/BOB would allow investigation of its expression in a model of T-cell activation driven by TSST-1, which displays affinity to GPR15/BOB positive cells compared with GPR15/BOB negative cells. We aimed to identify chemokine(s) stimulating calcium flux via the GPR15/BOB receptor and thus to identify the ligand for GPR15/BOB.

Methods: In this study a calcium flux assay was used to investigate GPR15/BOB receptor activation when a GHOST cell line expressing GPR15/BOB was compared with GPR15/BOB negative cells. We aimed to identify chemokine(s) stimulating calcium flux via the GPR15/BOB receptor and thus to identify the ligand for GPR15/BOB.

Results: A panel of 41 chemokines was screened in the calcium flux assay producing differential levels of flux with different chemokines and between cells positive or negative for GPR15/BOB expression.

Examination of endogenous cell-surface receptors on GPR15/BOB positive cells demonstrated presence of CCR1,2,4 and 5; and CXCR1,2 and 3 (all with MFI > 4.5), likely accounting for the fluorescence flux observed with cognate chemokine ligands to these receptors in the calcium flux assay. CCR3 was initially observed at very low level on the GHOST cells (MFI = 1.5) suggesting its ligand CCL11 which produced greater flux in GPR15/BOB positive compared with GPR15/BOB negative cells, may be signaling through GPR15/BOB. However further analysis of CCR3 expression using an alternate antibody demonstrated that the receptor was in fact present on the cells (MFI = 27.5) and at comparable levels to GPR15/BOB (MFI = 24.7).

Conclusions: Whilst initial observations suggested that CCL11 may be signaling through the orphan GPR15/BOB receptor in the absence of CCR3; further investigation demonstrated that CCR3 was present on GHOST cells suggesting that CCL11 was in fact signaling through CCR3.

Disclosures: The authors have declared no conflicts of interest.

215. ABATACEPT SENSITIVITY IS DETERMINED BY FACTORS THAT DEFINE THE STRENGTH OF T-CELL RECEPTOR SIGNALLING

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Background: Abatacept (CTLA-4 Ig) is a biologic DMARD that blocks T-cell activation at the level of CD28 costimulation. This study was in conjunction with blockade of the CD28-CD80/CD86 pathway which is regarded as the predominant source of T-cell costimulatory signalling. Variability in RA patient responses to abatacept implies differential CD28-costimulation contributions to T-cell activation; however the mechanisms underlying this are not fully understood. Therefore, the identification of factors that determine abatacept sensitivity or resistance can provide a basis upon which to appropriately target treatment.

Methods: CD4 + CD25– T cells were isolated from PBMCs derived from healthy donors and were cultured for 5 days in the presence of anti-CD3 or Toxic Shock Syndrome Toxin (TSST)-1 as T-cell receptor (TCR) stimuli and either CD80/CD86 transfected CHO cells or allogeneic human monocyte derived dendritic cells (DCs) as sources of costimulation. The impact of abatacept upon T-cell activation in these stimulations was identified in terms of effects upon proliferation of T-cell responders.

Results: When T-cell activation was driven by soluble anti-CD3 and CD80 or CD86 transfected, abatacept facilitated effective blockade of T-cell activation. However, when T-cell activation was mediated by soluble anti-CD3 in conjunction with DCs, CD80/CD86 saturating concentrations of abatacept had limited effect upon T-cell proliferation, although the level of inhibition became more significant at lower DC:T-cell ratios. This apparent abatacept resistance was however abrogated at significantly reduced anti-CD3 concentrations. Similarly, in a model of T-cell activation driven by TSST-1, which displays affinity for T cells expressing the Vbeta2 chain, high affinity T-cell responders (Vbeta2+) were resistant to abatacept at high doses of TSST-1 but were more inhibited with decreasing TSST-1 concentrations. Conversely, the activation of low affinity TSST-1 responders (Vbeta2−) was inhibited by abatacept regardless of TSST-1 concentration.

Conclusions: These data are consistent with a model in which T-cell activation occurs when a signalling threshold composed of variable proportions of TCR and costimulatory signalling is achieved. The efficacy of abatacept may therefore be limited by factors that enhance the strength of TCR stimulation. As such, in a situation in which TCRs display a degree of cross-reactivity that is associated with a range of affinities to a specific peptide, abatacept is likely to be most potent in preventing activation of low affinity T cells whilst high affinity T cells bypass the requirement for CD28 costimulatory signalling.

Disclosures: The authors have declared no conflicts of interest.

216. DIMINISHED ENVIRONMENTAL OXYGEN ALTERS MEMORY T-CELL RESPONSES TO STIMULATION, WITH SEVERE HYPOXIA DEPRESSING BOTH CYTOKINE PRODUCTION AND TH2 CELL DEVELOPMENT

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Background: The joint in RA is known to be hypoxic compared with the healthy joint. It has been observed that increasing macroscopic
Cytokines and inflammatory mediators

218. PKR ACTIVATES THE INTEGRATED STRESS RESPONSE FOLLOWING BACTERIAL INFECTION AND INITIATES PRO-INFLAMMATORY REPROGRAMMING OF THE CELL

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Background: Dendritic cells (DC) provide critical signals for the development of appropriate immune responses to pathogens by producing cytokines which stimulate an inflammatory response. However, inappropriate or exaggerated inflammation in response to infection can lead to joint disease, as seen in reactive arthritis. We have previously shown that infection of DC with Chlamydia trachomatis (an obligate intracellular parasite) activates a stress response pathway induced by eIF2α phosphorylation termed the Integrated Stress Response (ISR). Activation of this pathway leads to expression of the transcription factor, CHOP, which is crucial for IL-23 production.

Methods: Peripheral blood monocytes from healthy volunteers were differentiated into DC for 6 days using IL-4 and GM-CSF. HeLa or DC were infected with Chlamydia muridarum (CM). Transcriptional analysis was carried out by Q-RT-PCR and protein was assessed by western blot. Cytokine secretion was determined by ELISA. ROS generation was assayed by DCF staining and flow cytometry.

Results: Chlamydia infection induced eIF2α phosphorylation and expression of transcription factors ATF4/ATF3, which are associated with ISR activation. PKR was identified as the eIF2α kinase responsible, since infection of human DC or HeLa cells with CT or CM induced phosphorylation of PKR indicating PKR activation. Furthermore, chemical inhibitors of PKR activity prevented the induction of the ISR. To examine whether ROS production was a critical signal for PKR activation, we infected DC and HeLa cells in the presence of the anti-oxidant NAC, or specific chemical inhibitors of NOX-2 derived ROS. Blocking ROS with NAC had no effect on PKR activation or CHOP induction, and inhibition of NOX-2 had no effect on cytokine production. Significantly, inhibition of PKR activation reduced IL-23, IL-1β and IL-6 secretion.

Conclusions: Detection of intracellular bacterial pathogens such as Chlamydia results in ROS independent activation of PKR that stimulates IL-1β and IL-6 production. Furthermore, PKR acts as an eIF2α kinase, inducing the ISR and initiating pro-inflammatory transcriptional activity, leading to IL-23 production. We propose PKR to be a novel, crucial modulator of pro-inflammatory signalling during intracellular bacterial infection, and suggest PKR as a therapeutic target in preventing inappropriate inflammation in pathogen induced conditions such as reactive arthritis.

Disclosures: The authors have declared no conflicts of interest.

219. CHARACTERIZATION OF ENZYMES INVOLVED IN NITRICAMIDE ADENINE DINUCLEOTIDE BIOSYNTHESIS IN RHEUMATOID ARTHRITIS SYNOVIAL AND CYTOKINE-STIMULATED SYNOVIAL FIBROBLASTS

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Background: Cytokines can lead to the activation of intracellular signalling pathways that promote pro-inflammatory reprogramming of the host following intracellular bacterial infection. There are four eIF2α kinase candidates that might contribute to eIF2α phosphorylation: PKR, the cytosolic eIF2α kinase, is a novel, crucial modulator of pro-inflammatory signalling during intracellular bacterial infection.

Methods: Peripheral blood monocytes from healthy volunteers were differentiated into DC for 6 days using IL-4 and GM-CSF. HeLa or DC were infected with Chlamydia trachomatis (CT) or Chlamydia muridarum (CM). Transcriptional analysis was carried out by Q-RT-PCR and protein was assessed by western blot. Cytokine secretion was determined by ELISA. ROS generation was assayed by DCF staining and flow cytometry.

Results: Chlamydia infection induced eIF2α phosphorylation and expression of transcription factors ATF4/ATF3, which are associated with ISR activation. PKR was identified as the eIF2α kinase responsible, since infection of human DC or HeLa cells with CT or CM induced phosphorylation of PKR indicating PKR activation. Furthermore, chemical inhibitors of PKR activity prevented the induction of the ISR. To examine whether ROS production was a critical signal for PKR activation, we infected DC and HeLa cells in the presence of the anti-oxidant NAC, or specific chemical inhibitors of NOX-2 derived ROS. Blocking ROS with NAC had no effect on PKR activation or CHOP induction, and inhibition of NOX-2 had no effect on cytokine production. Significantly, inhibition of PKR activation reduced IL-23, IL-1β and IL-6 secretion.

Conclusions: Detection of intracellular bacterial pathogens such as Chlamydia results in ROS independent activation of PKR that stimulates IL-1β and IL-6 production. Furthermore, PKR acts as an eIF2α kinase, inducing the ISR and initiating pro-inflammatory transcriptional activity, leading to IL-23 production. We propose PKR to be a novel, crucial modulator of pro-inflammatory signalling during intracellular bacterial infection, and suggest PKR as a therapeutic target in preventing inappropriate inflammation in pathogen induced conditions such as reactive arthritis.

Disclosures: The authors have declared no conflicts of interest.
Background: Synovial fibroblasts (SF) display a ‘hyperactive’ phenotype in patients with RA. Nicotinamide adenine dinucleotide (NAD+) plays a role in cell metabolism, but may also be a key molecule in maintaining this activated phenotype. NAD+ can be synthesized from precursor vitamin molecules, nicotinamide (Nam), nicotinic acid (Na) and Tryptophan (TRP); with their respective phosphoribosyl transferases (NAMPT, NAPRT, ORPT) and Indoleamine (IDO) being the rate limiting enzymes involved in these pathways. NAMPT expression is enhanced in synovium from patients with RA and small molecule inhibition of NAMPT activity has been shown to alleviate experimental RA. Up until now, no studies have characterized the expression of the other NAD+ enzymes in synovial tissue; this study compared the expression of NAD+ biosynthesis enzymes in synovial tissue (ST) from patients with RA, OA and normal patients. Regulation of NAD+ enzyme expression and activity was explored in cytokine-stimulated SF isolated from RA patients.

Methods: qPCR analysis of NAD+ biosynthesis enzymes were assessed ex vivo in ST from RA, OA and normal patients and in vitro in SF subjected to 10 ng/ml of oncostatin M (OSM), IFN-γ, TNF-α or IL-1β. NAD+ precursor molecules; nicotinamide mononucleotide (NMN) and kynurenine (KYN) were quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: qPCR analyses showed that all NAD+ enzymes tested were constitutively expressed in vivo and in vitro, with the exception of NMN adenyltransferase (NMNAT)-3. IDO, NADSYN and NMNAT-2 in OA and RA were all significantly different to normal tissue expression; however only IDO and NAMPT were significantly different by RA compared with OA. (NAMPT reached statistical significance when patients on anti-TNF therapy were excluded). NAMPT and IDO were both significantly upregulated in vitro following stimulation with OSM and IFN-γ but only NAMPT was upregulated following stimulation with TNF-α and IL-1β. No other NAD+ biosynthesis enzymes were upregulated by these cytokines. KYN and NMN were detected in SF, but only KYN was significantly upregulated following IFN-γ stimulation.

Conclusions: Both NAMPT and IDO are significantly enhanced in RA patient synovium and both are upregulated following stimulation with either OSM or IFN-γ. However, unlike IDO, NAMPT is also upregulated by TNF-α and IL-1β. Despite IDO and NAMPT being upregulated in cytokine-stimulated SF, only IDO’s enzymatic end-product (KYN) was significantly upregulated; suggesting that NAMPT induction may not affect local NMN production. However, experiments are currently focused on monitoring rates of NMN consumption by these cells.

Disclosures: The authors have declared no conflicts of interest.
222. HOW IMPORTANT IS OCCUPATIONAL ACTIVITY IN DETERMINATION OF TOTAL FEMUR BONE MINERAL DENSITY? FINDINGS FROM THE HERTFORDSHIRE COHORT STUDY

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Background: Several studies have shown that weight bearing leisure time physical activity has a beneficial effect on bone mineral density (BMD). However, for female data are available relating occupational physical activity to BMD. We addressed this question using the Hertfordshire Cohort Study, a cohort of 1000 men and women in whom occupational activity exposure and BMD were available.

Methods: We studied 498 men and 468 women born in Hertfordshire between 1931 and 1939 who still lived there in adult life. These individuals attended a local clinic where a health questionnaire was completed, detailing past medical history, drug history (including HRT use) cigarette and alcohol consumption, occupational and leisure physical activity. Anthropometric data were recorded. Bone densitometry (DXA) was performed at the femoral neck using a Hologic QDR 4500 instrument. Measurement of lumbar spine BMD was not considered in this analysis due to the possible confounding effects of lumbar spine OA. Full ethical approval and patient consent were obtained. Analysis of occupational exposure was achieved through categorization of standing, lifting, sweating and manual work by tertile according to the number of years of exposure.

Results: Of the 498 men and 468 women recruited, the analysis was confined to 498 men and 402 women to exclude women who had not worked for 20 years or longer. The mean (s.d.) age of participants was 64.8 (2.54) in men and 66.5 (2.55) in women. A higher BMI was associated with a greater hip BMD in both sexes (P < 0.0001). In men, current HRT use was also associated with a higher BMD (P < 0.0001). In this cohort, using these crude measures of occupational activity exposure, there was no residual effect of occupational exposure after adjustment for confounders (age, BMI, smoking status, alcohol consumption, dietary calcium intake and years since menopause/ use of hormone replacement therapy among women).

Conclusions: These data suggest that enquiry regarding occupational exposure to standing, lifting, sweating or manual work would not be useful additions to the functional enquiry of patient being investigated for possible osteoporosis.

Disclosures: The authors have declared no conflicts of interest.

223. PEOPLE LIVING IN DEPRIVED AREAS DISPLAY GREATER DISABILITY AFTER 2 YEARS OF RHEUMATOID ARTHRITIS: THE ERAN COHORT

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Background: Socioeconomic deprivation may impact upon RA due to impaired access to healthcare/services, lifestyle factors or comorbidities. We aimed to assess whether early RA outcomes were associated with socioeconomic deprivation.

Methods: The Early Rheumatoid Arthritis Network (ERAN) is in inception cohort of early RA from 22 outpatient centres in UK and Eire. Social deprivation index (IMD2007) was measured from the postcodes of 900 people covering 73% of the cohort. IMD2007 is the current UK government index of deprivation, from the geocovnert website (geocovnert.mimas.ac.uk). A subset were analysed for radiographic progression. Data analysis used odds ratios (ORs), adjusted OR (aOR), 95% CI and logistic regression. The top England/Wales national tertiles were used as the most-deprived group, and significance was taken as P < 0.05.

Results: Within ERAN, 227 people resided within the most-deprived tertile of England and Wales. 414 people and 259 people lived in the middle and least deprived regions, which were pooled for analysis. People in the deprived areas showed higher CRP, pain, disability and smoking; and poorer mental health and vitality. At baseline, HAQ disability score was higher in people from deprived areas (median (IQR) deprived: 1.3 (0.7–1.9) vs not: 1.0 (0.4–1.5), P < 0.001) and at 2 years (deprived: 4.8 (3.7–5.9) vs not: 4.5 (3.4–5.7), P = 0.199) or 2 years (deprived: 3.8 (2.6–5.1) vs not: 3.5 (2.3–4.7), P = 0.068). At 2 years, deprivation was also associated with higher HAQ after univariate analysis (OR 1.91, 95% CI 1.24, 2.95) but not DAS28 (OR 1.24, 95% CI 0.80, 1.93). After logistic regression higher deprivation was associated with 2 year HAQ (see Table 1). Similar analysis did not yield a significant association with 2 year DAS28 (OR 1.27, 95% CI 0.72, 2.26, P = 0.409). Univariate analysis of radiographic progression (n = 161) did not show an association with deprivation.

Conclusions: Socioeconomic status may be associated with RA disability. This was not explained by smoking or DAS28. Further research should address how treatments to reduce disability from RA might be better targeted to people with RA living in areas of greater deprivation.

Table 1. Logistic regression showing deprivation associated with worse 2-year disability

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HAQ</td>
<td>2.95 (1.45, 4.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deposition</td>
<td>2.53 (1.24, 4.17)</td>
<td>0.011</td>
</tr>
<tr>
<td>SF36-Vitality</td>
<td>1.14 (1.66, 7.01)</td>
<td>0.021</td>
</tr>
<tr>
<td>SF36-Vitality</td>
<td>1.82 (1.12, 2.97)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Logistic regression for above median HAQ score at 2 years. High deprivation, high baseline HAQ, smoking and less vitality at baseline were all significantly associated with disability. Also adjusted for age, gender, DAS28, 1987 ACR criteria, BMI, DAS28, P, pain and mental health score.

Disclosures: D.M., Pfizer—Research Grant. D.W., Pfizer—Research Grant. Consultation. All other authors have declared no conflicts of interest.

224. IDENTIFYING SCOLIOSIS IN POPULATION-BASED COHORTS: DEVELOPMENT AND VALIDATION OF A NOVEL METHOD BASED ON TOTAL BODY DUAL ENERGY X-RAY ABSORPTIOMETRY SCANS

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Background: Scoliosis is lateral curvature of the spine >10 degrees, as measured on a standing spinal radiograph. The current knowledge about determinants of adolescent idiopathic scoliosis (AIS) is derived from studies in individuals, families with disease, or cases. However, there are no published studies that have investigated determinants of scoliosis using a prospective cohort design, making the establishment of cause and effect difficult. Several large population-based cohorts exist throughout the world with a wide range of clinical, biological and genetics data already collected, and while spinal imaging with traditional radiographs is not generally collected in these cohorts, total body dual energy X-ray absorptiometry (DXA) has been routinely collected at repeated time points for the study of determinants of bone size and density. We therefore wished to develop and validate a novel method of identifying scoliosis on total body DXA scans.

Methods: Scoliosis was identified on total body DXA scans by triaging to distinguish true curves from positioning errors, followed by a modified-Ferguson method to measure angles. Precision was assessed on 174 children from the Avon Longitudinal Study of Parents and Children (ALSPAC), who underwent repeat DXA scans at ages 15, 26 weeks apart. In addition, precision of angle estimation was evaluated on 20 scans measured 5 times. To evaluate accuracy, angle size was compared with spinal radiographs in 13 individuals with known scoliosis. Subsequently, this method was applied to estimate scoliosis prevalence rates and curve patterns from DXA scans previously obtained in 2798 ALSPAC participants at aged 9 and 5212 at 15.

Results: There was substantial agreement in identifying those with scoliosis on repeat DXA scans taken 2–6 weeks apart (Kappa of 0.74, 95% CI 0.59, 0.89). 95% of repeat angle measures were within 5 degrees, as measured on a standing spinal radiograph. The current knowledge about determinants of adolescent idiopathic scoliosis (AIS) is derived from studies in individuals, families with disease, or cases. However, there are no published studies that have investigated determinants of scoliosis using a prospective cohort design, making the establishment of cause and effect difficult. Several large population-based cohorts exist throughout the world with a wide range of clinical, biological and genetics data already collected, and while spinal imaging with traditional radiographs is not generally collected in these cohorts, total body dual energy X-ray absorptiometry (DXA) has been routinely collected at repeated time points for the study of determinants of bone size and density. We therefore wished to develop and validate a novel method of identifying scoliosis on total body DXA scans.

Methods: Scoliosis was identified on total body DXA scans by triaging to distinguish true curves from positioning errors, followed by a modified-Ferguson method to measure angles. Precision was assessed on 174 children from the Avon Longitudinal Study of Parents and Children (ALSPAC), who underwent repeat DXA scans at ages 15, 26 weeks apart. In addition, precision of angle estimation was evaluated on 20 scans measured 5 times. To evaluate accuracy, angle size was compared with spinal radiographs in 13 individuals with known scoliosis. Subsequently, this method was applied to estimate scoliosis prevalence rates and curve patterns from DXA scans previously obtained in 2798 ALSPAC participants at aged 9 and 5212 at 15.

Results: There was substantial agreement in identifying those with scoliosis on repeat DXA scans taken 2–6 weeks apart (Kappa of 0.74, 95% CI 0.59, 0.89). 95% of repeat angle measures were within 5 degrees. Angle size was underestimated by approximately 40%. Prevalence of scoliosis >10 degrees in ALSPAC was 0.3% at aged 9 and 3.5% at aged 15, and was higher in girls at both time points. Mean (s.d.) curve size was 12 (4) at aged 9 years, and 15 (7) degrees at aged 15.

Conclusions: We have developed and validated a novel method for identifying scoliosis from DXA scans. Comparison with prevalence data using more established techniques suggests our method provides valid estimates of scoliosis prevalence in population-based cohorts.

Disclosures: The authors have declared no conflicts of interest.

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225. T SCORE THRESHOLDS AS PREDICTORS OF FRACTURES IN MEN

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Background: Osteoporosis (OP) is diagnosed based on a T score of \( <-2.5 \) in either the femoral neck or the lumbar spine. This is based upon the number of standard deviations away from the average T score in a young healthy woman. 1 This was based upon data in women but may be an erroneous use in men who are at only half the risk of developing OP compared with women. However, 1 in 4 men over 50 years old will suffer a fragility fracture and so investigating the risk for developing fragility fractures in men is important.

The aims of this study are 2-fold: (i) to identify in which site (lumbar spine or femoral neck) best predicts fracture in men; and (ii) which T Score threshold best predicts fracture.

Methods: Male patients attending a District General Hospital for DEXA scanning between April 2004 and September 2010 were included in the study. BMD and T scores were measured in the L1–L4 vertebrae and the femoral neck. Of these patients, two groups were identified, a group who had sustained a fracture and a non-fracture group. The influence of femoral neck T scores was compared with the influence of T scores in L1–L4 using a logistic regression model. In addition, a receiver operator characteristics (ROC) curve was used to assess how strongly T scores in these areas predict fracture. The mean T score in these two areas were then divided into 10 thresholds starting at \(-1\) progressing in 0.25 increments. Using a logistic regression model, these thresholds were then used to predict fracture in order to see which threshold was the most strong predictor.

Results: Data on 2564 males were analysed of which 738 (29%) had sustained fractures, baseline demographics are shown in Table 1. The area under the ROC curve in the lumbar spine is more strongly associated with fracture than the femoral neck. The T score threshold which most strongly predicts fracture is \(<-2.0\) in the lumbar spine, with odds ratio 2.62 (95% CI 2.11, 3.25) and an area under the ROC curve 0.596.

Conclusions: The results of this study have shown that the BMD in the lumbar spine is more strongly associated with fracture than the femoral neck. In terms of which cut-off for T score most strongly suggests fracture, the results of this study have found that a T score of less than \(-2.0\) in the lumbar spine is the best predictor. This is the first time this has been demonstrated.

### Table 1. Demographics of males in the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fracture (n = 738)</th>
<th>Non-fracture (n = 1826)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.4 (13.7)</td>
<td>66.4 (13.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 (2.7)</td>
<td>26.9 (4.5)</td>
<td>1</td>
</tr>
<tr>
<td>Osteoporosis, n (%)</td>
<td>342 (46)</td>
<td>888 (49)</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>239 (32)</td>
<td>804 (44)</td>
<td>0.005</td>
</tr>
<tr>
<td>Alcohol excess, n (%)</td>
<td>77 (10)</td>
<td>221 (12)</td>
<td>0.23</td>
</tr>
<tr>
<td>Index of multiple deprivation score</td>
<td>19.5 (15.0)</td>
<td>18.3 (13.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>L1-L4 BMD</td>
<td>1.1 (1)</td>
<td>1.1 (2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>0.86 (0.14)</td>
<td>0.91 (0.14)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are mean (i.o.) unless otherwise indicated.

Disclosures: The authors have declared no conflicts of interest.

226. THE CONTRIBUTION OF THE PATIENT-REPORTED COMPONENTS OF DAS28 TO PREDICTION OF RADIOGRAPHIC PROGRESSION IN THE ERAN COHORT

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1NHS Trust, London and 2Alcohol Excess, Osteoporosis, Foundation Trust, Birmingham, 3Rheumatology Department, Royal Lancaster Infirmary, Lancaster, UK

Background: The Early Rheumatoid Arthritis Network (ERAN) is in inception cohort of early RA from 22 outpatient centres in UK and Eire. Radiographs of hands and feet were scored by one blinded assessor using the van der Heijde modified Sharp system. Radiographs from baseline and 2–4 years were analysed for progression, erosions and joint space narrowing (JSN) using odds ratio (OR), adjusted OR (aOR), 95% CI and logistic regression. Above/below median change in score was analysed and significance was P < 0.05.

Results: 459 people had baseline radiography data available and 166 provided follow up data for analysis. Baseline at the median (IQR) age was 58 (49–69) years, DAS28 4.6 (3.5–5.7) and DAS28-P 0.45 (0.14–0.50); 64% were female and 62% seropositive.

At baseline, the median (IQR) radiographic score was 6 (3–12) with erosions 2 (0–5) and JCN 4 (2–8). At follow up, the radiographic score was 14 (7–23) with erosions 5 (2–10) and JSN 7 (4–13). The changes in radiographic score were 6 (3–12), erosions were 3 (1–6) and JSN were 3 (1–7) (P < 0.001).

High radiographic score at baseline predicted above median progression in total radiographic score (aOR 2.03, 95% CI (1.15, 3.59), P = 0.015). Above median progression of erosions was associated with lower DAS28-P and better mental health (Table 1), and higher JSN progression was not associated with baseline variables.

Conclusions: Participants where patient-reported components contribute a greater proportion of DAS28 display less radiographic progression but are known to have worse pain prognosis. The relative contributions of DAS28 subcomponents may be important indicators for the balance needed between disease modifying and pain management therapies. Prospective clinical trials would be required to determine the utility of DAS28-P in treatment stratification.

### Table 1. Logistic regression for increase in erosion score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>aOR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Baseline erosions</td>
<td>Tertiles</td>
<td>2.10 (1.42, 3.25)</td>
</tr>
<tr>
<td>Age</td>
<td>Tertiles</td>
<td>1.92 (1.29, 2.86)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>1.10 (0.56, 2.08)</td>
</tr>
<tr>
<td>DAS28</td>
<td>EULAR</td>
<td>1.52 (0.95, 2.44)</td>
</tr>
<tr>
<td>Mental health</td>
<td>Tertiles</td>
<td>0.54 (0.35, 0.83)</td>
</tr>
<tr>
<td>Vitality</td>
<td>Tertiles</td>
<td>0.66 (0.43, 1.03)</td>
</tr>
<tr>
<td>Pain</td>
<td>Tertiles</td>
<td>0.67 (0.44, 1.01)</td>
</tr>
<tr>
<td>DAS28-P</td>
<td>Tertiles</td>
<td>0.57 (0.36, 0.92)</td>
</tr>
</tbody>
</table>

Disclosures: D.M., Pfizer—Research Grant. D.W., Pfizer—Research Grant, Consultancy. All other authors have declared no conflicts of interest.

227. HAS THE BASAL SEVERITY OF INFAMMATORY POLYARTHRITIS DIMINISHED OVER TIME?

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1Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, 2Department of Rheumatology, Norfolk and Norwich University Hospital, Norwich and 3Norfolk Arthritis Register, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

Background: Previous research has suggested that the severity of RA has decreased over time. This study examines the pattern of disease severity in patients with inflammatory polyarthritis (IP) at time of registration into the Norfolk Arthritis Register (NOAR).

Methods: NOAR is a primary-care-based cohort of adults with recent onset IP (+2 swollen joints lasting for >4 weeks). Disease related variables assessed at baseline include 51- swollen and tender joint count and the Health Assessment Questionnaire (HAQ). Blood is collected and C—reactive protein (CRP), Rheumatoid Factor (RF), and Anti-Citrullinated Peptide Antibodies (ACPA) are measured. The DAS28 (Disease Activity Score) is calculated using CRP level. In this study, patients with a symptom duration of <2 years at baseline were grouped into four cohorts depending on the NOAR recruitment phase: (1) 1990–1994; (2) 1995–1999; (3) 2000–2004; (4) 2005–2009. Three sub-samples were also evaluated: (i) referred first to NOAR by their general practitioner; (ii) Disease Modifying Anti-Rheumatic Drug (DMARD) naive at baseline; (iii) met the ACR/EULAR 2010 RA criteria at baseline. Linear or median regression analyses, depending on the distribution of the dependent variable, were conducted to examine baseline HAQ or DAS28 scores over time. A quadratic term for calendar year of assessment by NOAR was included as a predictor and if significant, cohort was included to examine if the rate of change

Risk of above median progression of erosions.

Disclosures: B.D., Balfour—Research Grant. D.W., Pfizer—Research Grant, Consultancy. All other authors have declared no conflicts of interest.

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in scores over time differed between cohorts. Confounders included gender, RF and ACPA positivity, and age at symptom onset.

**Results:** 3045 patients were evaluated within the total sample (Table 1). The calendar year of assessment was a significant predictor of lower DAS28 scores over time for the total sample (adj.= -0.0007, 95% CI = -0.001, -0.0001), and each sub-sample. Within the total sample, and the DMARD naive sub-sample, there was a significant effect of ‘Cohort’, and a significant ‘Calendar year by Cohort’ interaction. The calendar year of assessment was not a significant predictor of HAQ scores for the total sample (adj.=0.0002, 95% CI = 0.0002, 0.001).

**Conclusions:** Whilst baseline disease activity has decreased over time, there has been no change in levels of functional disability.

**Disclosures:** The authors have declared no conflicts of interest.

### 228. SMALLER BONES AT AGE 9 PREDICTS SCOLIOSIS AT AGE 15: RESULTS FROM A POPULATION-BASED BIRTH COHORT

**Background:** Scoliosis is lateral curvature of the spine and adolescent idiopathic scoliosis (AIS) accounts for the majority of cases of scoliosis. Understanding the aetiology of AIS may provide opportunities for early intervention, perhaps enabling limitation of curve size. One potential determinant of scoliosis that is of great interest is bone size and density. However, there are no published studies that have investigated determinants of scoliosis using a prospective cohort design making the establishment of cause and effect difficult.

**Methods:** This study was based on the Avon Longitudinal Study of Parents and Children (ALSPAC) which is a population-based cohort recruited from 14893 pregnant women in Avon with expected dates between April 1991 and Dec 1992. Data on total body (minus head) bone area were collected by DXA using a Lunar Prodigy scanner in 7333 children aged 10 years. Children with scoliosis already present at aged 10 were excluded. Data were collected on the presence or absence of scoliosis at aged 15 using a validated method. Other potential confounding variables were also measured. In addition, peripheral quantitative CT (pQCT) was used to measure bone circumference and cortical thickness at aged 15. Associations between bone variables and risk of scoliosis developing over the following 5 years were examined by logistic regression. Cross-sectional analyses were also carried out between pQCT variables and presence of scoliosis at 15.

**Results:** Of the 4022 children who were seen at both age 10 and age 15 in research clinics, 175 (4.4%) had developed scoliosis by age 15. Those with scoliosis were more likely to be female (72.6%) and no association was seen with ethnicity or socio-economic status. After adjustment for confounders, the odds ratio (OR) for scoliosis at aged 15 per s.d. increase in bone size relative to body size at aged 9 was 0.61 (95% CI 0.42, 0.89, P = 0.009). Bone area measured by DXA, adjusted by height, showed the strongest association with scoliosis at 15 (OR 0.58, 95% CI 0.44, 0.76). Girls with scoliosis at 15 had smaller pQCT variables: periosteal circumference (67.81.60 vs 68.86 mm, P = 0.05) and reduced cortical thickness (5.02 vs 5.16 mm, P < 0.01) compared with those without scoliosis.

**Conclusions:** Our results show that children with smaller bones at aged 9 are more likely to develop scoliosis. This is the first prospective study in this area and adds weight to the hypothesis that smaller bone size is associated with an increased risk of scoliosis.

**Disclosures:** The authors have declared no conflicts of interest.

### GENETICS

**229. USING ENCODE DATA TO IDENTIFY POTENTIAL FUNCTIONAL GENETIC VARIANTS AT THE SQ31 PSORIASIS ARTHRITIS SUSCEPTIBILITY LOCUS**

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3Royal National Hospital for Rheumatic Diseases and Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
4Department of Dermatology, Southern General Hospital, Glasgow and Royal Hospital for Sick Children, Glasgow, UK
5Department of Rheumatology, St Vincent’s University Hospital, UCD School of Medicine and Medical Sciences and Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

**Background:** PsA is a chronic inflammatory arthritis associated with psoriasis. PsA is thought to arise as a result of an environmental trigger in a genetically susceptible individual and multiple genetic factors contribute towards disease susceptibility. Based on family studies there is a strong genetic component to risk for developing PsA with heritability estimates 80-100%. There is evidence from subgroup analysis of a genome wide association study (GWAS) that a locus on chromosome Sq31 is specifically associated with PsA and not psoriasis. This result has been replicated in two independent studies. A recent GWAS performed in a UK population (unpublished data) has refined and strengthened this association to a region 500 kb upstream of the original GWAS. There is however substantial linkage disequilibrium within this region necessitating the need for functional data to determine the causal variant.

**Methods:** Genotype data for a total of 1182 817 single nucleotide polymorphisms (SNPs), which includes the Sq31 region, were available for 836 PsA cases and 4770 controls (www.wfccc.org.uk). Genotyping was performed as part of a wider GWAS using the Illumina 660W quad BeadChip and Affymetrix Genome-Wide Human SNP Array 6.0 arrays. A strict quality control process was applied to the dataset followed by single point analysis using the Armitage test for trend. The lead SNP from the Sq31 region was selected and SNPs highly correlated (R2 > 0.8, 1000 genomes project) to the lead SNP were identified. ENCODE and expression quantitative trait loci (eQTL) data were searched, using publicly commercial databases, to explore evidence for transcription factor binding, DNase peak and eQTL.

**Results:** The lead SNP rs4705928 (P = 5.77 x 10^-7 OR = 0.78) lies within an intergenic region and does not overlie a known functional site. 59 highly correlated SNPs were discovered. Bioinformatic interrogation revealed 13 SNPs with eQTL and transcription factor (TF) binding/DNase peak evidence, 1 SNP with TF binding and DNase peak evidence with predicted binding motif alterations and DNase footprint, 4 SNPs with TF binding and DNase peak evidence and 9
SNPs with DNase peak or transcription factor binding evidence. The genes with altered expression (P < 1 × 10−10) are P4HA2, SLC22A4, and SLC22A5. P4HA2 encodes prolyl 4-hydroxylase, a crucial enzyme in collagen synthesis.

## Methods:

In both cases, independent analysis of each array (6 RA patients vs 6 healthy subjects) revealed approximately 700 CpGs, representing approximately 450 genes, that were differentially methylated (change in -value > 0.1) between patients and healthy subjects. The majority (60%) of sites was hypermethylated and 55–60% were associated with a CpG Island or the surrounding shores/shelves.

## Results:

In both cases, independent analysis of each array (6 RA patients vs 6 healthy subjects) revealed approximately 700 CpGs, representing approximately 450 genes, that were differentially methylated (change in -value > 0.1) between patients and healthy subjects. The majority (60%) of sites was hypermethylated and 55–60% were associated with a CpG Island or the surrounding shores/shelves. Analysis of all 24 samples together (12 RA patients and 12 healthy subjects) identified 78 differentially methylated CpGs, approximately 60% of which were hypermethylated or were associated with a CpG Island or the surrounding shores/shelves. These 78 CpGs, which represented 46 different genes, included 11 discrete differentially methylated CpGs which mapped to the promoter region of a single gene, identified as the dual specificity phosphatase DUSP22. These 11 CpGs were hypermethylated in 10 of the 12 RA patients (~50% increase in methylation). Despite the increase in methylation observed, this was not associated with a reduction in DUSP22 gene expression in RA patients. There was also no difference in DUSP22 gene expression between patients and healthy subjects.

## Conclusions:

This study confirmed the potential role of DUSP22 in RA and identified a set of CpGs that may be useful for diagnostic and therapeutic applications. Further research is needed to understand the mechanisms underlying the observed changes in DUSP22 expression and methylation.
decent and were categorized according to three mutually exclusive autoantibody status: anti-topoisomerase1 (ATA), anticientromere (ACA) and antiRNA-polymerase (ARA). Patients were further classified into subphenotypes according to major organ involvement; pulmonary fibrosis (assessed by HRCT and lung function test with a restrictive pattern), pulmonary arterial hypertension (defined as an elevation in the mean pulmonary artery pressure > 25 mmHg with normal pulmonary capillary wedge pressure < 15 mmHg) on right heart catheterization) and renal crisis (defined by a rapidly progressive renal failure, new onset accelerated hypertension). All genotyping was performed by the KASP system (allelic specific PCR, KBiOscience, UK). All genotype data and sub-phenotype analysis was performed using PLINK.

Results: Our cohort consisted of 63 (9%) patients with renal crisis and 112 (15%) with pulmonary arterial hypertension. 155 (21%) patients were positive for ACA, 265 (35%) patients were positive for ACA and 140 (19%) patients were positive for ARA. The SSC cases and the healthy controls were genotyped and all SNPs and individuals passed quality control checks for Hardy-Weinberg equilibrium (P = 0.05) and missingness (P < 0.1). An overall case-control analysis was performed using PLINK, of which no association was found in any individual SNP or haplotype. However, sub-phenotype analysis showed associations between SNP rs2289805 with ACA (P = 0.012, OR = 0.64) and ARA (P = 0.002, OR = 1.73); hence demonstrating the dual role of SNP rs2289805 in SSC with a protective effect in ACA positive patients and a risk effect in ARA.

Conclusions: We report a novel association with SNP rs2289805 in both ACA and ARA positive SSC patients. JNK-1 is a transcription factor which enhances collagen gene activities through the induction of TGF-β. Polymorphisms in JNK-1 can lead to a deregulation of expression of collagen associated genes leading to increased collagen formation and fibrosis. These data suggest JNK-1 to be a good candidate gene in SSC and warrants further investigation.

Disclosures: The authors have declared no conflicts of interest.

233. FINE MAPPING THE FCGR2A ASSOCIATION WITH SUSCEPTIBILITY TO RHEUMATOID ARTHRITIS

James Robinson1, John Taylor1, Lubna Haroon Rashid1, Edward Flynn2, Stephen Eyre3, Jane Worthington4, Anne Barton4, John Isaacs5, John Bowes5, Anthony G. Wilson5, Jennifer H. Barrett4 and Ann Morgan4

1Leeds Institute of Molecular Medicine, University of Leeds, Leeds, 2Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, 3Institute of Cellular Medicine, University of Newcastle, Newcastle and 4Department of Infection and Immunity, University of Sheffield, Sheffield, UK

Background: Recent segmental duplication affecting the FCGR locus on chromosome 1 has led to structural variation and ambiguous mapping of underlying genetic variants. Consequently, the region is misrepresented in SNP databases, has been untested by genome wide association studies and dismissed as a potential contributor to genetic predisposition, despite encoding receptors which are known to bind IgG-containing immune complexes and autoantibodies. A recent large-scale study identified a polymorphism close to FCGR2A with reproducible association with RA.

Methods: Gene specific resequencing of paralogous FCGR genes was performed in a panel of 32 controls. A reduced number of confirmed FCGR2A markers were selected and genotyped in 1959 RA patients and 1120 healthy controls using Sequenom MassArray (518 RA cases on both platforms). Immunochip data for the FCGR locus from 3870 RA cases and 8430 healthy controls were combined with the FCGR pleiot test.

Results: Resequencing 21 kb of FCGR2A and its promoter confirmed 61 SNPs and identified 5 novel markers. Locus-specific genotyping combined with data from the Immunochip project were used to fine map the original association in FCGR2A. Combined analysis of locus specific and Immunochip data identified two groups of associated SNPs stratified by minor allele frequency, all confined to a single interval flanked by two recombination hotspots. Two potential causative nonsynonymous coding SNPs, which alter the affinity of the receptor for ligand, were in linkage disequilibrium with the index SNPs. A haplotype of these two risk markers showed strongest association with disease (P = 0.0003, OR 1.17; 95% CI 1.07, 1.28).

Conclusions: We identified an additional independent genetic risk factor at the FCGR2A locus in RA. The functional impact of these variants and potential pathogenic role for FCGR2A in RA will be presented with respect to the dual role of FCγRIIa in innate and adaptive immunity.

Disclosures: The authors have declared no conflicts of interest.

References

235. DOES AN ACUTE HOTE JOURT SECTIVE REDUCE ADMISSION AND LENGTH OF STAY?

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Background: The BSR/BOA guidelines emphasise the importance of early aspiration in the management of an acute hot swollen joint. A clinical pathway, admissions and length of stay would be reduced as previously acute hot joints were managed as an acute admission and delays of more than 24 - 48 h before joint aspiration were not uncommon.

Methods: The service was configured to ensure triage with high priority from accident and emergency (AandE) followed by referral to rheumatology between 9 am and 5 pm and to orthopaedics out of normal working hours. Patients who were systemically well with a temperature of $\leq 38^\circ C$, who had no contraindications to outpatient management were seen either in ambulatory care or clinic on the same or next day. All other patients were admitted to medical admissions unit (MAU) for assessment. GP referrals were triaged by phone. During September and October 2012 an audit proforma was completed for all referrals to the hot joint service. In addition to demographics and clinical information we collected details on synovial fluid analysis.

Results: 29 patients were referred. 23 (79%) referrals were received between 9am and 5 pm, Monday to Friday. 28/29 patients were seen on the same day. 1 patient with non infective olecranon bursitis was seen the following day. AandE referred the most—15 (52%), with the remainder coming from primary care 6 (20%), 1 from the helpline and 7 inpatient referrals (2 of which were on MAU). Following review of the 22 patients referred from the community 36% required admission and we were able to discharge 14 (64%) home. 4 were admitted to exclude septic arthritis following confirmed—infect ed olecranon bursitis—staphylococcus aureus (6), and a cellu litis, 3 were admitted for pain control or poor mobility and the final patient was found to have a non-rheumatological problem. The average length of stay for the patients admitted was 3.6 days. Only 1 patient was admitted to the MAU at the time of initial review. The median time overall from referral to aspiration was 60 min (average 172 min). The commonest inflamed joint was the knee (48%) followed by the wrist (21%) and the elbow (10%). The most common final diagnosis was crystal arthritis—9 (31%). No patients with septic arthritis presented during the study period.

Conclusions: The referrals to the service were appropriate and long delays prior to aspiration were abolished. The majority of patients referred from the community could be managed successfully as outpatients. There was a lower than expected incidence of septic arthritis suggesting this may have been overestimated in previous case series. We have shown that a specialist streamlined pathway for patients with acute hot joints reduces the time to diagnosis, reduces admissions and in turn reduces the pressure on MAUs and in patient beds.

Disclosures: The authors have declared no conflicts of interest.

236. AN AUDIT OF MISSED RHEUMATOLOGY OUTPATIENT APPOINTMENTS
Aamir Saeed1, Robert Coughlan2 and John J. Carey3
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Background: Rheumatology is an under-resourced specialty in many countries and thus waiting lists are among the longest in the medical profession. Non-attendance at outpatient clinics remains a challenge to the health service resulting in valuable appointments going unused. The failure to attend rate has been running at 20% for several years for our service. On July 7th 2011 an SMS text reminder system prior to patient clinic date was put in place at Rheumatology Department, Merlin Park/Galway University Hospitals to improve clinic attendance.

Aim: 1) To evaluate whether the SMS text reminder reduced the non-attendance rate in our outpatient clinic; 2) To identify the reasons for non-attendance after introduction of SMS text reminder system.

Methods: An anonymous Questionnaire was posted to all patients failed to attend Rheumatology out-patient clinic from July 7th 2011 till 31 December 2011 at our University Hospital asking them to indicate reasons for non-attendance. A self-addressed pre-stamped envelope was also included for reply. A follow-up telephone inquiry was made to those who didn’t respond to the postal Questionnaire. The study was approved by our local audit and ethics committee. All data were entered in XL sheets for analysis purposes.

Results: 498 patients (18.9%) didn’t show up at clinic. A total of 407 (81.7%) responded, 330 postal and 77 telephone. Almost half of all respondents claimed to have neither received the appointment letter (238) nor the SMS text reminder (238). Text reminder neither, 21% patients were unwell to attend clinic and about 29% did not write their diagnosis.

Conclusions: Nearly 1 in 5 patients fail to attend rheumatology appointments at our university hospitals. The most common reason cited was a lack of notification. The addition of an SMS text reminder had very little impact on the attendance rate. Improved communication resources are needed.

Disclosures: The authors have declared no conflicts of interest.

237. ARE WE MANAGING THE ACUTE HOT SWOLLEN JOINT ACCORDING TO THE NATIONAL GUIDELINE 5 YEARS ON?
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Background: Patients with acute, hot swollen joint/s usually present to the accident and emergency department. The British Society for Rheumatology (BSR) has set out clear guidelines on the management of the acute hot swollen joint including recommendations for early joint aspiration and specialist referral of all patients with suspected septic arthritis. We therefore investigated whether the management of patients with acute hot swollen joint/s at St Mary’s Hospital (SMH) Accident and Emergency (AandE) adheres to the BSR guidelines.

Methods: Patients who attended the SMH AandE department with acute hot, swollen joint/s over a 12 month period from Apr 2011 to Apr 2012 were identified by searching the SMH database using key words like: septic arthritis; joint effusion; tenosynovitis; and gout. Their medical notes, pathology and microbiology results, and discharge summaries were examined. Patients with clinical features consistent with an alternative diagnosis were excluded. Data were collected regarding the occurrence of joint aspiration, collection of blood cultures, antibiotic treatment, analgesia, and specialist referral.

Results: A total of 39 patients were included. In all, 20/39 (51%) patients had a joint aspiration performed with; 13/20 (65%) by orthopaedic surgeons; 4/20 (20%) by emergency physicians; and 3/20 (15%) by rheumatologists. All 5 prosthetic joints were referred to and managed by orthopaedic surgeons. In 13/19 (68%) patients the decision not to aspirate was not in accord with the BSR guidelines. The reason for not aspirating was clearly documented in 14/19 (73.7%) of cases. The most common reason was a low clinical probability of septic arthritis as assessed by the specialist (12/19, 63%), followed by 5/19 (26%) cases based on not elevated inflammatory markers. Inflammatory markers were measured in 35/39 (89.7%) patients. Blood cultures, however, were obtained in only 9/20 (45%) patients which yielded a positive result in 1 (5%) patient. A total of 12/39 (30.7%) patients were treated with antibiotics the choice of which was in accord with local policy in 9/12 (75%) patients. Of those with joint aspirations, 7/20 (35%) patients had received antibiotics, and in all (100%), this was after the aspiration. Average time to antibiotics was 3.9h. Analgesia was given to 36/39 (92.3%) of patients within 37 min of registering.

Conclusions: Our data indicated that despite clear guidance from the BSR on the management of acute hot swollen joint, adherence in clinical practice is not optimal. Consequently, we have designed a local AandE pathway adapted from the BSR guideline to be included in the induction programme for new staff. Several factors such as lack of awareness among junior doctors and insufficient experience in managing joints, may potentially explain the noted deviation from the BSR guidance.

Disclosures: The authors have declared no conflicts of interest.

238. WASTE NOT, WANT NOT: IS ANTI-TNF WASTAGE PREVENTABLE?
Carolyn Bell1, Sharon Petford1, Lisa-Marie Tibbetts1 and Karen M. J. Douglas1
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Background: Anti-TNF therapy (inhibitors of tumour necrosis factor (TNF) has revolutionized rheumatology but also made it an expensive specialty. Humira, enbrel and infliximab are independently within the top 10 selling pharmaceutical products 2012 with combined sales of $2.9 billion. In today’s NHS financial accountability is imperative and includes minimizing drug wastage, a concern that is independently recognized at a national level. The authors have declared no conflicts of interest.

Methods: Patients at our university hospital were selected for review who had failed to attend their scheduled anti-TNF appointment at the department. A review of clinical summaries was examined. Patients with clinical features consistent with an alternative diagnosis were excluded. Data were collected regarding the proportion of patients who were unable to attend appointments, reasons for non-attendance and the cost of anti-TNF waste.

Results: A total of 39 patients were included. In all, 20/39 (51%) patients had a joint aspiration performed with; 13/20 (65%) by orthopaedic surgeons; 4/20 (20%) by emergency physicians; and 3/20 (15%) by rheumatologists. All 5 prosthetic joints were referred to and managed by orthopaedic surgeons. In 13/19 (68%) patients the decision not to aspirate was not in accord with the BSR guidelines. The reason for not aspirating was clearly documented in 14/19 (73.7%) of cases. The most common reason was a low clinical probability of septic arthritis as assessed by the specialist (12/19, 63%), followed by 5/19 (26%) cases based on not elevated inflammatory markers. Inflammatory markers were measured in 35/39 (89.7%) patients. Blood cultures, however, were obtained in only 9/20 (45%) patients which yielded a positive result in 1 (5%) patient. A total of 12/39 (30.7%) patients were treated with antibiotics the choice of which was in accord with local policy in 9/12 (75%) patients. Of those with joint aspirations, 7/20 (35%) patients had received antibiotics, and in all (100%), this was after the aspiration. Average time to antibiotics was 3.9h. Analgesia was given to 36/39 (92.3%) of patients within 37 min of registering.

Conclusions: Our data indicated that despite clear guidance from the BSR on the management of acute hot swollen joint, adherence in clinical practice is not optimal. Consequently, we have designed a local AandE pathway adapted from the BSR guideline to be included in the induction programme for new staff. Several factors such as lack of awareness among junior doctors and insufficient experience in managing joints, may potentially explain the noted deviation from the BSR guidance.

Disclosures: The authors have declared no conflicts of interest.
significant events requiring αTNF cessation. It explored knowledge of the process of stopping αTNF including its delivery. Results: 390 patients received injectable αTNF and 25 stopped (4 ineffective, 12 side effects, 6 new contraindication, 3 other). 2 were deemed predictable (see Table 1). Analysis of the questionnaire identified several themes. Firstly, reluctance to stop αTNF in suboptimal efficacy; secondly sources of delay in stopping drug delivery with varied methods of communication to CNS staff (email/letter/direct) and uncertainty of the process of halting αTNF delivery. It revealed reliance on CNS staff to unite clinical decisions with prescription management. Conclusions: Unused αTNF amounted to £35 500 representing 1.4% of our £2.5 million annual biologics spend. Whilst only a small proportion, when dealing with large figures small percentages amount to considerable sums. Wastage was largely unpredictable; simply recognizing patients expected to stop is unlikely to be beneficial. The questionnaire identified sources of unnecessary drug delivery due to delays in stopping αTNF. Staff needs education and a streamlined pathway for αTNF cessation instituted. Currently deliveries are made quarterly; reducing this interval may minimize waste without extra cost, but an increased workload preparing and dispensing prescriptions is inevitable. To uncouple any dissociation between decision making and prescribing flagging prescription requests prior to assessment points (e.g. 6 months in RA) would ensure criteria are fulfilled and appropriate prescribing. We have identified local actions to reduce αTNF wastage. Our experience is unlikely to be unique and thus represents an area for considerable potential saving nationally.

Table 1. Anti-TNF wastage

<table>
<thead>
<tr>
<th>Gillima</th>
<th>Entrel</th>
<th>Humira</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>9</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Average: consumed per patient</td>
<td>3.8</td>
<td>6.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Average cost per patient, £</td>
<td>1340.63</td>
<td>1151.94</td>
<td>1643.32</td>
</tr>
<tr>
<td>Total cost, £</td>
<td>5362.50</td>
<td>10 367.47</td>
<td>19 719.84</td>
</tr>
</tbody>
</table>

Disclosures: The authors have declared no conflicts of interest.

239. SIGNIFICANT REDUCTION IN BIOLOGIC PRESCRIBING COSTS Whilst maintaining remission in rheumatoid arthritis, psoriatic arthritis and anklyosing spondylitis

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Background: Biologics prescribing costs are spiralling upwards as many patients remain on medication for many years. Long-term safety concerns are diminishing but the effects of decades of use are unknown. Optimal dosing, treatment duration, and effects of reducing medication for patients in or near remission are unclear. This abstract details one consultant’s experience of reducing biologic doses in patients with RA, PsA and AS for those with very low disease activity.

Methods: Patients with RA, AS or PsA on biologic medication with low disease activity or in remission for at least 6 to 12 months were identified during routine clinic appointments between May 2011 and October 2012. Patients were offered a biologic dose reduction condition that they could resume their previous dose in the event of a relapse. Etanercept dose was reduced to between 10 and 25mg weekly, infliximab from 3mg per kg to 2.5mg per kg, adalimumab from 40mg fortnightly to 40mg 3 weekly. DAS was subsequently monitored every 3 months and previous doses were resumed in the event of a flares.

Results: Of 52 patients with RA on biologic medication, 13 patients, all in remission (DAS28 <2.6, mean DAS28 2.1) had their dose of biologic medication reduced: 7/13 male, 6 female, average age 65 years, average disease duration 8 years. 1 patient stopped each of adalimumab and rituximab completely. 10/13 patients remained in remission (mean DAS28 2.5) after an average follow-up duration of 13 months. 3/10 who remained in remission were on their second biologic medication after primary failure of their first. 3/13 patients relapsed at between 3 and 5 months and were re-started on their previous dose with a rapid return to previous DAS28 scores. Out of 10 patients with AS on biologic medication, 5 with very low DAS (mean BASDAI 0.8, pain VAS 1.5) and 5 with moderate disease (mean BASDAI 3.8, pain VAS 3.0) had their dose of biologic reduced. 1 patient on each of etanercept and adalimumab stopped their biologic completely. All still had low DASs at an average follow-up duration of 8 months (BASDAI 0.5, pain VAS 0.3). 2 patients with PsA out of 6 on biologics succeeded in reducing their dose with no worsening of disease activity after 9 months of follow-up.

Conclusions: Remission was maintained on a reduced dose of biologic medication in almost 1 in 5 of this sample of patients with RA, even in some who had failed a prior biologic, in 1 in 2 patients with AS and in 1 in 3 patients with PsA with an estimated annual saving of around £82,000. This represents around 12% of the annual biologic costs for one consultant alone. Significant savings nationally may be possible. Further work should determine whether this apparent clinical stability is reflected in a long-term lack of progression and disability.

240. VARIATION IN CASE MIX AND SERVICE PROVISION ACROSS WESSEX RHEUMATOLOGY UNITS: AN UPDATE

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Background: Commissioning of rheumatology services is currently in the spotlight but much remains unknown about the spectrum of rheumatic disease seen in Rheumatology Units (RU) across the UK. 4 surveys assessing clinical practice in 8 RU in Wessex have been performed over the last 14 years.

Methods: Data have been collected on all patients attending 8 RU in Wessex over a 4 week period in 1998, 2004, 2008 and 2012. Information gathered included details on patient demographics, primary diagnosis, who the patient saw and follow up arrangements. Data from 2012 are reported and compared with 2008 data.

Results: 7350 patients (mean age 57 years, 63% female) were seen in the 8 RU in 2012, an increase of 8% since 2008. In 2012 the proportion of patients seen by a consultant varied hugely across 8 RU from a mean of 48%, range across RU 26–66%. The proportion of patients seen by nurses or other allied health professionals had increased in all RU with the mean increasing from 21% to 28% (range across RU, 11–33% and 16–37% respectively for 2008 and 2012).

In 2012 the proportion of patients seen as new referrals was relatively constant (mean 20%; range across RU, 16–26%) and had not changed significantly since 2008. In 2012 the proportion of patients discharged varied from 12–31% (7–26% in 2008) with an unchanged mean of 17%. As noted in 2008 only 1 RU discharged more patients than they saw as new referrals in 2012. The mean ratio of follow up/new (FU:N) patients seen increased from 3.4 to 4.0 from 2008 to 2012.

Conclusions: This survey highlights significant differences in who provides rheumatology services and what clinical conditions are seen within Wessex RU. Such factors need to be taken into consideration when rheumatology services are being reviewed and commissioned.

Disclosures: The authors have declared no conflicts of interest.
counselling. A maximum of 5 patients are seen per 40 min appointment with 1 appointment per DMARD and 1 clinic per week. Extra clinic slots are run if there is demand. Prior to the clinic the nurses check that the criteria of the appointment has been completed and are acceptable and if not the appointment is delayed. Patients felt not to be appropriate for group clinic are given single clinic slots. After counselling the patient signs a consent form for treatment. Our aim is to initiate DMARDs promptly while reducing the nurse’s clinic time but maintaining high levels of patient satisfaction.

**Methods:** The number of patients attending DMARD clinic over a 3 month period was recorded along with time from referral to appointment. Patients were asked to return a patient satisfaction questionnaire (25 returns). The results were compared with findings of the same survey given to patients counselled individually before the group clinic was set up (16 returns). Questions included:

- I felt welcomed by the nurse?
- The amount of room in clinic was satisfactory?
- What was the quality of verbal information given?
- What was the quality of written information given?
- The appointment was helpful?
- My questions were answered satisfactorily?
- I feel confident to start my medication?

**Results:** Answers were scored using a likert scale with a maximum score of 5 meaning very satisfied.

**Conclusions:** Group DMARD clinics allow us to keep up with demand for clinic slots while freeing up our nurses to undertake other duties. Patient satisfaction remains very high in the group clinic although we are not to address all of our patient’s ideas, concerns and expectations with regards to taking the new drug.

**Disclosures:** The authors have declared no conflicts of interest.

### 242. COST-EFFECTIVENESS OF JOINT PROTECTION AND HAND EXERCISE FOR HAND OSTEOARTHRITIS

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1Research Institute for Primary Care and Health Sciences, Keele University, Keele, 2Health Economics Unit, School of Health and Population Sciences, University of Birmingham, Birmingham, UK, 3Faculty of Health, Simon Fraser University, Burnaby, Canada and 4Centre for Health, Sport and Rehabilitation Research, Salford University, Greater Manchester, UK

**Background:** European guidelines have proposed that joint protection and hand exercise should be used in the management of hand OA. However, the evidence regarding the cost-effectiveness of these interventions has not been well established. A 2x2 factorial trial was carried out to compare the effectiveness of joint protection (JP), hand exercise (HE), joint protection plus hand exercise and leaflet and advice (LA). The trial demonstrated JP was the most effective option as indicated by the primary outcome measure (GARI/OMERACT responder criteria), at 6 month follow-up. The primary aim of this study is to assess the cost-effectiveness of management options for hand OA. In addition, given the absence of consensus regarding the conduct of economic evaluation alongside factorial trials, we compare different analytic methodologies.

**Methods:** A cost-utility analysis was undertaken over a 12 month period. Patient level resource use and EQ-5D data were obtained from postal questionnaires, and mean costs and quality-adjusted life years (QALYs) were calculated for each trial arm. Incremental cost-effectiveness ratios (ICERs) were estimated and cost-effectiveness acceptability curves constructed. The base case analysis used a within the table analysis methodology, which involves comparing LA, JP plus HE, JP alone and HE alone. Two further methods were explored: the at-the-margins approach, and a regression-based approach with or without an interaction term.

**Results:** 257 patients were randomized to receive one of the interventions. Mean costs (S.D.) recorded in each treatment arm were £50.24 (265.40) for LA, £104.40 (93.28) for JP plus HE, £28.29 (108.22) for JP and £57.21 (76.88) for HE. Mean QALYs (S.D.) associated with each trial arm were 0.662 (0.166) for LA, 0.658 (0.164) for JP plus HE, 0.599 (0.157) for JP and 0.681 (0.138) for HE. In the base case analysis, hand exercise was the most cost effective option with an ICER of £367 per QALY gained compared with leaflet and advice, and with an 80% chance of being cost-effective at a threshold of £30,000 per QALY gained. With the alternative analysis methods, HE remained the most cost-effective management strategy, with ICERs consistently less than £2,000 per QALY gained.

**Conclusions:** The results of this study showed that HE was the most cost-effective option in the absence of the intervention. Additional findings should be viewed in the context of both management options being very inexpensive and the associated clinical findings that indicated joint protection was the most effective option at 6 months. Possible reasons for this disparity include the use of different outcome measures (responder criteria vs QALYs), measurement at different time points (6 months for the primary clinical outcome vs 12 months for the economic analysis), reduced statistical power and more generally, the conduct and pragmatic objective of the study.

**Disclosures:** The authors have declared no conflicts of interest.

### 243. BIOLOGIC THERAPIES FOR RHEUMATOID ARTHRITIS: ELIGIBILITY CRITERIA IN THE UK

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**Background:** The British Society for Rheumatology (BSR) Guidelines recommends biologic therapies for the treatment of patients with RA as measured by DAS28 >3.2 (moderate disease activity). Current UK reimbursement Guidance recommends use for biologics to treat patients with RA who have a DAS28 of >5.1 only (severe RA). There is a growing body of evidence that shows treatment of RA should be started as early as possible to minimize damage to joints and prevent long-term disability. For optimal outcomes, the clinical consensus is that treatment with biologic therapies should commence within 3 months of symptom onset. Our objective is to highlight the need for a review of the eligibility criteria for use of biologic therapies to treat RA in the UK, and to illustrate the number of patients with RA who would be eligible to receive biologic therapies if the criteria of DAS28 >3.2 were to be applied.

**Methods:** The UK-population estimate (n = 62,262,000) was applied to the NICE costing template for biologics for RA, and the number of RA patients eligible to receive biologic treatment was calculated.

**Results:** Prevalence rates were based on Symmons et al. [1] Percentages have been reworked by reference to the population age and sex profile. Based on the Commissioning Guide for biologic therapies, which incorporates estimates of patients with a DAS28 >5.1 in whom treatment with DMARDs has failed; 10% patients with RA are eligible for treatment with biologics. Based on clinical opinion collected from a number of leading UK rheumatologists the proportion of patients eligible for treatment with biologics at a DAS28 score >3.2 was estimated to be approximately 50%.

**Conclusions:** The total estimated prevalence of patients with RA is 4.022. Utilizing the restrictions outlined in current guidance and applying a DAS28 score >5.1 results in 42 102 RA patients being eligible to receive treatment with biologics. Whereas 210 511 patients would be treated if a DAS28 score >3.2 were to be applied.

**Disclosures:** Restrictions on UK HTA guidance leave a significant number of patients untreated compared with international clinical guidance. There is widespread agreement that there is a need to make these drugs available to those patients most likely to respond to them.

**Reference**


### 244. A BRIEF EXERCISE AND SELF-MANAGEMENT PROGRAMME IMPROVES UPPER LIMB DISABILITY IN PEOPLE WITH EARLY RHEUMATOID ARTHRITIS

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1School of Medicine, King’s College London, London, 2School of Rehabilitation Sciences, St George’s University of London and 3Faculty of Health Science, Simon Fraser University, Burnaby, Canada

**Background:** Previous prevalence of early RA (ERA) has been 3.2 (moderate disease activity). Current UK reimbursement Guidance recommends use for biologics to treat patients with RA who have a DAS28 >3.2 (moderate disease activity). Current UK reimbursement Guidance recommends use for biologics to treat patients with RA who have a DAS28 >5.1 only (severe RA). There is a growing body of evidence that shows treatment of RA should be started as early as possible to minimize damage to joints and prevent long-term disability. For optimal outcomes, the clinical consensus is that treatment with biologic therapies should commence within 3 months of symptom onset. Our objective is to highlight the need for a review of the eligibility criteria for use of biologic therapies to treat RA in the UK, and to illustrate the number of patients with RA who would be eligible to receive biologic therapies if the criteria of DAS28 >3.2 were to be applied.

**Methods:** The UK-population estimate (n = 62,262,000) was applied to the NICE costing template for biologics for RA, and the number of RA patients eligible to receive biologic treatment was calculated.

**Results:** Prevalence rates were based on Symmons et al. [1] Percentages have been reworked by reference to the population age and sex profile. Based on the Commissioning Guide for biologic therapies, which incorporates estimates of patients with a DAS28 >5.1 in whom treatment with DMARDs has failed; 10% patients with RA are eligible for treatment with biologics. Based on clinical opinion collected from a number of leading UK rheumatologists the proportion of patients eligible for treatment with biologics at a DAS28 score >3.2 was estimated to be approximately 50%.

**Conclusions:** The total estimated prevalence of patients with RA is 4.022. Utilizing the restrictions outlined in current guidance and applying a DAS28 score >5.1 results in 42 102 RA patients being eligible to receive treatment with biologics. Whereas 210 511 patients would be treated if a DAS28 score >3.2 were to be applied.

**Disclosures:** Restrictions on UK HTA guidance leave a significant number of patients untreated compared with international clinical guidance. There is widespread agreement that there is a need to make these drugs available to those patients most likely to respond to them.

**Reference**

**Background:** Upper limb dysfunction occurs early in RA and deteriorates as the disease progresses, impacting on independence and work capacity. Exercise is an important component in the management of upper limb disability yet studies focus on the hand in isolation, not addressing proximal motor deficits. Individualized home exercise regimens are required to address global upper limb dysfunction and encourage long-term self-management. This study evaluated a global upper limb home exercise programme, supplemented with supervised education, self-management, and exercise sessions, for improving upper limb disability. Education and eXercise Training in early Rheumatoid Arthritis (EXTRA programme).

**Methods:** 108 adults with RA, of 5 years (26 males, mean (SD) age: 55 (15) years, disease duration: 20 (19) months) were randomized to receive either Usual Care (n = 52) or the EXTRA programme (n = 56).

**Results:** Compared with a Usual Care control group, participants who completed the EXTRA programme demonstrated improved disability, function, and non-dominant grip strength, with no adverse effects on disease activity (Table 1).

**Conclusions:** The EXTRA programme is efficacious for improving upper limb dysfunction and may be easily implemented into clinical practice.

**Disclosures:** The authors have declared no conflicts of interest.

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**Methods:** LoS has been examined in two very similar multi-centre inception cohorts, the Early RA Study (ERAS) (n = 1465, 1986–1999) and the Early RA Network (ERAN) (n = 1236, 2002–2010). Details of orthopaedic interventions included date, type of procedure and LoS, obtained from clinical and national datasets (National Joint Registry and Hospital Episode Statistics). Follow-up was based on the National Death Register. Standardized event rate data during the last 10 years were used to investigate factors affecting LoS with univariate and multivariate regression analysis.

**Results:** A total of 1602 procedures were performed in 770 (29%) of 2701 patients in ERAS and ERAN. 40% were major, of which 88% were total joint replacements (mainly hand/foot surgery) and 16% minor (soft tissue surgery). A gradual reduction in the median LoS was noted over 25 years for all procedures: 10, 4 and 2 days respectively (IQRs 7–15, 3–7, 1–4) in ERAS and 7, 3 and 1 days (IQRs 5–8, 1–7, 1–2) in ERAN. The improvement in median LoS over time and in comparison with national data for the commonest types of surgery will be displayed graphically. Extrapolation of national data suggests that in the 1990s TKRs resulted in longer LoS than in the 2000s. The cost of a TKR based on 5 days LoS currently in the UK is £2576, and the decline in LoS across most procedures has resulted in reduced costs. In multivariate analyses LoS varied significantly by type of procedure, with LoS 8.2 (4.7, 5.9) days in TKRs, 6.8 (4.4, 5.5) days in hip, and 5.3 (3.1, 4.5) days in knee.

**Conclusions:** LoS in RA-related orthopaedic surgery has declined over the last 25 years, which could be a reflection of improved management of RA, and better medical and surgical treatment for patients. Normal baseline HB, low baseline HAQ and low LoS at 1 year were found to be significant predictors for reduced LoS.

**Disclosures:** The authors have declared no conflicts of interest.
monitoring at interval recommended by rheumatologists. We carried out service redesign using DAWN monitoring system to address the issue of improving compliance and reduce avoidable hospital admissions.

Methods: Implementing monitoring service redesign
Jan 2011 Gathering evidence of deficiencies within the current practice
Feb 2011 Sharing the vision with the trust board—Business case
Mar 2011 Patient focus group 1—gaining patient perspectives
Apr 2011 Trust executive approval of funding for monitoring software only
May 2011 Secure further funding for IT interface work
Jun 2011 Commence procurement process of monitoring software system.
July 2011 Site visit and building monitoring team—the key to sustainability.
Aug 2011 Commencement of IT interface work for the next 6 weeks
Sep 2011 System Goes Live! Clinical data entry for the next 2 months
Oct 2011 Call to action group 2—patients help perfect the service
Nov 2011 Presentation at Simulation and Patient Safety Conference, UK

Results: We piloted first 500 RA patients out of potential 6000 patients in our catchment area. The new monitoring service allows 100% early detection of patients that are non-compliant. 80 reminder letters were sent, and 78 patients responded with 2 weeks, monitoring compliance has improved from 76.0% to 97.6%. Reduce human error and speed up delivery of blood tests to specialists, allowing quicker action to be taken on abnormal results.

Conclusions: This patient centred and service driven pilot project has not only improved patient safety by early detection of missing blood tests, it has also greatly improved compliance rate to 97.6%, leading to potential reduction of avoidable hospital admissions. Active patient involvement throughout this project and bearing the patient’s perspective in mind are the key to the successful adoption of the project by both healthcare professionals and patients. We now have successful pilot evidence to show that this DMARDS monitoring service must be seriously considered for commissioning not only in the Portsmouth area but throughout NHS South Central and beyond.

Disclosures: E.W., Abbott, Roche—Research Grant, Pfizer—Consultation Fees. All other authors have declared no conflicts of interest.

MISCELLANEOUS RHEUMATIC DISEASES

247. IS OSMIUM SYNOVECTOMY USEFUL?
A RETROSPECTIVE OUTCOME AUDIT
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Background: The possible value of osmium tetroxide synovectomy has been found to be a useful alternative to radio-isotope synovectomy. This generally safe technique is not widely used in the UK. At Wrightington Hospital we have been carrying out this procedure for the last 10 years. We present the results of a patients’ satisfaction survey who had osmium synovectomies done at Wrightington Hospital between 5/8/2002 and 16/9/2009.

Methods: A total of 61 patients had the procedure done, questionnaires were posted to all of them and we have received 25 replies (a response rate of 40%).

Results: 16 patients were males and 9 were females, minimum age was 30 years and maximum age was 75 years, mean age was 54.28 years. Mean duration since the procedure was carried out was 49.08 months (minimum 22 months and maximum 93 months). All patients had inflammatory arthritis. Single joints were injected in 18 patients and multiple joints injected in 6 (only knee and ankle joints were injected). 10 patients (40%) were very satisfied with the procedure, 7 (28%) quite satisfied, 6 (24%) quite disappointed and 2 (8%) were very disappointed. 18 patients stated they were willing to have the procedure done again if needed and 7 were not willing. The majority of patients did not experience skin burns, worsening of pain or any other problems as a result of the procedure. The majority of patients (88%) experienced improvement in the pain after the procedure with the effect lasting for 14.16 months on an average. The majority of patients did not need a repeat procedure (88%) and only a minority needed repeat procedure (12%). 24 patients (86%) did not have joint replacement since the procedure and 1 (4%) needed joint replacement.

Conclusions: Osmium synovectomy is an effective treatment for persistent synovitis of large joints when the conservative treatment has failed to control the inflammation.

Disclosures: The authors have declared no conflicts of interest.

248. A SYSTEMATIC ANALYSIS OF THE SAFETY OF PRESCRIBING OF ANTI-RHEUMATIC, IMMUNOSUPPRESSIVE AND BIOLOGIC DRUGS IN MEN TRYING TO CONCEIVE
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Background: Prescribing of anti-rheumatic and immunosuppressive drugs in men with active rheumatic disease trying to conceive is required to control disease activity and thus increase the chance of successful conception. This area of prescribing however is complicated by concerns regarding the safety of many of these drugs. These concerns arise from safety information based mainly on experimental and animal studies. Human data are limited to inadvertent exposure described in case reports/series and population registries. Previous systematic reviews have identified a risk of oligospermia with SSZ and gonadal toxicity with cyclophosphamide in men trying to conceive, as well as theoretical concerns for Lef and biologics.

Methods: A systematic search of PubMed and Embase was carried out using relevant keywords for pregnancy, men, conception and drugs commonly prescribed in patients with rheumatic disease from 1966 onwards. The drug categories included analgesics, disease modifying anti-rheumatic drugs, biologics and steroids.

Results: Five studies were selected for detailed review, describing relevant drug use in men with rheumatic disease, IBD, post-transplantation, psoriasis, multiple sclerosis and leukaemia. The studies consisted of 2 case reports, 6 case series, 4 cohort studies and 3 case-controlled studies, of which only 4 had a comparator control group. These studies identified 2015 drug exposures (705 NSAIDs, 514 steroids, 368 AZA, 164 ciclosporine, 111 MTX, 59 SSZ, 46 etanercept, 16 infliximab, 13 HCG, 11 rituximab, 6 adalimumab, 2 Lef) in 1743 men trying to conceive, leading to 1778 pregnancies. There were limited reports of the effects upon fertility (in 133 men) and one retrospective questionnaire study of 30 men taking AZA reported an increased rate of infertility (~1 year to conception) of 15.2% vs 8.3% of controls. The confounding effects however, of underlying (Crohn’s) disease and the possibility of female infertility, were a limitation of this study. Of the 1706 live births, 32 congenital malformations were reported which were not specific to any drug. In the remaining 72 pregnancies which miscarried the precise number of elective terminations was not stated in all studies.

Conclusions: This systematic review did not find an increased risk of adverse pregnancy outcomes in partners of men taking anti-rheumatic, immunosuppressive and biologic drugs whilst trying to conceive. Although the small numbers of patients taking newer anti-rheumatic and biologic therapies mean there remains insufficient evidence to advocate the safe use of these drugs. This information however, is useful when counselling men of potential risk particularly after accidental conception.

Disclosures: The authors have declared no conflicts of interest.

249. PREDICTORS OF AORTIC ANEURYSMS FOR GIANT CELL ARTERITIS SUBJECTS
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A systematic search of PubMed and Embase was carried out using relevant keywords for pregnancy, men, conception and drugs commonly prescribed in patients with rheumatic disease from 1966 onwards. The drug categories included analgesics, disease modifying anti-rheumatic drugs, biologics and steroids.

Results: Twenty-five studies were selected for detailed review, describing relevant drug use in men with rheumatic disease, IBD, post-transplantation, psoriasis, multiple sclerosis and leukaemia. The studies consisted of 2 case reports, 6 case series, 4 cohort studies and 3 case-controlled studies, of which only 4 had a comparator control group. These studies identified 2015 drug exposures (705 NSAIDs, 514 steroids, 368 AZA, 164 ciclosporine, 111 MTX, 59 SSZ, 46 etanercept, 16 infliximab, 13 HCG, 11 rituximab, 6 adalimumab, 2 Lef) in 1743 men trying to conceive, leading to 1778 pregnancies. There were limited reports of the effects upon fertility (in 133 men) and one retrospective questionnaire study of 30 men taking AZA reported an increased rate of infertility (~1 year to conception) of 15.2% vs 8.3% of controls. The confounding effects however, of underlying (Crohn’s) disease and the possibility of female infertility, were a limitation of this study. Of the 1706 live births, 32 congenital malformations were reported which were not specific to any drug. In the remaining 72 pregnancies which miscarried the precise number of elective terminations was not stated in all studies.

Conclusions: This systematic review did not find an increased risk of adverse pregnancy outcomes in partners of men taking anti-rheumatic, immunosuppressive and biologic drugs whilst trying to conceive. Although the small numbers of patients taking newer anti-rheumatic and biologic therapies mean there remains insufficient evidence to advocate the safe use of these drugs. This information however, is useful when counselling men of potential risk particularly after accidental conception.

Disclosures: The authors have declared no conflicts of interest.
Background: GCA is the most common form of systemic vasculitis in the UK with presenting features including headache, scalp tenderness, jaw claudication and visual loss. Aortic involvement can also be present in patients with GCA. This study investigated the predictors of aortic aneurysm (AA) in patients with GCA.

Methods: A 20 year longitudinal study of GCA subjects was conducted from 01/01/1991 to 31/12/2010. From the General Practice Research Database (GPRD), 6999 patients with GCA were identified using Read codes. All GCA subjects were aged over 40 at the time of diagnosis. Aortic aneurysms were defined by Read codes in the GPRD, and ICD10 and OPCS codes were used in linked Hospital Episode Statistics (HES) data. Variables assessed included age, BMI, gender, smoking status and alcohol consumption, prior medical conditions including a previous history of hyperlipidaemia, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, peripheral vascular disease and previous prescriptions for anti-hypertensives, lipid lowering and diabetics medications. Subjects were observed from the date of GCA diagnosis to the earliest of date of death, transfer out (left the study), end of study date or date of aortic aneurysm diagnosis. Sub-hazard ratios (SHR) were derived from a survival model with death as the competing risk adjusting for potential confounders. We used multiple imputation to account for missing values of BMI (25%), smoking status (10%) and alcohol status (19%).

Results: The mean (±SD) age at GCA diagnosis was 71.9 (10.7) years, BMI was 26.6 (5.3) kg/m², 28.3% were male, 43.3% were ex/current smokers and 65% consumed alcohol. The median (IQR) follow-up was 4.1 (1.6–7.7) years and the median age at aortic aneurysm was 75.5 (69.5–80.9) years. At the time of GCA diagnosis, 5.2% had a previous history of hyperlipidaemia, 28.7% had hypertension, 9.8% had diabetes, 9.6% had cardiovascular disease, 9.0% had cerebrovascular disease, 2.8% had peripheral vascular disease, 15.6% had received lipid lowering medication and 41.0% had received anti-hypertensives. The independent predictors of AA during follow-up, associated with an increased risk, were male gender (SHR 2.1 (95% CI 1.4, 3.2) for ex-smokers, (SHR 2.2 (95% CI 1.2, 4.0), current smoker (SHR 3.8 (95% CI 2.2, 6.5), and prior prescriptions for anti-hypertensives (SHR 1.6 (95% CI 1.0, 2.6). A previous history of diabetes (SHR 0.2 (95% CI 0.1, 0.8) was associated with a lower risk of aortic aneurysm. The UK National Amyloidosis Centre has seen 540 patients in whom a full genetic screen of the fever genes has been performed in an attempt to determine any difference in disease inflammatory markers pre-treatment and the prevalence of AA amyloidosis.

Conclusions: This large UK GPRD cohort study of patients with GCA demonstrates an increased risk of developing an aortic aneurysm in patients who are male and have a history of smoking. In the general population, diabetes has been shown to have a protective effect against aortic aneurysm. This is the first study to demonstrate this association in patients with GCA.

Disclosures: The authors have declared no conflicts of interest.

250. THE PHENOTYPIC CONSEQUENCES OF MUTATIONS IN MORE THAN ONE GENE ASSOCIATED WITH AN INHERITED PERIODIC FEVER SYNDROME

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Background: The Inherited Periodic Fever Syndromes (IPFS) are rare genetic autoinflammatory disorders characterized by self-limiting recurrent episodes of febrile illness and acute inflammation in the absence of autoantibody production or infection. Four major main genetic sequence variant group. Consistent with this, individuals affected with multiple sequence variants were at increased risk of developing AA amyloidosis, with 57% of such patients over the age of 40 having the disease.

Conclusions: These data suggest that the presence of variants in more than one fever gene is associated with an increased risk of AA amyloidosis in older patients who have not been effectively treated for these syndromes. Given that the development of AA amyloidosis can be prevented by keeping the inflammatory response under control, it is important to diagnose IPFS as early as possible so that the appropriate treatment can be commenced.

Disclosures: The authors have declared no conflicts of interest.

251. AUTONOMIC NEUROPATHY IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS: PERIPHERAL SYMPATHETIC AND CARDIOVASCULAR AUTONOMIC FUNCTION ASSESSMENT

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Background: Autonomic nervous system (ANS) involvement has been studied in both RA and AS but with conflicting results and varying degrees of involvement. However Sodoucan a simple, non-invasive device for quick and quantitative assessment of sudomotor function, which has recently become available (Impeto Medical Device, Paris, France) and has not yet been employed for assessment of ANS function in RA and AS. Sodomotor function has also never been correlated with cardiovascular autonomic neuropathy (CAN). We aimed to investigate in RA and AS: (i) ANS functions utilizing both traditional CAN and using the novel sophisticated Sodoucan; (ii) relationship between the sudomotor function and indicators of CAN.

Methods: 15 patients with RA, mean (±SD) age 41.87 (11.80), 15 patients with AS, mean (±SD) age 32.27 (10.98), and 15 age-matched control subjects were selected from healthy clinic staff with mean (±SD) age 32.93 (1.62) years. The peripheral sympathetic autonomic function was assessed by Sodoucan through measurement of electrochemical skin conductance (ESC). CAN responses were assessed by the four standard cardiovascular reflex tests. Sympathetic dysfunction was examined by applying: blood pressure (BP) response to standing and BP response handgrip test. Parasympathetic dysfunction was examined by applying: heart rate (HR) response to deep breathing and HR response to standing.

Results: 60% patients with RA and AS had both parasympathetic and sympathetic CAN dysfunction. 60% (n = 9) RA patients and 33% (n = 5) AS patients had peripheral sympathetic autonomic dysfunction. None of the healthy volunteers had abnormal CAN dysfunction. Patients with RA and AS had significantly higher HR response to standing (P = 0.04), BP response to handgrip (P = 0.01) and Sodoucan (P = 0.002) compared with healthy controls. Lower ESC was associated with higher number of abnormal CAN results, and patients with ESC < 60 µs were approximately 2.5 times likely to have one or more abnormal CAN response compared with patients with ESC > 60 µs. Sodomotor function significantly correlated with HR response to standing (P < 0.05) and BP response to handgrip (P < 0.05) but not with BP response to standing. Significant correlation was found between HR response to deep breath and sudomotor function in RA but not in AS.

Conclusions: Prevalence rate of CAN among RA and AS is same but the frequency of sudomotor function is approximately half in AS compared with RA. Patients with lower ESC, indicating sudomotor dysfunction showed more prevalence of CAN dysfunction and it suggests that prevalence rate of CAN dysfunction is increases with worsening peripheral sympathetic autonomic dysfunction.

Disclosures: The authors have declared no conflicts of interest.
252. A SYSTEMATIC ANALYSIS OF THE SAFETY OF PRESCRIBING OF ANTIMUSCULAR, IMMUNOSUPPRESSIVE AND BIOLOGIC DRUGS IN PREGNANT WOMEN WITH AUTOIMMUNE RHEUMATIC DISEASE

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Background: Prescribing of anti-rheumatic and immunosuppressive drugs in pregnant women with active autoimmune rheumatic disease (ARD) is complicated by safety concerns. These concerns arise from safety information based mainly on experimental and animal studies. Human data are limited to inadvertent exposure described in case reports/series and population registries. Previous systematic reviews have identified risks with various anti-rheumatic and therapeutic concerns for LEF and biologics. This systematic review updates information on this subject.

Methods: A systematic search of PubMed and Embase was carried out using relevant keywords for pregnancy, lactation, SLE, antiphospholipid syndrome (APS), Sjögren’s Syndrome (SS) and Scleroderma (SSc) and drugs commonly prescribed in patients with rheumatic disease from 1966 onwards. Non-English language papers were excluded.

Results: The search strategy identified 124 papers, describing relevant drug use in pregnant women with SLE, APS, SS and SSc. These studies identified over 5850 drug exposures during pregnancy to: anti-hypertensives; endothelin receptor antagonists; aspirin; non-steriodals; bisphosphonates; heparin; warfarin; anti-rheumatics; antimalarials; immunosuppressives; intravenous immunoglobulin; plasmapheresis and steroids. Multiple case-reports/series/controlled studies reported increased congenital malformations following exposure to angiotensin converting enzyme inhibitors (ACEI). Two systematic reviews of HQC found no increased risk of miscarriage, prematuity or congenital defects and showed reduced SLE disease activity during pregnancy. Miscarriages and congenital malformation were frequently observed in a small number of pregnancies exposed to MMF (n = 16), MTX (n = 11) and CYC (n = 9). Of 10 patients treated with abatacept there were 4 spontaneous and 2 elective miscarriages, although 8 of these patients had concomitant MTX (n = 7) or LEF (n = 1) therapy. From 31 additional reports of anti-TNFthalpha exposure in pregnant patients with ARD since a 2008 update, there were 24 live births with one congenital abnormality as well as 5 spontaneous and 2 elective miscarriages. No other consistent adverse pregnancy outcomes were observed with the other drugs reviewed.

Conclusions: This systematic review highlighted the safety of HQC in pregnancy, in addition to its beneficial effects upon lupus disease activity. It also confirmed an increased risk of adverse pregnancy outcomes in patients taking ACEI, MTX, MMF and CYC therapy. The small numbers of pregnancies exposed to biologic therapies mean there remains insufficient evidence to advocate the safe use of these drugs during pregnancy. This information however, is useful when counselling women of potential risk before treatment and particularly after accidental conception whilst taking these therapies.

Disclosures: The authors have declared no conflicts of interest.

253. SYSTEMATIC INVESTIGATION OF MOLECULAR IMMICYR CANDIDATES IN IDIOPATHIC INFLAMMATORY MYOPATHIES IDENTIFIES POTENTIAL NOVEL AUTOANTIGENS

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Background: The idiopathic inflammatory myopathies (IIM) are autoimmune disorders characterized by acquired proximal muscle weakness and inflammatory cell infiltrates in muscle biopsies. The aetiology of IIM is largely unknown but is likely to be caused by environmental risk factors in genetically predisposed individuals. An estimated 80% of adult IIM cases have myositis-specific autoantibodies or antibodies against a novel or unidentified autoantigen. Several infectious agents have been reported to cause a primary inflammatory response of the muscle, including a homology between human and pathogen derived peptides may facilitate activation of T cells which are cross reactive to self-antigens (known as molecular mimicry). We hypothesized that autoantibodies are directed against antigens in IIM due to recognition of linear sequence epitopes from non-human proteins.

Methods: 13 viruses, 3 bacteria and 1 parasitic protozoan previously associated with myositis were identified from the published literature. Systematic in silico comparison of non-human proteins to the human proteome was carried out using an adaptation of a molecular mimicry pipeline to identify homologous linear sequences, using BLASTp and an overlapping sliding window of 14 amino acids (14-mer). For each proteome, after removal of conserved proteins, we recorded the number of 14-mer molecular mimicry candidates, the number of unique proteins these mapped to, and the most significant 14-mer BLASTp e-value. Shannon entropy scores were recorded for each mimicry candidate as a measure of sequence complexity to eliminate repeat sequences. Result significance was assessed by 1000 permutations of a randomly shuffled protein sequence, whilst maintaining the amino acid composition.

Results: A number of notable molecular mimicry candidates were identified (permuted P < 0.001) including a 134 amino acid region of Toxoplasma gondii Gag-Pol polyprotein aligned to CCHC-type zinc finger, nucleic acid binding protein (CNBP); and Toxoplasma gondii zinc finger (CCHC4-type) protein aligned to CRP containing protein 60 (TRIM60). These results are supported by previously identified functions or structural motifs of known myositis autoantigens. Several human proteins, including bile salt export pump and sperm associated antigen 5, also showed homology to multiple bacterial or viral sequences.

Conclusions: We have identified a number of potential signatures of molecular mimicry in IIM which may indicate novel autoantigens. This provides a rationale for experimental investigation of autoantibodies against these proteins in individuals with IIM as a fruitful area for future research. This approach is broadly applicable and may potentially elucidate etiological mechanisms in other autoimmune disorders.

Disclosures: The authors have declared no conflicts of interest.

254. RETROSPECTIVE ANALYSIS OF THE OUTCOME OF PATIENTS WITH POLYMYOSITIS AND DERMATOMYOSITIS

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Background: Polymyositis (PM) and dermatomyositis (DM) are rare diseases, designated as idiopathic inflammatory myopathies (IIM). Several factors have been implicated in their prognosis, including age, male sex, delay in diagnosis, neoplasia, creatinine kinase level, serological pattern, electromyography results, age, mortality in IIM patients diagnosed in a single centre between 1979 and 2007.

Methods: This was a retrospective study of the patients diagnosed with PM or DM who have been followed for at least 5 years in our rheumatology department. Demographic features, extramuscular involvement, CK level, serological pattern, electromyography results, treatment and outcome were analysed.

Results: 90 patients were identified. The female: male ratio was 2:5.1 and the mean age at diagnosis of 38.5 years (s.d. 15.03). 62.2% of the patients were White, 17.8% Afro-Caribbean and 17.8% Asian. 47.8% had adult-onset PM (APM), 30.0% adult-onset DM (ADM), 15.6% overlap and 6.7% juvenile-onset DM (JDM). The median delay in diagnosis was 5.0 months (IQR 9.00). Among the extramuscular features, 27.8% had cutaneous, 18.6% pulmonary, 6.7% cardiac and 3.3% gastrointestinal involvement. In 70.8%, CK was greater than the upper normal limit of 20.0% of the patients were anti-Jo1 positive and 3.3% anti-SRP positive. Prednisolone was prescribed in 98.9% and DMARDs in 87.8%. 33.3% received intravenous immunoglobulin, 12.2% cyclophosphamide, 5.6% mofetil mycophenolate and 11.1% rituximab. 31.1% had monophasic, 30.0% relapsing and remitting and
27.8% continuous progressive course of the disease. 6.7% fully recovered. The median follow up was 11.5 years (IQR 12.00). 14.4% of the patients died, 30.8% due to infection, 30.8% to cardiovascular events, and 11% due to neoplasia. The 1, 5, and 10-year survival was respectively, 100%, 97.8% and 92.2%. Of the 13 patients who died, male gender (Odds Ratio 3.561; 95% CI 1.065, 11.910), chronic progressive course (Odds Ratio 10.306; 95% CI 1.960, 54.197) and use of B-cell depletion drugs (Odds Ratio 5.259; 95% CI 1.243, 22.259) were the only risk factors to be statistically significantly associated with death (P < 0.05).

Conclusions: Survival in patients with IIM is generally quite good—the 10-year survival in our group was 92.2%. The factors most closely linked to mortality were male sex, chronic progressive disease and treatment with rituximab—the last two factors are clearly related to more severe disease.

Disclosures: The authors have declared no conflicts of interest.

OSTEOARTHRITIS: CLINICAL FEATURES

255. JOINT SPACE NARROWING OVER 5 YEARS PREDICTS FUTURE KNEE REPLACEMENTS UP TO 15 YEARS LATER
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Background: The primary outcome measure recommended by regulatory agencies for structure modifying drugs in OA is a reduction in joint space narrowing (JSN) over 3 years. While JSN is an established feature of knee OA on X-ray, its relationship with knee replacement (TKR) is not well understood. This study evaluated 5-year change of joint space and the future risk of a TKR over a 15 year follow-up.

Methods: A nested case control study was performed using the Chingford Women’s Cohort, a UK population-based study with a twenty-year follow-up. At the knee level, 40 TKRs (cases) were observed between year 5 and year 20 visits (of which 10 were bilateral). Cases and controls (1:10 ratio) were matched by baseline age (within 3 years), side of TKR and time. Subjects had to have baseline and year 5 X-rays, and not to have a TKR over this period. Digitized X-rays were read for minimum quantitative joint space width (mJSW) (using the KneeMorf software program) as well as categorical joint space narrowing (cJSN) using a standard atlas (grade 0 [normal] through grade 3 [bone-on-bone]). Reproducibility for mJSW was calculated using intraclass correlations (ICC) on 50 X-rays read by two readers. Reproducibility has previously been reported to be good for cJSN and Kellgren and Lawrence (K/L) grade (ICC > 0.7). S-year change was calculated as an increase of one or more grades for cJSN and K/L grade, and as any change of joint space for mJSW (widening and narrowing). Multivariable conditional logistic regression was used to analyse risk of TKR in relation to change in JSN and K/L grade.

Results: The ICC’s for inter-observer reproducibility for medial mJSW were 0.96 (95% CI 0.93, 0.98) and 0.81 (95% CI 0.69, 0.89) for mJSW in the lateral compartment. Cases (n = 40 knees) had a higher mean BMI (27.0 vs 25.3, P = 0.05) and more knee pain at year 5 (54.3% vs 16.7%, P = 0.001) compared with controls (n = 383). The mean mJSW at baseline was 4.2 mm (1.2 S.D.) for cases and 4.4 mm (0.8 S.D.) for controls. Over 5 years, 20% of cases and 7% of controls showed medial cJSN narrowing, while 52% of cases and 53% of controls showed any medial mJSW narrowing. S-year change in cJSN was significantly associated with TKR in both the medial [OR 3.32 (95% CI 1.34, 8.19)] and lateral compartment [OR 4.29 (95% CI 1.0, 18.28)]; a commensurate increase in risk was observed with change in K/L grade [OR 2.98 (95% CI 1.37, 6.49)], 5-year change in quantitative mJSW was not significant in either the medial [OR 1.04 (95% CI 0.65, 1.65)] or lateral compartment [OR 0.79 (95% CI 0.60, 1.05)].

Conclusions: These results show that 5-year change in categorical joint space and overall K/L grade predict future TKRs up to 15 years later. Quantitative joint space change was not predictive, perhaps due to the large number of subjects whose values remained within the normal range over this period of follow-up. The performance characteristics of these measures require further evaluation.

Disclosures: The authors have declared no conflicts of interest.

256. SELF-REPORTED AND CLINICAL OSTEOARTHRITIS ARE ASSOCIATED WITH LOW PHYSICAL PERFORMANCE ACROSS SIX COUNTRIES: THE EUROPEAN PROJECT ON OSTEOARTHRITIS
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Background: Poor physical performance (PP) is associated with disability, lower quality of life and higher mortality rates. Knee and hip OA can both cause joint pain and restrict range of movement. In this study we examined relationships between hip and knee OA defined by self-report or clinical American College of Rheumatology (ACR) criteria and PP, before and after adjustment for pain scores, in a cohort representing 6 European countries.

Methods: The European project on OA (EPOSA) study comprises 2942 men and women aged 65–85 years from the Netherlands, Germany, Sweden, Spain, Italy and the UK. Participants completed a questionnaire detailing self-reported OA, demographics, lifestyle and WOMAC. Clinical OA was defined based on ACR criteria. PP was determined from assessments of walking speed, chair rises and balance (tandem stand) to create a composite score (0–12); low PP was defined as < 9.

Results: The mean (±s.d.) age of the study population was 74.2 ± 5.1 years. Advanced age, female gender, lower educational attainment, abstinence from alcohol, and higher BMI were independently associated with low PP. Having clinical knee OA, hip OA, or both were associated with a higher risk of low PP: OR (95% CI) 2.93 (2.36, 3.64), 3.79 (2.49, 5.76), and 7.22 (3.63, 14.38) respectively, with relationships robust to adjustment for the confounders above and WOMAC pain score. Self-reported OA was also associated with low PP, but relationships were attenuated after adjustment for confounders, and relationships were not observed at the knee in Sweden. Low PP was associated with low self-reported WOMAC physical function score (P < 0.001).

Conclusions: OA at the hip, knee, or both are associated with low PP, and relationships are robust to adjustment for pain for a clinical diagnosis. This is important as an individual with low PP is more likely to report poor physical function.

Disclosures: The authors have declared no conflicts of interest.

257. SELF-REPORTED AND CLINICAL HAND OSTEOARTHRITIS ARE ASSOCIATED WITH LOW GRIP STRENGTH INDEPENDENT OF PAIN ACROSS SIX COUNTRIES: THE EUROPEAN PROJECT ON OSTEOARTHRITIS
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Background: Grip strength is a powerful predictor of disability, morbidity and mortality and is increasingly used in clinical practice across Europe. Whilst OA of the knee has been shown to be associated with quadriceps weakness and poor physical performance, relationships between OA hand, grip strength and hand function have been little studied. We examined these relationships in a cohort representing 6 European countries.

Methods: The European project on OA (EPOSA) study comprises 2942 men and women aged 65–85 years from the Netherlands, Germany, Sweden, Spain, Italy and the UK. Participants completed a questionnaire detailing self-reported OA, demographics, lifestyle and relationships robust to adjustment for pain scores, in a cohort representing 6 European countries.
osteoarthritis: Pathogenesis and Animal Models

259. Structural associations of pain in people with knee osteoarthritis

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Background: Although joint pathology makes an important contribution to OA pain, the precise relationship between pain and structural pathology is not entirely clear. Imaging studies have indicated possible associations between pain and synovitis, subchondral changes or osteoarthropathy, but associations with histopathology have not been explored in detail. We aimed to identify histopathological features that are associated with symptomatic human knee OA as a first stage towards identifying specific molecular and cellular changes that may contribute to OA knee pain.

Methods: Medial tibial plateaux and synovium were obtained from patients undergoing total knee replacement (TKR) for OA and post-mortem (PM) cases who had not sought help for knee pain. First, 26 consecutive TKR cases (TKR1) were compared with 26 aged-matched PM controls (PM1), to determine which histological features were associated with end-stage OA. Secondly, 21 TKR cases (TKR2) were compared with 21 PM cases (PM2) with similar total macroscopic chondroarthropathy, to indicate which structural features are associated with symptomatic OA, assuming TKR2 experienced greater levels of knee pain than PM2. OA changes and synovial inflammation were histologically graded.

Results: Total knee replacement cases (TKR1 [median age 61 years, 31% male] displayed more severe (each P < 0.05) cartilage surface changes, tidemark breaching, proteoglycan loss, synovitis and subchondral bone marrow replacement by fibrovascular tissue than post-mortem controls (PM1 [median age 61 years, 62% male]). A second group of total knee replacement cases (TKR2 [median age 71 years, 62% male] and post-mortem cases (PM2 [median age 73 years, 48% male]) displayed similar macroscopic chondroarthropathy scores (207 v. 193, respectively, P = 0.05). In univariate analyses, severity of cartilage surface changes, synovitis and subchondral bone marrow replacement by fibrovascular tissue were significantly greater in TKR2 than PM2 cases. Synovitis and cartilage changes remained significant after using logistic regression to adjust for macroscopic chondroarthropathy (P = 0.05).

Conclusions: Synovitis, tidemark breaching, subchondral bone marrow replacement, loss of proteoglycans and cartilage surface integrity are associated with end-stage OA, although most of these features are also found in some PM cases who have not sought TKR. Symptomatic OA is associated with greater synovitis and loss of cartilage surface integrity, than in PM cases with similar macroscopic joint surface appearances who did not seek TKR. Synovitis may be a key structural feature associated with symptoms in OA, which is consistent with previous data obtained from MRI studies. Further research is being undertaken to determine specific inflammatory mechanisms in OA that may be associated with pain, and to develop targeted treatment strategies for the relief of OA pain associated with synovitis.

Disclosures: The authors have declared no conflicts of interest.

260. Magnetic resonance imaging and histological assessment of bone marrow lesions in the osteoarthritic hip

Claire Wenham1,2, Patricia Shore3, Richard Hodgson1, Andrew Grainger1, Jean Aaron1, Lesley Hordon3 and Philip Conaghan1,2

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Background: The relationship between joint pathology and OA pain is not entirely clear. Imaging studies have indicated possible associations between pain and synovitis, subchondral changes or osteoarthropathy, but associations with histopathology have not been explored in detail. We aimed to identify histopathological features that are associated with symptomatic human knee OA as a first stage towards identifying specific molecular and cellular changes that may contribute to OA knee pain.

Methods: Medial tibial plateaux and synovium were obtained from patients undergoing total knee replacement (TKR) for OA and post-mortem (PM) cases who had not sought help for knee pain. First, 26 consecutive TKR cases (TKR1) were compared with 26 aged-matched PM controls (PM1), to determine which histological features were associated with end-stage OA. Secondly, 21 TKR cases (TKR2) were compared with 21 PM cases (PM2) with similar total macroscopic chondroarthropathy, to indicate which structural features are associated with symptomatic OA, assuming TKR2 experienced greater levels of knee pain than PM2. OA changes and synovial inflammation were histologically graded.

Results: Total knee replacement cases (TKR1 [median age 61 years, 31% male] displayed more severe (each P < 0.05) cartilage surface changes, tidemark breaching, proteoglycan loss, synovitis and subchondral bone marrow replacement by fibrovascular tissue than post-mortem controls (PM1 [median age 61 years, 62% male]). A second group of total knee replacement cases (TKR2 [median age 71 years, 62% male] and post-mortem cases (PM2 [median age 73 years, 48% male]) displayed similar macroscopic chondroarthropathy scores (207 v. 193, respectively, P = 0.05). In univariate analyses, severity of cartilage surface changes, synovitis and subchondral bone marrow replacement by fibrovascular tissue were significantly greater in TKR2 than PM2 cases. Synovitis and cartilage changes remained significant after using logistic regression to adjust for macroscopic chondroarthropathy (P = 0.05).

Conclusions: Synovitis, tidemark breaching, subchondral bone marrow replacement, loss of proteoglycans and cartilage surface integrity are associated with end-stage OA, although most of these features are also found in some PM cases who have not sought TKR. Symptomatic OA is associated with greater synovitis and loss of cartilage surface integrity, than in PM cases with similar macroscopic joint surface appearances who did not seek TKR. Synovitis may be a key structural feature associated with symptoms in OA, which is consistent with previous data obtained from MRI studies. Further research is being undertaken to determine specific inflammatory mechanisms in OA that may be associated with pain, and to develop targeted treatment strategies for the relief of OA pain associated with synovitis.

Disclosures: The authors have declared no conflicts of interest.
Background: The role of the trabecular bone in OA is not yet well understood but MRI-detected bone marrow lesions (BMLs) are associated with pain and progression of OA. Recent studies have assessed BML histology with the hypothesis that enlarged trabecular spacing and decreased trabecular numbers using micro CT. Normal trabecular architecture is crucial to the load-bearing function of the subchondral bone. This study was to assess the histology of BMLs in 8 people with OA, in particular to describe the trabecular structure and architecture.

Methods: 8 patients underwent MR imaging prior to hip arthroplasty. Femoral heads were immobilized in a plastic frame and MR-imaged within 24 h of surgery. Fixed external markers such as the fovea capitatum ensured calculation of an exact angle for the plane of section including the BML. The femoral head was sectioned with a bandsaw and embedded in methyl methacrylate; 10 and 300um slices were taken with a microtome. A previously reported and validated technique, initially developed for osteoporosis, was used, which allows direct measurement of trabecular bone interconnection by measuring the trabecular termini within 300um slices. This technique was applied to areas with and without BMLs using an overlying slide marked with a 1cm2 grid. Slices were also assessed for vascularity (vessel count), cysts and fibrosis.

Results: The areas corresponding to BML showed trabecular architecture disruption; trabecular interconnection was markedly lower in the BML area compared with the non-BML area (median termini count 3.4/cm2 vs 12.2/cm2, P = 0.03). BML areas showed higher vascularity (median number of 5 vessels/cm2) compared with 2/cm2 in the non-BML area. Descriptively, the BML areas demonstrated multiple areas of cystic change containing adipose cells and fibrous tissue, often surrounded by thickened trabeculae. There was evidence of increased bone formation around the cysts as demonstrated by an osteoid border of unmineralized bone. Marked osteopenic areas as shown by fragmented trabeculae were also noted within the BML area, usually adjacent to cystic change. Marrow fibrosis and oedematous adipocytes were common, in agreement with previous studies.

Conclusions: The results confirmed that OA BMLs demonstrate marked changes within the subchondral trabecular bone, with osteopenic areas and increased osteoid tissue. Although the sample size is small, for the first time an increase in the vascularity of BML areas has been demonstrated. A novel direct measure of the trabecular connectivity noted increased trabecular disconnection, which will alter the load-bearing function of the subchondral bone. Alendronate has been shown to allow for the preservation of normal trabecular interconnection, as assessed by this histological method. Recent work shows that bisphosphonate may be due to the preservation of normal trabecular structure.

Disclosures: The authors have declared no conflicts of interest.

OSTEOARTHRITIS: TREATMENT

261. A 2-YEAR FOLLOW-UP STUDY ON THE EFFECT OF A FOOT-WORN BIOMECHANICAL DEVICE AND TREATMENT FOR REDUCED PAIN AND IMPROVED FUNCTION IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Background: This report presents a follow up study conducted in continuation to an original double blind, prospective study which assessed the effectiveness of a foot-worn biomechanical device and treatment (AposTherapy). The biomechanical device comprises four individually calibrated elements attached onto foot-worn platforms and enables unloading of the diseased articulating surface and simultaneously train neurovascular control by controlled perturbations. The purpose of this study was to examine the long-term effectiveness of this biomechanical treatment in reducing pain and improving function in patients with knee OA.

Methods: 35 patients with knee OA volunteered to continue the follow-up for additional 24 months. 26 of them were in the active group and 9 patients were in the control group. Patients continued the treatment with the device that had been individually calibrated to accommodate a diminished-pain joint alignment and train neurovascular control. Patients were assessed 12 months and 24 months after the original study ended. Primary outcome measures were the WOMAC index and the Aggregated Locomotor Function (ALF) assessment. Secondary outcome measures were the SF-36 health survey and the Knee Society Score.

Results: At 12 and 24 months, the active group maintained the significant pain relief and improved function that were obtained at the end of the original study, showing a decrease of 3.5 cm and 3.5 cm, in the WOMAC-Pain subcategory, representing a mean improvement of 68% and 66%, after 12 and 24 months respectively (P < 0.001). Patients also showed a decrease of 3.5 cm and 3.5 cm, in the WOMAC-function subcategory, representing a mean improvement of 69% and 65%, after 12 and 24 months respectively (P < 0.001). Patients maintained the improved ALF score after 12 and 24 months showing a decrease of 13.9 sec and 12.9 sec, representing a mean improvement of 37% and 34%, after 12 and 24 months respectively (P < 0.001).

Conclusions: The reduced pain and improved function following treatment with the biomechanical device was maintained after 12 and 24 months indicating that this therapy might be an effective, long-term treatment for patients with knee OA.

Disclosures: The authors have declared no conflicts of interest.

262. A NON-INVASIVE FOOT-WORN BIOMECHANICAL DEVICE AND TREATMENT FOR PATIENTS WITH HIP OSTEOARTHRITIS

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Background: Physical therapy and biomechanical interventions for patients with hip OA should aim to reduce pain, improve function and restore or maintain gait patterns close to normal. The purpose of this study was to evaluate the effect of a biomechanical therapy on the pain, function, quality of life and spatio-temporal gait patterns of patients with hip OA.

Methods: 60 patients with hip OA were examined before and after 12 weeks of using the biomechanical device and treatment (AposTherapy). Patients were evaluated using the WOMAC questionnaire for pain and function and the SF-36 Health Survey for quality of life. Patients also underwent a computerized gait test.

Results: After 12 weeks of treatment, a significant improvement was found in the patients’ velocity, step length and cadence (P < 0.001). WOMAC-pain, WOMAC-stiffness and WOMAC-function subscales were significantly improved compared with baseline (P < 0.001). SF-36 physical score subscale improved significantly (P = 0.007) whereas the SF-36 mental subscale improved but did not reach the statistical significance threshold.

Conclusions: Patients with bilateral hip OA treated with the examined therapy for 12 weeks showed statistically and clinically significant improvements in pain, function and gait patterns. These findings suggest that this treatment may be an additional useful tool for conservatively treating patients with hip OA. Further RCT studies are needed to evaluate the effect of the examined therapy on hip OA population.

Disclosures: A.E., Apos—Share Holder. A.M., Apos—Share Holder. G.S., Apos—Employee. All other authors have declared no conflicts of interest.

263. SEQUENTIALLY PROGRAMMED MAGNETIC FIELD THERAPY: A NOVEL TREATMENT FOR OSTEOARTHRITIS: OUR EXPERIENCE

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Background: Osteoarthritis (OA) is biologically characterized by degradation of articular cartilage and subchondral bone leading to joint pain, bone deformation and reduced mobility. Previous research published in the Scientific Medicine Journal (2009)

Downloaded from https://academic.oup.com/rheumatology/article-abstract/52/suppl_1/i135/1929007/Basic-Science208-Stem-Cell-Factor-Expression-is by guest on 15 September 2017
has shown that Sequentially Programmed Magnetic Field (SPMF) therapy is effective in ameliorating the signs and symptoms of OA, and inducing regenerative activity in the chondrocytes by an increase in the cartilage thickness. The objective of this study was to evaluate the efficacy of SPMF therapy on a larger group of patients with confirmed knee OA. This study was conducted on patients with varying grades of OA, using the American Knee Society rating system.

**Methods:** 1000 patients with clinically confirmed knee OA were recruited for the follow up study to evaluate the efficacy of SPMF therapy. Patients were exposed to SPMF for 21h for 21 consecutive days. The dosage was calculated depending on the grade of OA and the amount of subchondral bone involved. The SPMF therapy was delivered to the target area by a computer controlled device, which generates the Sequentially Programmed Magnetic Field, by specially designed Magnetic Field Generators (MFGs). SPMF therapy is based on the principle that exposure to SPMF can recreate the piezoelectric stimuli, which enhances mitosis and cell regeneration by normalizing the aberrant electromagnetic fields of micro tubules forming the centrioles. All subjects were evaluated with Total Knee Score (TKS) and Total Functional Score (TFS); pre-treatment, post treatment at 21days and at 3 months.

**Results:** This study showed statistically significant improvement in TKS and TFS in all the patients, who were able to walk comfortably for considerable distances at the end of the treatment and this improvement persisted when they were re-evaluated at 3 months. Further, patients with mild to moderate OA reported fairly fast reduction of pain and improvement in walking abilities during the treatment. TFS scores improved from 42.825 (sd. = 15.50) pre-treatment to 51.8 (sd. = 16.09) at 21days and 56.295 (sd. = 17.52) at 3 months. The TKS score was 56.68 (sd. = 17.61) at pre-treatment, which improved to 71.51 (sd. = 16.71), 77.52 (sd. = 17.85) at 21days and at 3 months respectively.

**Conclusions:** SPMF is an effective treatment for knee OA as it can reverse the OA process by regeneration of cartilage, decreasing pain, increasing mobility and stability of the joint and normalizing the life of an osteoarthritic patient. SPMF therapy being non-invasive and without any side effects, should be the first line of management of OA.

**Disclosures:** The authors have declared no conflicts of interest.

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**SCLERODERMA AND RELATED DISORDERS**

**264. DIFFERENTIAL GENE EXPRESSION SIGNATURES IN RESIDENT LUNG FIBROBLASTS GOVERN SUSCEPTIBILITY OR RESISTANCE TO EXPERIMENTAL LUNG FIBROSIS**

Emma Derrett-Smith1, Rachel Hoyles1, Korsa Khan1, David J. Abraham2 and Christopher Denton1

1Centre for Rheumatology and Connective Tissue Diseases, University College London, London, UK

**Background:** In scleroderma (SSc), lung fibrosis is linked to epithelial damage and dysregulated repair mechanisms. Resident lung fibroblasts may have effects on multiple cell types including epithelium, endothelium, smooth muscle cells and fibrocytes. We have used two complementary transgenic mouse strains with altered TGFβ signalling to better understand the regulatory role of resident lung fibroblasts in defining susceptibility to fibrosis.

**Methods:** The TIRILk-k-fib mouse model of SSc, in which TGFβ signalling is upregulated in fibroblasts, is susceptible to fibrotic lung injury whereas the TIRIL-null-fib strain, in which TIRIL is conditionally knocked out in fibroblasts, is resistant to bleomycin-induced lung fibrosis. We have used an illumina microarray platform to profile lung or skin fibroblasts from these two strains and identified a cohort of genes that determine susceptibility or resistance to experimental lung fibrosis. With a control group using the TIRILk-k-fib model with a control strain of TIRILk-k-fib animals and wild type littermates (n = 3) on the same microarray platform. Technical validation of data and additional quantitation of gene and protein expression was performed with replicate samples.

**Results:** Functional classification of the TIRILk-k-fib lung fibroblast gene expression signature includes key genes that are implicated as pathogenic drivers of fibrosis and inflammation and potential biomarkers in SSc. Conversely, many of these genes are downregulated in TIRIL-null-fib mice, including BMP4 (fold reduction in TIRIL-null-fib 31.8, P < 0.02; fold upregulation in TIRIL-null-fib compared with WT 2.01, P < 0.6); elastin (TIRIL-null-fib 17.8, P < 0.14); TIRILk-k-fib 1.86, P < 0.09); CCL2 (TIRIL-null-fib 56.8, P < 0.09); TIRILk-k-fib 1.72, P = 0.03) and MMP13 (TIRIL-null-fib 13.2, P < 0.08); TIRILk-k-fib 3.6, P = 0.4). CTGF (CCN2) was strongly upregulated in TIRILk-k-fib lung fibroblasts, but showed less downregulation than other genes in the TIRIL-null-fib, probably reflecting multiple pathways of activation. No gene expression differed between patients with SSc and controls.

**Conclusions:** These data define a cohort of genes differentially expressed in fibroblasts that associate strongly with susceptibility or resistance to experimental lung fibrosis. These transcripts include many that are important in tissue repair and that have previously been shown to be over expressed in SSc skin samples. They suggest that resident fibroblast gene expression signature may govern fibrosis in lung and skin.

**Disclosures:** The authors have declared no conflicts of interest.

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**265. SEVERE GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS IS FREQUENTLY ASSOCIATED WITH HAEMODYNAMICALLY SIGNIFICANT CARDIAC INVOLVEMENT**

Amara Ezereonyi1, Gagandeep Takhar1, Christopher Denton1 and Ipoon Ong1

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**Background:** Gastrointestinal tract (GI) and cardiac disease (CD) are important complications of systemic sclerosis (SSc). In this study we ask whether patients with severe GI tract SSc have increased frequency of cardiac complications during their disease course.

**Methods:** 168 SSc patients with prominent GI symptoms were identified from the research database of a major tertiary referral centre using key words: malnutrition, pseudo-obstruction and enteral or total parenteral nutrition (TPN). Severe GI disease was defined as those presenting with at least 3 episodes of pseudo-obstruction requiring hospital admission or nutritional support, malabsorption syndrome or diarrhoea and weight loss (without malnutrition) responding to antibiotics. Cases that had developed CD at any point in their disease course were collated. Manifestations of significant CD (excluding pulmonary arterial hypertension) included arrhythmia, conduction block, pericardial effusion, cardiac failure, ischaemic heart disease or myocardial abnormality on cardiac MRI.

**Results:** 31 patients (18.4%) were identified with severe GI disease and CD. There were 16 females. 55% of cases had diffuse cutaneous SSc (3 myositis overlap, 1 SLE overlap). Median age at presentation of CD was 52 (n = 21) range 36–81. Median time from diagnosis of SSc to onset of CD was 60 months (n = 22) (range 5–256). Severe GI disease occurred in 26–61% of cases. Small bowel thickening or dilated small bowel loops including pneumomatoses cytoktes of the colon were demonstrated on CT in 23% of patients. 26% of patients required nutritional support (5 TPN, 3 percutaneous endoscopic gastrostomy or percutaneous enterojugal insertion), Surgical intervention including decompression was necessary in a minority (16%). Of this cohort of patients, 35% developed significant atrial tachycardias requiring antiarrhythmics. Two patients had episodes of non-sustained VT. One, this was associated with low potassium and magnesium. One patient had a cardiac arrest on developing renal crisis. 19% developed significant conduction blocks (5 requiring permanent pacemaker), 23% had severe left ventricular dysfunction, 19% myocardial infarction and 6% required emergency pericardectomy for large pericardial effusions. Two patients had evidence of myocardial fibrosis on cardiac MRI. Two developed restrictive cardiomyopathy and 1 restrictive myocardiitis.

**Conclusions:** We described a cohort of patients with severe GI disease who developed significant CD. The majority of these were arrhythmias and in some, electrolyte imbalance was a major contributory factor. The potential association of severe cardiac and GI disease in SSc is important for management and may indicate a shared pathogenic mechanism.

**Disclosures:** The authors have declared no conflicts of interest.
266. VIDEO-CAPILLAROSCOPY ASSESSMENT OF PERICALCINOSTIC SKIN INDICATES SPECIFIC FEATURES OF SEVERE VASCULOPATHY ASSOCIATED WITH CALCIUM DEPOSITS IN SYSTEMIC SCLEROSIS

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Background: Calcium deposits (calcinos) in systemic sclerosis (SSc) are clinically heterogeneous both for site and severity of involvement. Despite often leading to complications such as digital ulcers and driving poor hand function, little attention has been paid to the pathogenesis of calcinos and the therapeutic options remain limited. The presence of calcinos in limited cutaneous SSc as well as in the diffuse form suggests that the condition may be associated with vasculopathy rather than fibrosis, however to date, no formal studies have addressed this hypothesis. We performed video-capillaroscopy of peric-calcinotic skin and unaffected skin in the same but contra-lateral region of interest (ROI), to determine whether we could detect any calcinos-specific change in the capillaroscopic pattern.

Methods: Eighteen calcinos deposits and contra-lateral ROIs were analysed with an Optima Digital video-capillaroscopy system equipped with 200x magnification lens. For each calcinos deposit we captured images in the 4 surrounding quadrants within 3 millimetres of the lesion. Images from each quadrant were captured, identified and stored in an electronic database. Analysis of the images was performed by two rheumatologists fully trained in video-capillaroscopy and blinded to the clinical details. Presence of enlarged capillaries, giant capillaries, haemorrhages, drop-out, disorganization and capillary ramifications were assessed independently. McNemar tests were employed for statistical analysis.

Results: Twelve of the 18 calcinos deposits were located at the distal phalanx, 3 at the proximal phalanx, 1 at both the middle and proximal phalanx and two at the palmer metacarpal. Drop out areas were observed in at least 1 quadrant of all 18 calcinos deposits vs 7 contra-lateral control ROIs (P = 0.05). Enlarged capillaries were observed at 17 deposits vs 11 ROIs (P = 0.05), giant capillaries, disorganization and capillary ramifications were observed respectively at 7, 9 and 5 deposits, respectively, while none were observed in any ROIs (P < 0.05 for all). Haemorrhages were observed at 5 deposits and 2 ROIs, (P = 0.05).

Conclusions: This pilot study suggests that specific features of severe vasculopathy such as drop out areas, giant capillaries and disorganization of the vascular array are observable in plain skin video-capillaroscopy and may be specifically associated with calcinos deposits in SSc. Further studies are warranted both to unravel the role of vasculopathy in the pathogenesis of calcinos and to determine potential benefit of therapeutic options targeting peripheral vasculopathy.

Disclosures: L.L., Actelion—Travel Grant. All other authors have declared no conflicts of interest.

267. A COMPARISON OF NEAR-INFRARED SPECTROSCOPY AND LASER DOPPLER FLOWMETRY AS TOOLS FOR ASSESSING SEVERITY OF HAND ISCHAEMIA IN SYSTEMIC SCLEROSIS

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Background: High magnification nailfold videocapillaroscopy (NVC) is currently the ‘gold standard’ for identifying nailfold capillary abnormalities suggestive of a systemic sclerosis (SSc) spectrum disorder, but is not widely available to all clinicians. The dermatoscope (magnification in the order of x10) is a small, inexpensive and easily portable piece of equipment, with good intra- and inter-observer reliability in identifying capillary abnormalities suggestive of a connective tissue disease. We investigated the ability of individuals with an interest in SSc and general rheumatologists to classify nailfold capillary images obtained by NVC and dermoscopy, and compared the two techniques. We set out to test the hypothesis that graders were more likely to be able to grade capillary by NVC (because of better visualization) and that more capillaries would be graded abnormal by NVC.

Table 1. Performance of LDF and NIRS in evaluation of hand ischaemia

<table>
<thead>
<tr>
<th>Test</th>
<th>LDF</th>
<th>NIRS (RSO2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) for HC</td>
<td>342 PU (159–429)</td>
<td>76% (66–83)</td>
</tr>
<tr>
<td>Dynamic range</td>
<td>121 PU (33–289; P = 0.01)</td>
<td>73% (60–74; P ns)</td>
</tr>
<tr>
<td>Ratio</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Coefficient of variation for HC</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>Reproducibility between trial protocol visits</td>
<td>Pearson’s correlation coefficient r (P = 0.01)</td>
<td>0.47 (P = 0.001)</td>
</tr>
<tr>
<td>Reproducibility between trial and outpatient protocol visits</td>
<td>Pearson’s correlation coefficient r (P = 0.01)</td>
<td>0.56 (P = 0.0001)</td>
</tr>
<tr>
<td>Detection of improvement post-iloprost</td>
<td>Paired t-test</td>
<td>ns P = 0.001</td>
</tr>
</tbody>
</table>

HC: healthy controls; IQR: interquartile range; PU: perfusion units; T1, T2: first and second trial protocol visits; Tav: average from trial protocol visits, ns: not significant.
Methods: NVC and dermoscopy images were acquired from 32 subjects (10 nailbeds, 320 sets of images) with a spectrum of nailfold capillary characteristics (normal to grossly abnormal). A secure web-based interface was configured. Images were blinded and algorithmic processing of the images was conducted. Individuals with an interest in SSc (identified through clinician SSC networks) and consultant rheumatologists in the north west of England were invited to participate. Each rater was randomly assigned the images from a subset of 4 subjects i.e. 4 subjects x 10 (fingers) x 5 (random hand repeated) x 45 images for each technique. Images were assessed on a 0–3 ordinal scale of severity of abnormality: normal, mildly abnormal, definitely abnormal, grossly abnormal and rating 4 unable to classify. The rater could not return to previous images. Only the results for ability to classify (rating 4) are presented here.

Results: 48 raters from 12 countries participated in the study (3 specialists, 22 general) with 1920 paired ratings for each technique. Capillary images were gradable by both NVC and dermoscopy in 1289 (67.1%) of instances, alone by NVC in 360 (18.8%), by dermoscopy alone in 105 (5.5%) and by neither in 166 (8.7%). The ability to grade images against clinician subgroup, by image type is presented in Table 1.

Conclusions: Most images could be graded by NVC and dermoscopy (but more by NVC). No difference was seen between the specialist and general rheumatologists in the ability to grade NVC images, but specialists were slightly more likely to grade dermoscopy images. Further work is warranted to validate dermoscopy in the assessment of patients with SSc-spectrum disorders.

Table 1. Results

<table>
<thead>
<tr>
<th>General rheumatologists</th>
<th>Specialists</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVC classifiable YES</td>
<td>757 (86.0)  892 (85.8)</td>
</tr>
<tr>
<td>NVC classifiable NO</td>
<td>123 (14.0)  148 (14.2)</td>
</tr>
<tr>
<td>Dermoscopy classifiable YES</td>
<td>615 (69.9)  779 (74.9)</td>
</tr>
<tr>
<td>Dermoscopy classifiable NO</td>
<td>265 (30.1)  261 (25.1)</td>
</tr>
</tbody>
</table>

Data are n (%).

269. IMPACT OF DIGITAL ULCERS IN SCLERODERMA ON WORK AND DAILY ACTIVITIES: A SUBGROUP ANALYSIS OF UK PATIENTS ENROLLED IN THE DUO REGISTRY

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Background: Digital ulcers (DUs) are frequent and persistent clinical manifestations of systemic sclerosis (SSc). They occur in up to 30% of all patients with SSc and cause considerable disability. Previous analyses of the multinational DUO Registry have shown that the number of DUs in patients with SSc negatively impacts work and daily activities. As UK-specific data on work and daily activity impairment are relevant for the management of DU disease in the UK, this subgroup analysis investigated the impact of DUs in UK patients enrolled in the DUO Registry.

Methods: The DUO Registry is a European, multicentre, prospective, observational cohort study of SSC patients with a history of DU. Data were collected from 2008 to 2012. The registry included 311 patients who were enrolled in the registry. 311 patients provided images. Images were blinded and algorithmic processing of the images was conducted. Individuals with an interest in SSc (identified through clinician SSC networks) and consultant rheumatologists in the north west of England were invited to participate. Each rater was randomly assigned the images from a subset of 4 subjects i.e. 4 subjects x 10 (fingers) x 5 (random hand repeated) x 45 images for each technique. Images were assessed on a 0–3 ordinal scale of severity of abnormality: normal, mildly abnormal, definitely abnormal, grossly abnormal and rating 4 unable to classify. The rater could not return to previous images. Only the results for ability to classify (rating 4) are presented here.

Results: From April 2008 to May 2012, 333 patients from the UK were enrolled in the DUO Registry. 311 patients provided images. Images were blinded and algorithmic processing of the images was conducted. Individuals with an interest in SSc (identified through clinician SSC networks) and consultant rheumatologists in the north west of England were invited to participate. Each rater was randomly assigned the images from a subset of 4 subjects i.e. 4 subjects x 10 (fingers) x 5 (random hand repeated) x 45 images for each technique. Images were assessed on a 0–3 ordinal scale of severity of abnormality: normal, mildly abnormal, definitely abnormal, grossly abnormal and rating 4 unable to classify. The rater could not return to previous images. Only the results for ability to classify (rating 4) are presented here.

Conclusions: This sub-analysis of UK patients enrolled in the DUO Registry shows that there is a relationship between the number of DUs and impact on work and daily activities. Functional impairment appears to increase with the number of DUs, reflected by higher impairment of work and daily activities, as well as increased hours of unpaid help needed. These results are in line with those observed in the overall registry population.


270. IL6 AND CCL2 CO-REGULATE FIBROBLAST-DEPENDENT TRANSSENDOTHELIAL MIGRATION OF MONONUCLEAR CELLS AND FIBROTIC RESPONSE IN SCLERODERMA

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Background: IL6 is a key mediator recently implicated in activation of extracellular matrix (ECM) proteins in scleroderma (SSc) fibroblasts. CCL2 is a proinflammatory chemokine that is overexpressed in diffuse cutaneous systemic sclerosis (dcSSc). We explored interaction between these two major mediators that may be critical in the recruitment of inflammatory cells into lesional skin and whether this may affect fibroblast ECM production.

Methods: Dermal fibroblasts were cultured from skin biopsies from healthy controls (n = 4) and early stage dcSSc (n = 4). Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples of the latter group. Expression of CCL2 and IL6 were assessed using immunoblotting with specific markers CD3, CD14, CD56 and CD41 on PBMCs. IL6 activation of CCL2 and the ability of SSc fibroblast derived CCL2 to induce PBMC migration through an endothelial layer was studied in vitro using Transwell migration assays, and the effect of the PBMCs-fibroblast interaction on production of ECM proteins, z-smooth muscle actin (zSMA) and Collagen type-I (Col-I) was measured using neutralizing antibodies against CCL2 and IL6 ligand-receptor axis.

Results: Stimulation of normal and SSc dermal fibroblasts with recombinant human IL6/IL-6R led to a dose dependent increase of the CCL2 (mean ± S.E.M. % basal expression) with IL6 25 ng/ml and sIL-6R 20 ng/ml at 48 hours, inducing the production of the maximum concentration of CCL2 (91 ± 4%). IL6 trans-signalling increased migration of PBMCs (n = 3) up to (25 ± 3.5 % P < 0.05) in normal fibroblasts and (44 ± 2.3 % P < 0.02) in SSc fibroblasts. The migration of PBMCs was abrogated by the addition of neutralizing antibodies against CCL2 and IL6 ligands (18 ± 6.3 % P < 0.04) and (13 ± 8.2 % P < 0.04) respectively in the presence of control fibroblasts and (25 ± 5.1 % P < 0.03) (18 ± 5.4 % P < 0.04) respectively with SSc fibroblasts. IL6 trans-signalling significantly increased CCL2 expression (33 ± 2.7 % P < 0.03 and 45 ± 5.6 % P < 0.04) in control and SSc fibroblasts respectively. This was more prominent in SSc fibroblasts and reduced in the presence of anti-IL6R and/or anti-CCL2 antibodies in both control and SSc fibroblasts. Monoclonal antibodies CD68, and T cells CD3 confirmed localization of CCL2 to monocytes but no expression of IL6 ligand was confirmed.CCL2 induced migration of PBMCs the production of ECM proteins at 24 h in the presence of SSc fibroblasts with increased levels of zSMA (53 ± 5.9 %, P < 0.05) and Coll-I (22 ± 3.6 %, P < 0.03) compared with SSc fibroblasts.

Conclusions: Our results suggest that PBMCs are recruited via fibroblast-derived CCL2. The recruited PBMCs further activate ECM
synthesis from SSc fibroblasts and have a particularly strong effect on the production of nSMA. These data suggest interplay between fibroblast-mononuclear cells may mediate the fibrotic response and that the FDR model axis represents a potential therapeutic target for fibrosis in SSc.

Disclosures: C.D., Actelion, Roche—Consultation Fees. V.O., Roche—Research Support. All other authors have declared no conflicts of interest.

271. ORGAN-BASED COMPLICATIONS AND SURVIVAL IN MALE AND FEMALE PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Although significant female gender predominance is seen in majority of large systemic sclerosis (SSc) cohorts, studies have suggested that male gender associates with more severe disease and worse outcome. We explore disease characteristics in male and female patients with SSc from a single centre cohort.

Methods: We analysed a cohort of incident cases of SSc that developed between 1995 and 1999 and were followed up for up to 15 years.

Results: A total of 398 SSc patients were included. Of those 54 (14%) were male. Mean age at onset was 49 years in male and 48 years in female patients. A higher proportion of men had diffuse cutaneous (dc) subset of SSc compared with women (48% (n = 26) vs 35% (n = 120), P < 0.001). Duration of Raynaud’s phenomenon (RP) with relation to onset of first non-RP symptom of SSc was significantly shorter in male patients with mean (range) of 30 (12 to 339) months compared with 81 (29 to 744) months in females (P = 0.003). Comparison between frequencies of autoantibodies demonstrated significant differences only in anti-centromere antibody (ACA) positivity, which was twice as common among women—30% (n = 96) compared with 15% (n = 8) in men (P = 0.022). At disease onset a larger proportion of men were current (24%) or past (44%) smokers compared with 14% and 25% respectively among women, P = 0.001.

There was a significantly higher proportion of male patients with some degree of pulmonary fibrosis (PF) confirmed on HRCT compared with females—74% (n = 39) vs 50% (n = 169), P = 0.001. Cumulative incidence of clinically significant (cs)PF over the entire follow-up period was 55% in male and 28% in female patients (P = 0.002), being 33% and 44% in men and 22% and 27% in men at 5 and 10 years of follow-up. We found no significant association between smoking history and development of csPF. There were no differences in incidence of pulmonary hypertension (PH), cardiac involvement or scleroderma renal crisis (SRC) between genders. At 5 years 6% of men and 4% of women had developed PH, 2% of men and 3% of women—cardiac SSc; and 2% of men and 6% of women—SRC while at 10 years PH was found in 16% of men and 13% of women, SRC in 4% of men and 7% of women and there were no new cases of cardiac SSc in either group.

There was no significant difference in survival between genders with 10% (6/67) of both male and female patients being alive at 5 years. Over the entire follow-up survival was 56% in males and 66% in females. In comparison, the expected survival of the general population with matched age was 99.7% at 5 years and 96.5% at 15 years for women and 91% of both male and female patients being alive at 5 years. Over 5 years and were followed up for up to 15 years. Clinically significant (ca) PF was defined as the presence of fibrosis on high-resolution CT with either forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) >55% or a 15% decline from baseline in FVC or DLCO. PH was confirmed by right heart catheter with mean pulmonary arterial pressure of >25 mmHg; cases with elevated pulmonary capillary wedge pressure were excluded.

Results: 146 diffuse cutaneous (dc) SSc and 252 limited cutaneous (lc) SSc cases were included. During the entire follow-up, 48% of the dcSSc and 24% of the lcSSc patients developed csPF (P < 0.001). Approximately half of the subjects developed csPF within the first 3 years of disease (23% of dcSSc and 11% of lcSSc). The earliest cases of PH were diagnosed within the first 3 years from SSc onset. Five and 10 year incidence of PH was 4% and 13% for dcSSc and 5% and 15% for lcSSc patients, P = 0.558.

Significant predictors of pulmonary complications from univariable and multivariable Cox proportional hazards analysis are summarized in Table 1. The variables that remained significant independent predictors of csPF in a multivariable analysis were subset, FVC, DLCO, anti-Sc 70 antibodies and anti-centromere antibodies (ACA).

Background: Systemic sclerosis (SSc) is a rare disease characterized by autoimmunity, fibrosis and vasculopathy. P2Y7 is a transmembrane G-protein coupled receptor found in the basal layer of keratinocytes, involved in control of keratinocyte proliferation. P2X7 is an ATP receptor cation channel, involved in terminal differentiation of keratinocytes in the stratum corneum. These receptors play an important role in inflammation and immunity. Epidermal injury induces ATP release and P2X7 signal transduction activates the local innate response. We have previously found altered terminal differentiation in the epidermis in SSc patients. We hypothesized that ATP-P2X7 signalling amplifies innate responses in the epidermis in patients with SSc, possibly leading to the development of downstream fibrosis and autoimmunity.

Methods: We sampled the epidermis of 6 patients with diffuse cutaneous SSc, and 6 healthy controls using a dermal suction blister method. Using immunohistochemistry we stained for P2X7 (Caltag Labs) and P2Y1 (Abcam). In total 5 high power fields from each of 6 SSc and 6 control individuals were studied. The results were analysed using Chi-Squared tests. Dermal blister fluid samples (healthy control n = 9, diffuse SSc n = 12) were profiled by Luminex array for inflammatory cytokines, chemokines, and growth factors.

Results: The distribution of P2Y1 was uniform throughout the epidermis in 6/6 healthy controls and 6/6 patients. P2X7 was found in 6/6 healthy controls in the terminally differentiated cornified layer of the epidermis. 0/6 SSc patients showed this normal terminal differentiation pattern (P < 0.001 Chi Squared). One third of the patients showed focaly induced over expression of the P2X7 receptor throughout the epidermis, compared with none of the healthy controls. The remaining two-thirds of patients showed decreased expression of P2X7 in the cornified layer of the epidermis. This was to be found not significant on Chi-Squared test. Luminex array profiling of the dermal blister fluid suggested increased inflammatory cytokines (mean IL-8 in SSc 527 pg/ml vs 147 pg/ml in controls, mean IL-1beta in SSc 3.7 pg/ml vs 2.4 pg/ml), and growth factors (HGF 247 pg/ml SSc, 112 pg/ml controls P = 0.02, and VEGF-A 208 pg/ml in SSc, 87 pg/ml in controls).

Conclusions: The expression of P2X7 receptors were found in an abnormal density across the epidermis of patients with SSc compared with healthy controls. This was not the case with the P2Y1 receptor which is important in the proliferation and differentiation of keratinocytes within the epidermis. Our data show that there is altered terminal differentiation within the stratum corneum of patients with diffuse SSc. The expression of P2X7 receptors in defined foci and altered cytokine profile, indicate active inflammation in the epidermis which provides an insight into the pathogenesis of SSc and the role of the epidermis and its transdifferentiation.

Disclosures: The authors have declared no conflicts of interest.

273. INCIDENCE AND PREDICTORS OF PULMONARY COMPLICATIONS IN SYSTEMIC SCLEROSIS

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Background: We explore incidence and predictors of pulmonary fibrosis (PF) and pulmonary hypertension (PH) in patients with systemic sclerosis (SSc).

Methods: We analysed incident cases of SSc that developed over 5 years and were followed up for up to 15 years. Clinically significant (ca) PF was defined as the presence of fibrosis on high-resolution CT with either forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) <55% or a 15% decline from baseline in FVC or DLCO. PH was confirmed by right heart catheter with mean pulmonary arterial pressure of >25 mmHg; cases with elevated pulmonary capillary wedge pressure were excluded.

Results: 146 diffuse cutaneous (dc) SSc and 252 limited cutaneous (lc) SSc cases were included. During the entire follow-up, 48% of the dcSSc and 24% of the lcSSc patients developed csPF (P < 0.001). Approximately half of the subjects developed csPF within the first 3 years of disease (23% of dcSSc and 11% of lcSSc). The earliest cases of PH were diagnosed within the first 3 years from SSc onset. Five and 10 year incidence of PH was 4% and 13% for dcSSc and 5% and 15% for lcSSc patients, P = 0.558.

Significant predictors of pulmonary complications from univariable and multivariable Cox proportional hazards analysis are summarized in Table 1. The variables that remained significant independent predictors of csPF in a multivariable analysis were subset, FVC, DLCO, anti-Sc 70 antibodies and anti-centromere antibodies (ACA).
Because of the significant association of the markers of renal function and PH in the univariable analysis, anti-RNA polymerase antibody (ARA) was also included in the multivariable analysis. The final prediction model for PH included age, DLCO, ARA, anti-U3RNP and anti-Scl 70.

Conclusions: While csPF is significantly more frequent among dcsSc patients, PH has similar incidence in both subsets. DLCO was the strongest predictor for both csPF and PH. ARA increased while anti-Scl 70 antibodies reduced the hazard for PH development. There was no association between PH and ACA in this unselected SSC cohort.

Disclosures: The authors have declared no conflicts of interest.

SJÖGREN’S SYNDROME AND OTHER CONNECTIVE TISSUE DISORDERS

274. AN UNUSUAL COMPLICATION OF RITUXIMAB: SEVERE CMV COLITIS IN PRIMARY SJÖGREN’S TREATED WITH A SINGLE CYCLE OF RITUXIMAB

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Background: Current data show no direct significant association between rituximab and infection rates in rheumatological cohorts. Studies of rituximab therapy in primary Sjögren’s have not reported serious or opportunistic infections.

Methods: We describe, to our knowledge, the first reported case of severe CMV colitis in a patient with primary Sjögren’s treated with a single cycle of rituximab.

Results: A 67-year-old lady, background of essential hypertension, epilepsy and Crohn’s disease (diagnosed aged 17, treated with right colectomy, in remission without immunosuppression) was referred to rheumatology by the ophthalmology team to exclude systemic causes for her retinal vascular changes and recurrent vitreous haemorrhage. A diagnosis of primary Sjögren’s with retinal vasculitis and recurrent vitreous haemorrhage was made (sicca syndrome; positive schirmer test and labial biopsy histology; Ro positive RF 46; ENA 32) and she responded well to high dose prednisolone. There were multiple recurrences of vitreous haemorrhage on steroid reduction despite starting AZA (steroid-sparing agent) in June 2011. In February 2012, rituximab was considered (recent trials of B-cell depletion have shown promising resuscitation and thrombocytopenia and leucopenia (platelet 67 x 10⁹/l, white cell count and progressive leucopenia. On admission, investigations showed culture negative for bacteria/parasitic/clostridium difficile infection)

Conclusions: While csPF is significantly more frequent among dcsSc patients, PH has similar incidence in both subsets. DLCO was the strongest predictor for both csPF and PH. ARA increased while anti-Scl 70 antibodies reduced the hazard for PH development. There was no association between PH and ACA in this unselected SSC cohort.

Disclosures: The authors have declared no conflicts of interest.

275. ACCUMULATION OF CIRCULATING AUTOREACTIVE NAÎVE B CELLS REVEALS DEFECTS OF EARLY B-CELL TOLERANCE CHECKPOINTS IN PATIENTS WITH SJÖGREN’S SYNDROME

Elisa Consiero1, Nurhan Sutcliffe1, Hedda Wardemann2, Costantino Pitzalis1 and Michele Bombardieri1
1Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, London, UK and 2Molecular Immunology Group, Max Planck Institute for Infection Biology, Berlin, Germany

Background: Sjögren’s syndrome (SS) is an autoimmune disease characterized by high affinity circulating autoantibodies and peripheral B-cell disturbances with predominance of naïve and reduction of memory B cells. The stage at which errors in B-cell tolerance checkpoints accumulate in SS is unknown. Here we determined the frequency of self- and poly-reactive B cells in the circulating naïve compartment of SS patients.

Methods: Single CD27–IgD+ B cells were sorted by FACS from peripheral blood of SS patients and healthy donors (HD). RNA was used to amplify Ig VH and VL genes and PCR products were cloned and expressed as recombinant monoclonal antibodies displaying identical specificity of the original B cells. Recombinant antibodies were tested towards different antigens to determine the frequency of autoreactive and polyreactive clones.

Results: 66 recombinant antibodies were generated from naïve B cells of 4 SS patients and compared with 45 clones from 2 HD. Analysis of the VH and VL gene usage showed no significant differences between SS and HD. Conversely, we observed accumulation of circulating autoreactive naïve B cells in SS as demonstrated by increased reactivity towards Hep2 cells (43.1% SS vs 25% HD) and ENA (19.6% SS clones vs none). Among ENA+ clones, 6 displayed reactivity towards Ro/SSA and/or La/SSB.

Conclusions: Here using an efficient strategy to express recombinant monoclonal antibodies from single B cells we demonstrated an elevated frequency of autoreactive naïve B cells in the circulation of SS patients supporting the existence of early defects in B-cell tolerance checkpoints in SS.

Disclosures: The authors have declared no conflicts of interest.

Table 1. Results

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The authors have declared no conflicts of interest.

276. TOLERANCE CHECKPOINTS IN PATIENTS WITH SJÖGREN'S SYNDROME

Elisa Consiero1, Nurhan Sutcliffe1, Hedda Wardemann2, Costantino Pitzalis1 and Michele Bombardieri1
1Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, London, UK and 2Molecular Immunology Group, Max Planck Institute for Infection Biology, Berlin, Germany

Background: Sjögren’s syndrome (SS) is an autoimmune disease characterized by high affinity circulating autoantibodies and peripheral B-cell disturbances with predominance of naïve and reduction of memory B cells. The stage at which errors in B-cell tolerance checkpoints accumulate in SS is unknown. Here we determined the frequency of self- and poly-reactive B cells in the circulating naïve compartment of SS patients.

Methods: Single CD27–IgD+ B cells were sorted by FACS from peripheral blood of SS patients and healthy donors (HD). RNA was used to amplify Ig VH and VL genes and PCR products were cloned and expressed as recombinant monoclonal antibodies displaying identical specificity of the original B cells. Recombinant antibodies were tested towards different antigens to determine the frequency of autoreactive and polyreactive clones.

Results: 66 recombinant antibodies were generated from naïve B cells of 4 SS patients and compared with 45 clones from 2 HD. Analysis of the VH and VL gene usage showed no significant differences between SS and HD. Conversely, we observed accumulation of circulating autoreactive naïve B cells in SS as demonstrated by increased reactivity towards Hep2 cells (43.1% SS vs 25% HD) and ENA (19.6% SS clones vs none). Among ENA+ clones, 6 displayed reactivity towards Ro/SSA and/or La/SSB.

Conclusions: Here using an efficient strategy to express recombinant monoclonal antibodies from single B cells we demonstrated an elevated frequency of autoreactive naïve B cells in the circulation of SS patients supporting the existence of early defects in B-cell tolerance checkpoints in SS.

Disclosures: The authors have declared no conflicts of interest.
276. A PHASE IV PILOT STUDY TO ESTABLISH WHETHER AN INTRAMUSCULAR STEROID INJECTION IS AS EFFECTIVE AS AN INTRALESIONAL STEROID INJECTION IN THE TREATMENT OF TENNIS ELBOW?
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Background: Multiple studies and a systematic review suggest a steroid injection for tennis elbow improves many short-term (6 weeks) outcome measures including pain and thereby allow a quicker return to work. The aim of this study was to establish if an intramuscular (IM) steroid injection was as effective in the short term (6 weeks) for pain relief and functional disability as an intralesional (IL) steroid injection in tennis elbow. Secondly to establish if an IM steroid injection was less painful than an IL steroid injection at the point of delivery and for 48 h later.

Methods: The study was a prospective, randomized controlled trial. 19 patients who had not had treatment for tennis elbow in the preceding 3 months were recruited from the investigators clinic. 9 patients were randomized to receive an 80 mg IM depomedrone injection into their gluteal muscle. 9 patients were randomized to receive a 40 mg depomedrone intralesional injection into the affected arm. 1 patient was withdrawn from the final analysis as their recruitment was deemed a protocol violation.

The primary outcome measures were pain severity and functional disability as assessed by a Patient Rated Tennis Elbow Evaluation (PRTEE) Questionnaire and pain severity at the site of the injection was assessed by a 10 point Likert scale. The later was assessed, immediately after the injection, 24 h later and then 48 h later. The secondary outcome was complications of treatment.

Results: Mean age in the IM arm was 40 years and IL arm was 43.5 years. 83% of patients had problems with their dominant arm. Six weeks after the treatment there were reduction in pain symptoms, improvement in function and total PRTEE scores in both IM and IL groups (P < 0.008). A statistically significant result (P = 0.001) in favour of IM causing less pain at the injection site was noted at the time of injection; however, statistical significance was not reached at 24 h (P = 0.031) or at 48 h (P = 0.113). The IL Total PRTEE mean change was 43 points whilst IM Total PRTEE change was 38 points at 6 weeks. The difference between IL and IM therapy was –5 points in favour of IL therapy. This was less than the –10 points that was taken as the acceptable MCID. However the CI interval was large ranging from –26 points to +16 points.

Conclusions: The results indicate that 6 weeks after both an IM and an IL steroid injection, pain, function and total PRTEE scores improved in both groups. The IM route caused significantly less pain at the time of injection at the time of injection. Both treatments were considered to be safe. This study did not however confirm non-inferiority of the IM over the IL procedure.

Disclosures: The authors have declared no conflicts of interest.

SPONDYLOARTHROPATHIES (INCLUDING PsA)

278. REFERRAL PATTERNS AND DIAGNOSIS OF PATIENTS WITH AXIAL SPONDYLOARTHRITIS: RESULTS OF AN INTERNATIONAL SURVEY
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Background: This analysis compares referral patterns and diagnostic tools for axial SpA (axSpA) used by rheumatologists working in academic centres and in community clinical practice settings.

Methods: The MAXIMA (Management of Axial SpA International and Multicentric Approaches) survey asked respondents questions pertaining to referral, diagnosis, and management of patients with axSpA. The survey was completed anonymously online by participants from 42 countries in Europe, Latin America, and North America. The MAXIMA survey was funded by Abbott Laboratories and conducted by a third-party vendor with guidance and approval of the questionnaire by a steering committee of SpA experts. None of the participants were compensated for completing the survey.

Results: 500 surveys were completed by 141 rheumatologists in academic practice settings (28%) and 359 rheumatologists in community practice settings (72%). Only 58% of academic rheumatologists compared with 72% of clinical rheumatologists agreed that the concept of axial SpA is clear to the rheumatology community. However, responses to various questions about referral and diagnostic work-up for patients with axSpA were generally similar in both practice settings. The majority of respondents (87%) reported that primary care providers referred patients with chronic back pain for 3 months and onset <45 years old; 47% of respondents received referrals from other specialists such as dermatologists, gastroenterologists, and ophtalmologists. Other than chronic back and inflammatory back pain, referrals from non-rheumatology specialists were triggered by the occurrence of uveitis (82% of respondents), IBD (48%) and skin lesions (48%). At the time of referral to a rheumatologist, 48% reported that patients had inflammatory back pain for >3 years. The ASAS criteria were cited by 85% of respondents as the most common classification criteria that guide respondents in the diagnosis of axSpA in clinical practice, compared with the modified New York criteria for AS (23%), ESSG (8%), and Amor (6%). In terms of diagnostic work-up, approximately half systematically request HLA-B27 typing. MRI of the sacroiliac joints is systematically request HLA-B27 typing. MRI of the sacroiliac joints is

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the most commonly used imaging test (by 93% of respondents), closely followed by pelvic X-rays (86%).

**Conclusions:** Results of the MAXIMA survey show general agreement in current patterns and use of diagnostic tools by rheumatologists in academic and clinical practice settings when evaluating patients for axSpA. Patients are being referred to half of the rheumatologists several years after onset of symptoms, which indicates the need for appropriate early referral.


**279. THE ARTHRITIS NEW ZEALAND ANKYLOSING SPONDYLITIS AWARENESS CAMPAIGN AND ITS EFFECTS ON RATE OF REFERRAL TO RHEUMATOLOGY SERVICES**

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1Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin; 2Arthritis New Zealand, Wellington; 3Department of Rheumatology, Waikato Hospital, Hamilton.

**Background:** AS is a condition affecting young people with a peak onset between 20 and 30 years. AS has an insidious onset and public awareness of AS appears to be low. This is reflected by a mean disease duration before diagnosis of 4–9 years which contrasts with 3–9 months in RA. A further barrier to diagnosis is the large caseload of mechanical low back pain in primary care which makes identification inflammatory back pain challenging. Arthritis New Zealand (ANZ) is the national voluntary organization representing the interests of those with arthritis and providing information and support. ANZ embarked on a media campaign in newspapers and on television to promote awareness of AS.

**Method:** Data were collected on telephone enquiries and website activity by ANZ before and after the campaign. The number of referrals with suspected AS collected in three centres (Dunedin, Hamilton and Wellington) over a 3-month period following the campaign were compared with referral data for the 3 months prior to the campaign. Age, gender, likelihood of diagnosis of AS and prevalence were recorded.

**Results:** Market research showed little awareness of ANZ or its campaigns before the advert (5% awareness). This increased to 84% prompted awareness after the campaign. There was a notable increase in telephone and website activity over this period, resulting in a further 25% increase to a helpline. Following the campaign, AS referrals to rheumatology increased from 54 in the 3 months before the campaign to 89 after, an increase of 64%. Referral rates for all other rheumatological conditions remained constant over this period. The male:female ratio was 2.1. The mean age for diagnosis was 39.7 years prior to the campaign and 41.7 after the campaign. The referral rate resulting in a final diagnosis of AS in the three centres combined pre campaign was 2 per 100,000 population over the study period.

**Conclusions:** The campaign led to a much greater public awareness of AS with over 1000 people seeking information and support from ANZ. The campaign also led to a significant increase in referrals for suspected AS. The male:female ratio suggests AS is more common in females than previously suggested. The rate of referral resulting in a diagnosis of AS more than doubled following the campaign. The increase in age of patients diagnosed with AS following the campaign suggests that the increase in diagnosis of AS was not driven by the identification of patients with early disease. However, extrapolating from incidence data in other countries it is likely that a large proportion of patients with AS are still not being identified.

**Disclosures:** The authors have declared no conflicts of interest.

**281. ACHIEVING ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE C-PROTEIN REACTIVE PROTEIN MAJOR IMPROVEMENT AND INACTIVE DISEASE IN PATIENTS WITH ANKYLOSING SPONDYLITIS AFTER TREATMENT WITH GOLIMUBAM IS ASSOCIATED WITH NORMALIZED HEALTH-RELATED QUALITY OF LIFE: 2-YEAR RESULTS FROM GO-RAISE**

Desiree van der Heijde1, Atul Deodhar2, Jurgen Braun3, Michael Mack4, Ben Hsu5, Tim Gathany6, Chenglong Han6 and Robert D. Inman7

1Rheumatology, Leiden University Medical Centre, Leiden, Netherlands; 2Rheumatology, Oregon Health and Science University, Portland, OR, USA; 3Rheumatology, Rheumazentrum Ruhrgebiet, Herne, Germany; 4Biostatistics, Janssen Research and Development, LLC, Spring House, PA; 5Immunology, Janssen Research and Development, LLC, Spring House, PA; 6Health Economics, Janssen Global Services, LLC, Malvern, PA, USA and 7Rheumatology, University of Toronto, Toronto, ON, Canada

**Background:** Significantly greater improvements in health-related quality of life (HRQoL) and reduction of impact of disease on work productivity were observed in patients with AS treated with golimumab (GLM) compared with placebo at weeks 14 and 24. We examined the association of ASAS major improvement and inactive disease with these improvements and the maintenance over 2 years.

**Methods:** In GO-RAISE, 356 patients with AS by the modified NY criteria were randomized (1:8.1:8.1) to SC GLM 50 or 100 mg or placebo q4w. HRQoL was assessed using the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36. Self-reported employment data, defined as currently working or able to work if a job is available, were collected. Impact of disease on productivity in daily work, school or home was assessed using a visual analogue scale (0–10). ASAS (using CRP) inactive disease was defined as a score <1.3 and major improvement was defined as an improvement from baseline ≥2. An ANOVA on van der Waerden

**Background:** Disease activity in axial SpA has traditionally been defined by clinical scoring methods such as the BASDAI. However, there has recently been interest in developing methods for quantifying disease activity based on inflammation as detected by MRI. In the setting of anti-TNF trials, changes in disease activity on MRI have been shown to correlate with clinical response. However, outside of this setting the relationship between MRI and clinical DAS is unclear. We aimed to determine the utility of MRI DASs in the assessment of a wide range of patients with axial SpA, representative of the variety encountered in everyday practice.

**Methods:** Patients meeting Assessment of Spondyloarthritis International Society (ASAS) criteria for axial SpA who were attending for MRI of whole spine and sacroiliac joints (SIJs) had measurement of inflammatory markers (CRP, ESR) and completed clinical DAS questionnaires [BASDAI, AS disease activity score (ASDAS)] within 24 h of their MRI scan. All images were then assessed for spinal and SIJ inflammation by two blinded observers using the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system. The data were analysed to determine whether correlation existed between MRI score and clinical scores, and between MRI score and CRP/ESR levels.

**Results:** 23 patients met ASAS criteria and completed the study. Axial inflammation was present in 70% (16/23) of patients. There was significant correlation between total SPARCC score and ASDAS-CRP (P = 0.44, P = 0.04) but not between BASDAI (P = 0.30, P = 0.16), ASDAS-ESR (P = 0.31, P = 0.15), ESR alone (P = 0.31, P = 0.15) or CRP alone (P = 0.37, P = 0.08). SPARCC score for the spine alone was significantly correlated with ASDAS-CRP (P = 0.57, P = 0.05), ASDAS-ESR (P = 0.54, P = 0.007) and ASDAS-ESR (P = 0.47, P = 0.02). SPARCC score for SIJs alone was significantly correlated with only ASDAS-CRP (P = 0.49, P = 0.03), not BASDAI (P = 0.3, P = 0.192) or ASDAS-ESR (P = 0.41, P = 0.08). Patients with axial inflammation (SPARCC > 0) had significantly higher ASDAS-CRP than those with no axial inflammation (P = 0.04), but not significantly higher BASDAI (P = 0.12) or ASDAS-ESR (P = 0.07).

**Conclusions:** There is some correlation between MRI DASs and clinical DASs. MRI scores should be considered a useful adjunct in the assessment of patients with axial SpA. ASDAS-CRP was more closely correlated with MRI disease activity than ASDAS-ESR or BASDAI, suggesting that it may be the optimal score for reflection of overall disease activity. More work is needed to determine the utility of MRI scores in larger populations. MRI scores could potentially be used more routinely, for example, to select patients suitable for anti-TNF therapy.

**Disclosures:** The authors have declared no conflicts of interest.
normal scores was used for numeric comparisons and chi-square tests for dichotomous comparisons.

**Results:** At weeks 14 and 24 the combined GLM groups had greater median improvements in ASDAS compared with placebo (1.6 vs 0.4 and 1.7 vs 0.3, respectively, \( P < 0.001 \) for both). At weeks 52 and 104, when all patients received GLM, all groups had comparable improvements in ASDAS (range: 1.9–2.3). At weeks 52 and 104, 33.4% and 46.6% of patients achieved ASDAS inactive disease, and 45.1% and 52.9% had a major improvement. For patients achieving ASDAS inactive disease at weeks 52 and 104, 57.1% and 65.5%, respectively, had PCS ≥ 50 and 64.8% and 74.1% had MCS ≥ 50. Of patients achieving ASDAS major improvement, 37.9% and 48.3% had PCS ≥ 50 and 62.1% and 63.1% had MCS ≥ 50 at weeks 52 and 104. Improvements in productivity were greater for patients with ASDAS inactive disease compared with non-inactive disease at weeks 52 and 104 (5.8 vs 2.9 and 5.8 vs 3.1, \( P < 0.001 \) for both). Similar results were achieved for ASDAS responders vs nonresponders (5.4 vs 2.4 and 5.8 vs 2.6, \( P < 0.001 \) for both). At baseline, 40 patients were unemployed because of AS. At week 52, 6 of 7 (85.7%) patients who achieved inactive disease regained employability, while only 11 of the 15 (73.3%) patients who had major improvement regained employability. At week 104, 7 of 7 (100.0%) patients who achieved inactive disease regained employability, and while 13 of 14 (92.9%) patients who had major improvement regained employability.

**Conclusions:** Achieving ASDAS inactive disease or major improvement after GLM is associated with improvements in HRQOL and productivity in AS patients. A trend towards regaining employability was observed for patients with clinical improvements, but this association would need to be substantiated in larger studies.


**282. DISEASE SEVERITY AND MOOD DISTURBANCE IN ANKYlosing SPONDYLITIS: A PROSPECTIVE STUDY**

Nicola Cooper-Moss1, Jonathan Packham1,2 and Vicky Strauss3

1Arthritis Research UK Primary Care Centre, Keele University, Keele and 2Haywood Rheumatology Centre, Haywood Hospital, Burslem, UK

**Background:** AS is a chronic inflammatory disorder, causing progressive pain and stiffness of the spine and peripheral joints. A systematic review of the literature revealed a high prevalence of possible depression (23–36%) and possible anxiety (45–57%) in patients with AS. However, few existing studies have focused on the relationships between mood and AS severity. The aim of this study was to explore the cross-sectional and prospective relationships of disease severity and mood disturbance in patients with AS.

**Methods:** 812/1000 AS patients responded at baseline and 470/812 at 6 months. The majority of baseline responders were male (72.2%), with a mean age of 50.80 (s.d. 12.22) years and mean symptom duration of 22.57 (s.d. 12.37) years. The baseline prevalence of possible depression and anxiety were 32% and 45%, respectively. Possible depression was associated with increased disease activity (OR 3.09, 95% CI 1.63, 5.86), pain (OR 2.65, 95% CI 1.38, 5.09) and functional impairment (OR 3.10, 95% CI 1.61, 5.97). Similarly, possible anxiety was associated with increased disease activity (OR 2.70, 95% CI 1.57, 4.65) and pain (OR 2.6, 95% CI 1.50, 4.55) but less so with functional impairment (OR 1.96, 95% CI 1.12, 3.42). Severity of mood disturbance at baseline was not associated with any significant changes in AS activity, function and pain at baseline was not associated with any significant change in anxiety or depression at 6 months.

**Conclusions:** Patients with increased depression and/or anxiety had both greater disease activity and pain. However, depressive symptoms were more likely to occur in patients with functional restriction. Longer follow-up studies of more than 6 months may be required to investigate any causative inter-relationships between mood and disease severity.

**Disclosures:** The authors have declared no conflicts of interest.

**283. IS THERE SUB-CLINICAL JOINT DISEASE IN EARLY PsORIATRIC ARTHRITIS: CLINICAL COMPARISON WITH POWER DOPPLER ULTRASOUND**

Jane E. Freeston1, Laura Coates1, Jackie Nam1, Anna R. Moverley1, Philip Hellivil1, Elizabeth Hensor1, Richard Wakefield1, Paul Emery1 and Philip Conaghan1

1Division of Rheumatic and MSK Disease, University of Leeds, Leeds, UK

**Background:** In line with RA, the emphasis in PsA is to treat early to minimize damage and functional disability. Traditionally, clinical examination (CE) in the form of the tender (TJC) and swollen joint (SJC) counts has been used to assess disease activity. In RA, multiple studies have shown sub-clinical disease using ultrasound (US) assessment of disease activity. The aim of this study was to compare CE and US findings in an early PsA cohort.

**Methods:** 49 patients with new onset PsA, according to the CASPAR criteria, were recruited. They were all DMARD naïve and had a symptom duration <24 months. All patients underwent grey-scale (GS) and power Doppler (PD) US of 40 joints as well as tender/swollen joint counts of 66/66 joints. GS and PD were scored separately on a 0–3 semi-quantitative scale for each joint imaged. A clinically active joint was defined as tender and/or swollen and a GS score of ≥2 and/or a PD score ≥1 were used to identify active joints.

**Results:** Of the 49 patients, 38 were classified clinically as polyarthritis (5 or more active joints) and 11 oligoarthritis (4 or less active joints). Of the 11 clinical oligoarthritis patients, US evidence of sub-clinical synovitis identified 9 (81.8%) of these as having polyarthritis. A total of 47/49 patients (96%) had at least one joint showing sub-clinical synovitis. Sub-clinical synovitis (defined as GS ≥ 1 and/or PD ≥ 0 in a joint) in the absence of tenderness or swelling was seen most frequently in the wrist 40.8%, knee 32.7%, MTP1 33.7% and MTP2 38.8%. Clinical over-estimation of synovitis occurred most commonly at the shoulder (38% joints) and ankle (28.6%).

**Conclusions:** This study has shown that sub-clinical synovitis, as identified by US, is very common in early PsA. Clinically this finding is as important as US evidence of sub-clinical synovitis led to 81.8% of oligoarthritis patients being reclassified as polyarthritic. Further study on the potential importance of sub-clinical synovitis on structural progression is required.

**Disclosures:** The authors have declared no conflicts of interest.

**284. EFFECT OF CERTOLIZUMAB PEGOL ON SIGNS AND SYMPTOMS IN PATIENTS WITH PSORIATIC ARTHRITIS WITH OR WITHOUT PRIOR ANTI-TNF EXPOSURE: 24-WEEK RESULTS OF A PHASE III DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED STUDY**

P. Mease1, R. Fleischmann2, J. Wollenhaupt1, A. Deodhar4, D. Kielar5, F. Woltering6, C. Stach6, B. Hoepekens6, T. Arledge7 and Desiree van der Heijde8

1Swedish Medical Centre and University of Washington, Seattle, WA, 2University of Texas SW Medical Centre, Dallas, TX, 3Schoen Klinik, Hamburg, Germany, 4Oregon Health and Science University, Portland, OR, USA, 5UCB Pharma, Brussels, Belgium, 6UCB Pharma, Monheim am Rhein, Germany, 7UCB Pharma, Raleigh, NC, USA and 8Department of Rheumatology, Leiden University Medical Centre, Leiden, Netherlands

**Background:** Certolizumab pegol (CZP) has shown efficacy in reducing signs and symptoms of PsA. RAPID-PsA is the first report of a biologic in PsA to include patients with prior anti-TNF exposure.

**Methods:** Patients had active PsA and had failed ≥1 DMARD. Patients were randomized to placebo (PBO), or CZP loading dose (LD: 400 mg every 2 weeks (q2W)) followed by CZP either 200 mg q2W or 400 mg q4W. PBO patients who failed to achieve ≥10% decrease in tender/swollen joint counts at both weeks 14/16 were rescued and randomized to receive CZP 250 mg q2W or 400 mg q4W following LD. The primary endpoint for PsA signs/symptoms was ACR20 at week 12. Secondary outcomes were PASI75, Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI) and Modified Nail Psoriasis Severity Index (mNAPSI), Impotum; NRI for ACR/PASI75; LOCF for LEI/LDI/mNAPSI.

**Results:** Baseline (BL) demographics were similar between groups, 19.1% and 19.8% of PBO and CZP (combined dose) patients received

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prior anti-TNF. Week 12 ACR20 response was significantly higher in each CZP arm vs PBO [58.0% and 51.9% vs 24.3% (P < 0.001 for both)] and was observed as early as week 1 (21.0% [P = 0.001] and 23.0% [P < 0.001] vs 7.4%). Similar effects were observed for ACR50/70 (Table 1). Week 24 PASI75 response for patients with >3% psoriasis body surface area at BL (61.6%) was 62.2% with CZP 200 mgq2W and 60.5% with 400 mgq4W vs 15.1% PBO (P < 0.001 for both). In patients with BL enthesitis (64.3% RS) LEI change from BL at week 24 was –2.0 with CZP 200 mgq2W (P = 0.001) and –1.8 with 400 mgq4W (P = 0.003) vs –1.1 PBO. For patients with BL nail disease (73.3% RS) week 24 mNAPSI change from BL was –1.6 with CZP 200 mgq2W and –3.7 mgq4W vs –1.1 PBO. No differences in LDI change from BL were observed in patients with BL dactylitis. Week24 ACR response rates were similar between CZP arms, irrespective of prior anti-TNF exposure (Table 1). Adverse events (AEs) occurred in 62% vs 68% and SAEs in 7% vs 4% in CZP (combined dose) vs PBO, respectively. Two deaths occurred up to week 24, one sudden death of unknown cause and one myocardial infarct. No new safety signals were observed.

Conclusions: Rapid improvements in the signs/symptoms of PsA, as well as psoriasis skin manifestations and nail disease, were observed across both CZP dosing regimens. Similar ACR response rates with CZP were observed in patients with and without prior anti-TNF exposure.

Table 1. ACR 20/50/70 response over time (%)

<table>
<thead>
<tr>
<th>Week</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>PBO</td>
<td>7.4</td>
<td>23.5</td>
<td>47.4</td>
</tr>
<tr>
<td>n</td>
<td>138</td>
<td>286</td>
<td>424</td>
</tr>
</tbody>
</table>

**DISCUSSIONS:**

**ACR20:**

- **Prior anti-TNF:** No Yes No Yes No Yes
- **PBO:** 26.4% 11.5% 14.5% 3.8% 4.5% 3.8%
- **CZP combined:** 60.3% 59.3% 41.6% 44.6% 26.0% 25.9%

**DISCUSSIONS:**

- **ACR50:**
  - **PBO:** 40.5% 22.4% 5.9% 6.2% 9.7% 9.7%
  - **CZP combined:** 77.9% 72.9% 35.9% 37.4% 22.1% 22.1%

**DISCUSSIONS:**

- **ACR70:**
  - **PBO:** 23.0% 23.0% 7.4% 12.4% 18.5% 18.5%
  - **CZP combined:** 63.8% 58.9% 33.8% 35.3% 23.5% 23.5%

**RESULTS:**

- **At Week 12:**
  - **SF-36a MCS:** BL week 12 week 24 42.4 (12.5) 29.3 (12.5)
  - **SF-36a PCS:** BL week 12 week 24 33.8 (7.9) 26.8 (7.9)
  - **HAQ-DI:** BL week 12 week 24 1.3 (0.7) –0.2 (0.4)

**CONCLUSIONS:**

- Rapid improvements in the signs/symptoms of PsA, as well as psoriasis skin manifestations and nail disease, were observed across both CZP dosing regimens. Similar ACR response rates with CZP were observed in patients with and without prior anti-TNF exposure.

**RESULTS:**

- **At Week 12:**
  - **SF-36a MCS:** BL week 12 week 24 42.4 (12.5) 29.3 (12.5)
  - **SF-36a PCS:** BL week 12 week 24 33.8 (7.9) 26.8 (7.9)

**ACR20:**

- **Prior anti-TNF:** No Yes No Yes No Yes
- **PBO:** 26.4% 11.5% 14.5% 3.8% 4.5% 3.8%
- **CZP combined:** 60.3% 59.3% 41.6% 44.6% 26.0% 25.9%

**DISCUSSIONS:**

- **ACR50:**
  - **PBO:** 40.5% 22.4% 5.9% 6.2% 9.7% 9.7%
  - **CZP combined:** 77.9% 72.9% 35.9% 37.4% 22.1% 22.1%

**DISCUSSIONS:**

- **ACR70:**
  - **PBO:** 23.0% 23.0% 7.4% 12.4% 18.5% 18.5%
  - **CZP combined:** 63.8% 58.9% 33.8% 35.3% 23.5% 23.5%

**RESULTS:**

- **At Week 12:**
  - **SF-36a MCS:** BL week 12 week 24 42.4 (12.5) 29.3 (12.5)
  - **SF-36a PCS:** BL week 12 week 24 33.8 (7.9) 26.8 (7.9)

**ACR20:**

- **Prior anti-TNF:** No Yes No Yes No Yes
- **PBO:** 26.4% 11.5% 14.5% 3.8% 4.5% 3.8%
- **CZP combined:** 60.3% 59.3% 41.6% 44.6% 26.0% 25.9%

**DISCUSSIONS:**

- **ACR50:**
  - **PBO:** 40.5% 22.4% 5.9% 6.2% 9.7% 9.7%
  - **CZP combined:** 77.9% 72.9% 35.9% 37.4% 22.1% 22.1%

**DISCUSSIONS:**

- **ACR70:**
  - **PBO:** 23.0% 23.0% 7.4% 12.4% 18.5% 18.5%
  - **CZP combined:** 63.8% 58.9% 33.8% 35.3% 23.5% 23.5%
Table 1. Productivity (per month) in RAPID-PsA study (LOCF)

<table>
<thead>
<tr>
<th>WPS</th>
<th>PBO</th>
<th>CZP 200 mg q2W</th>
<th>CZP 400 mg q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Productivity at work</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>BL week4 week24</td>
<td>BL week4 week24</td>
</tr>
<tr>
<td>Work days missed</td>
<td>6</td>
<td>2.6 2.1</td>
<td>2.0 1.0</td>
</tr>
<tr>
<td>Days with work productivity reduced by ≥50%</td>
<td>6</td>
<td>3.2 2.3 3.5</td>
<td>2.3 1.3 3.5</td>
</tr>
<tr>
<td><strong>Rate of arthritis interference with work productivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>ALL</td>
<td>136</td>
</tr>
<tr>
<td>Household work days missed due to arthritis</td>
<td>6</td>
<td>5.7 4.7 5.9 4.2 5.5 3.2</td>
<td></td>
</tr>
<tr>
<td>Household work days with productivity reduced by ≥50%</td>
<td>6</td>
<td>8.6 7.6 7.1 5.2 7.1 5.3</td>
<td></td>
</tr>
<tr>
<td>Days missed of family/social/leisure activities</td>
<td>6</td>
<td>3.7 2.8 4.1 1.1 3.2 1.1</td>
<td></td>
</tr>
<tr>
<td>Days with outside help hired</td>
<td>6</td>
<td>2.1 1.9 2.4 1.4 2.7 1.5</td>
<td></td>
</tr>
<tr>
<td>Rate of arthritis interference with household work productivity</td>
<td>6</td>
<td>4.9 4.5 4.1 2.6 4.2 3.9</td>
<td></td>
</tr>
</tbody>
</table>

1 Only employed patients. 2 Does not include work days missed counted in the previous question. *0–10 scale, 0 = no interference and 10 = complete interference. *P < 0.05 vs PBO.

287. USTEKINUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS: RESULTS OF THE PHASE III, MULTICENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED PSUMMIT I STUDY.

Iain McInnes,1 Arthur Kavanaugh,1 Alice B. Gottleib,2 Lluis Puig,3 Protowon Lwoo,3 Christopher Ritchlin4,-Shu Li,5 Yuhua Wang7,8,9 Iain McInnes1, Arthur Kavanaugh2, Alice B. Gottlieb3, Lluis Puig4,5, Yuhua Wang7,8,9

288. THE FEASIBILITY, RELIABILITY AND SENSITIVITY TO CHANGE OF FOUR RADIOGRAPHIC SCORING METHODS IN PATIENTS WITH PSORIATIC ARTHRITIS

William Tilt1,2, Deepak Jadon1, Gavin Shaddick2, Charlotte Cavi3,4, Graham Robinson5, Raj Sengupta6, Elena Korendovych7, Corinne de Vries8,9 and Neil McHugh5,6,7

1Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, UK; 2Department of Mathematics, University of Bath, Bath; 3Rheumatology, Bath Institute for Rheumatic Diseases, Bath; 4Radiology, Royal United Hospital, Bath; 5Pharmacy and Pharmacology, University of Bath, Bath, UK

Background: Radiographic damage is an important outcome measure in PsA. Four scoring systems are currently used; the PsA-Modified Sharp Score (MSS), the Sharp/van der Heijde (VDH), the modified Mankin score (MSS), the Steinbrocker (STB) and the Ratingen score (RAT). The RAT is the only system to include bone proliferation, the only radiographic finding sufficiently specific to PsA to be included in the CASPAR criteria for Psoriatic Arthritis (CASPAR). There is no consensus amongst experts on which score should be used in long term observational studies.
POSTER VIEWING III

Thursday 25 April 2013, 10.30–11.30 I165

289. THE ROLE OF BIOMECHANICS-RELATED FACTORS IN ANKYLOSING SPONDYLITIS AS ASSESSED BY REPORTED EFFECTS OF EXERCISE FROM PHYSIOTHERAPY AND SPORTING PARTICIPATION: RESULTS FROM A NATIONAL PATIENT SURVEY

Rebecca C. Thomas1, Yoshitide Shuto2, Noemi Busquets-Pérez3, Helena Marzo-Ortega4 and Dennis McGonagle5
1Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds, UK, 2Department of Rheumatology and Orthopaedics, Chiyoda Hospital, Miyazaki, Japan and 3Department of Rheumatology, Hospital General de Granollers, Barcelona, Spain

Background: It is increasingly recognized that factors related to skeletal biomechanics may play a key role in the pathogenesis of AS and related SpA. Physiotherapy and regular exercise are advocated in the management of AS, being beneficial for the management of pain, fatigue and depression in AS. Physical activity and mechanical injury have also been linked to joint inflammation in PsA. This study aimed to explore the perception of the effect of physiotherapy on SpA, the effect of AS on sport participation, and to assess the prevalence of recalled injury and its temporal association with AS onset.

Methods: An online questionnaire was devised and disseminated electronically to members of the National Ankylosing Spondylitis Society (NASS).

Results: A total of 1026 responses were received. The majority of respondents (61.4%, n = 636) classified themselves as having either "very active" or "quite active" participants in sport prior to diagnosis with AS. A third (28.5%, n = 292) reported that they had given up a sport completely after diagnosis. A further 228 (22.2%) had otherwise reduced participation in sport, and 244 (23.8%) switched to a less strenuous sporting activity. 294 (28.7%) reported that the recommended physiotherapy exercises led to a flare of their symptoms. 332 (32.4%) reported modification of their recommended exercises to lessen disease flares. 452 (44.1%) respondents recalled an instance of trauma prior to the onset of AS that they felt had triggered their disease; 30% reported some instance of trauma weeks or days before onset and 70% recalled trauma months or years before onset of back pain.

Conclusions: The authors have declared no conflicts of interest.

DISCLOSURES: The authors have declared no conflicts of interest.

(staff)
291. CASELOAD AND IMPACT OF THE LEEDS COMBINED RHEUMATOLOGY AND GASTROENTEROLOGY CLINIC

Toshihide Shuto1, Helena Marzo-Ortega2, Rebecca C. Thomas2, Sarah Bingham2, Laura Coates2, Paul Emery2 and P. John Hamlin4 1Department of Rheumatology and Orthopaedics, Chiyoda Hospital, Miyazaki, Japan, 2Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds, 3Department of Rheumatology, Leeds Teaching Hospitals NHS Trust, Leeds and 4Department of Gastroenterology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Background: The relationship between SpA and IBD is well established. Musculoskeletal symptoms are commonly reported in IBD. Conversely, it has been reported that a high proportion (over 60%) of patients with AS, the prototypical SpA exhibit subclinical mucosal gastrointestinal inflammation. Management of individuals with overlapping IBD and SpA can be challenging for both gastroenterologists and rheumatologists. To improve patient care, a combined rheumatology and gastroenterology clinic (CRGC) was established in Leeds in 2008 and runs once every 2 months. Here we report the diagnoses, reasons for referral and first-visit interventions seen in this clinic.

Methods: A service development review was conducted. The records of all patients referred to the clinic were reviewed and information gathered on diagnosis, source of referral, and initial outcomes.

Results: A total of 86 individuals (29 male) were referred between the inception of the clinic in June 2008 and April 2012. 41.8% (n = 36) referrals were made by the Gastroenterology department, and the remainder by the Rheumatology department. The most common reason for referral was for an opinion from either a gastroenterologist or rheumatologist (46.5%, n = 40), followed by joint decision-making regarding treatment or ongoing care (40.7%, n = 35). Outcomes from the first CRGC visit are summarized in Table 1. 23.3% (n = 20) of patients received a new diagnosis at this visit. Combined decision-making led to a change in treatment for 51.2% (n = 44) of patients at the first visit. 86% (n = 74) of patients referred had a diagnosis of IBD; the non-inflammatory bowel complaints included dyspepsia and irritable bowel syndrome. One patient received a diagnosis of OA induced colitis. 57.7% (n = 47) of patients had a diagnosis of SpA. A further 18.6% (n = 16) had symptoms suggestive of an inflammatory arthritis, while 9.3% (n = 8) had a diagnosis of RA.

Conclusions: In total, 61 of 86 patients (70.9%) had a change in diagnosis and/or treatment facilitated by attendance at the combined clinic. This highlights the role of the combined rheumatology and gastroenterology clinic as an appropriate, efficient setting for the management of patients with complex overlapping gastrointestinal and musculoskeletal manifestations of inflammatory disease.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change/start synthetic DMARD</td>
<td>20 (21.7)</td>
</tr>
<tr>
<td>Change/start biologic treatment</td>
<td>15 (16.3)</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>IA injection (s)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Further investigations requested</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>New diagnosis made</td>
<td>15 (16.3)</td>
</tr>
<tr>
<td>Watch and wait</td>
<td>20 (21.7)</td>
</tr>
</tbody>
</table>

Some patients received >1 intervention; n = 92.

Disclosures: The authors have declared no conflicts of interest.

References

1. Feldtkeller E, Khan MA, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int 2003;23:61–6.


292. EARLY INFLAMMATORY BACK PAIN SERVICE TO PROVIDE ASSESSMENT, DIAGNOSIS AND PROMPT TREATMENT FOR PATIENTS WITH AXIAL SPONDYLOARTHROPATHIES

Rebecca Adship1, Susannah Cambridge1, Simon Donnelly1 and Hassan Tahiri1 1Rheumatology, Whips Cross University Hospital Trust, London, UK

Background: Inflammatory back pain (IBP) is a characteristic feature of SpAs. Our service provides a model and screening pathway to assist others setting up early inflammatory back pain services. Several factors contribute to long delays in diagnosis of AS, deferring specialist referral until irreversible structural damage has occurred [1]. Early assessment and diagnosis is fundamental to provide effective treatment and prevent physical, emotional and socioeconomic consequences [2]. Objectives: (i) To develop an Early Inflammatory Back Pain Service (EIBPS) pathway, and (ii) to implement an educational campaign focused on early diagnosis of IBP raising awareness to GPs, allied healthcare practitioners (AHPs) and secondary care colleagues. Methods: Patients with suspected IBP were screened in the EIBPS referred from primary and secondary care. Each was assessed for IBP (Berlin criteria) and other SpA features. Bloods including HLA-B27 were taken for those with IBP or suspected axial SpA, X-ray of SIJs and/or MRI taken (if sacroiliitis not evident on plain film). An educational campaign was undertaken—circulating posters to local community areas, writing local newspaper leads and formal education on IBP for GPs, AHPs and secondary care colleagues. Results: 137 patients with suspected IBP were screened in the EIBPS over 24 months (Table 1). 107/137 patients (78%) were screened within 3 weeks of referral. 77/137 patients (56%) were male. 105/137 patients (77%) had symptoms suggestive of IBP and or other SpA features and were therefore investigated further. 45/105 patients (39%) fulfilled Modified New York or ASAS criteria. 60/105 patients (57%) had symptoms suggestive of IBP but did not at this stage fulfil criteria for a specific SpA. 38/45 of the patients who fulfilled the Modified New York or ASAS criteria (84%) commenced NSAIDs at diagnosis, 21/45 of the patients who fulfilled Modified New York or ASAS criteria (47%) were referred appropriately for TNF therapy through either the NHS or a clinical study. Conclusions: The EIBPS demonstrates that screening patients with suspected IBP can successfully diagnose those with SpA within weeks of referral, facilitating prompt diagnosis, early treatment and educational support. Our service provides a model to assist others in setting up early IBP services.

<table>
<thead>
<tr>
<th>TABLE 1. Patient diagnostic categories within our EIBPS cohort</th>
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<td>n</td>
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<td>-----------------------------------</td>
</tr>
<tr>
<td>Total number of patients referred</td>
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<tr>
<td>Patients presenting with MLBP</td>
</tr>
<tr>
<td>Patients investigated further</td>
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<tr>
<td>Patients diagnosed with AS (Mod NY criteria)</td>
</tr>
<tr>
<td>Pre-radiographic SpA (ASAS criteria)</td>
</tr>
<tr>
<td>Postural/core dysfunction on assessment</td>
</tr>
<tr>
<td>PsA</td>
</tr>
<tr>
<td>Episodes of disc disease</td>
</tr>
<tr>
<td>Scheuermann’s disease</td>
</tr>
<tr>
<td>Juvenile arthritis</td>
</tr>
<tr>
<td>Ischial tuberosity enthesis</td>
</tr>
<tr>
<td>Structural spinal deformity</td>
</tr>
<tr>
<td>Neck pain</td>
</tr>
<tr>
<td>Fibromyalgia</td>
</tr>
</tbody>
</table>

Disclosures: The authors have declared no conflicts of interest.

References

1. Feldtkeller E, Khan MA, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int 2003;23:61–6.


293. AN ASSOCIATION BETWEEN PERIODONTAL DISEASE, ORAL HEALTH RELATED QUALITY OF LIFE AND DISEASE ACTIVITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: There is convincing evidence for an association between RA and chronic periodontitis (PD). However, there is a lack of evidence regarding an association between PD and other rheumatic diseases. Recently, a large study has suggested an association between AS and PD, supporting three earlier smaller studies in different populations.

The oral cavity represents the second largest reservoir of commensal micro-organisms in the human body after the intestinal tract. Evidence suggests that microbial dybiosis plays a role in the initiation and perpetuation of AS. Identification of oral pathology and an association with disease activity would suggest that this process may begin in the mouth. As yet, no studies have investigated a potential association between disease activity in AS and PD, although such an association has been reported in RA.

The aim of this study was to compare the prevalence of periodontal disease in patients with AS, to assess their oral health status, disease activity and oral health related quality of life and to compare this with healthy controls.
Methods: Forty-one patients with AS fulfilling the modified New York criteria and 49 healthy controls individually matched for age, sex and ethnicity (mean age 42.5 years; s.d. 13.7) participated in this case-control study. Data collection included probing pocket depth, attachment loss, CAL, bleeding on probing (BOP), plaque index, oral mucosal conditions, caries status and salivary flow rate (SFR). Sociodemographic characteristics, medical history and oral-health-related quality of life (OHQoL) were measured using the OHIP-14 questionnaire. Disease activity in AS patients was assessed using the BASDAI.

Results: AS Patients had a higher prevalence of periodontalitis (>2 sites with >5 mm) than the healthy controls (87.8% vs 71.4%; P = 0.06). A positive gradient was observed between BASDAI DAS in AS and periodontal disease severity. The mean plaque score and the extent of BOP were significantly higher in cases than controls (P < 0.05). The other oral health characteristics and the mean SFR were similar in both groups. Mean OHIP-14 scores were higher in cases than controls (P < 0.05).

Conclusions: Within the limitations of this study, the findings support the hypothesis that periodontal disease may be a risk factor for AS. Further investigation is warranted to confirm these results.

Disclosures: The authors have declared no conflicts of interest.

294. IS THERE CLINICAL VALUE TO ANA MONITORING IN ANKYLOSING SPONDYLITIS PATIENTS TREATED WITH INFliximab: A RETROSPECTIVE STUDY OF 77 PATIENTS

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Background: TNF inhibitors such as infliximab (INF) are used in the treatment of AS but have been linked with vasculitis and lupus-like syndromes that are associated with autoantibodies such as ANA. Current regional guidelines recommend ANA screening every 3 to 4 months in all patients exposed to INF. This audit aimed to determine compliance with regional ANA monitoring guidelines; report prevalence of antibody seroconversion and assess clinical significance in a cohort of AS patients exposed to INF.

Methods: Retrospective analysis of AS patients exposed to INF between May 2001 and Dec 2011. Data were collected on length of drug exposure; concomitant DMARD use; antibody profile prior to and during treatment. ANA titres >1/80 were deemed positive. New symptoms were recorded from clinical notes.

Results: 70 patients were identified (52 male; mean (s.d.) age 40 (11); disease duration 10 (10.3) years; 58 (83%) were HLA B27 positive and 60 (86%) had sacroiliitis on imaging. Fifty one (72%) had exposure to at least one DMARD whilst on INF. Mean (s.d.) INF exposure was 4.8 (3.7) years. Clinical trials accounted for 38 patients starting INF prior to NICE TAI143.

Ten patients (14%) tested positive for ANA at some point prior to starting INF but only 6 (8.6%) were positive at drug initiation. Four patients with a positive ANA test did not have repeat ANA testing during the treatment period; 66 (94%) patients had a total of 1306 ANA tests [mean (s.d.) tests per pt 19.79 (16.24); mean (s.d.) interval between tests 3.8 (2.5) months] during drug exposure. Of these, 40 (61%) became ANA positive at a median time of 1.3 years (IQR 0.6–2.3) after initiating therapy. After an initial positive test, 68% (IQR 0.36) of subsequent tests remained positive.

Two patients developed lupus-like or vasculitic symptoms: i) after 15 months INF monotherapy a male (age 52, disease duration 24 years) developed nail fold infarcts, ulnar mononeuropathy, positive ANA, dsDNA, and non-specific ANCA. Symptoms resolved with 3 pulses of cyclophosphamide and i.v. methylprednisolone. ii) after 44 months INF and MTX a female with psoriatic spondylitis (age 43, disease duration 5 years) became ANA positive in a speckled pattern later changing to PCNA: highly specific for SLE. Two years later she developed a malar rash, photosensitivity, hair loss, and mouth ulcers. ANCA, dsDNA and c-ANCA remained normal. Symptomatic resolution after stopping steroids and HCQ. Treatment was not altered in either case prior to the development of new symptoms despite seroconversion and close monitoring. ANA reverted to negative after discontinuation of INF.

Conclusions: ANA seroconversion is common in AS patients treated with INF and remains persistent during drug exposure. Although ANA seroconversion was widespread, development of new symptoms was rare and did not occur after withdrawal of drug. This questions the value of such frequent ANA monitoring in the absence of additional symptoms.

Disclosures: M.B., Pfizer, MSD, UCB, Roche and Abbott—Honoraria, Consulting Fees and/or Grants. P.E., Abbott, MSD, Pfizer, UCB, BMS and Roche—Honoraria, Consulting Fees and/or Grants. H.M., Abbott, MSD, Pfizer, and UCB—Honoraria, Consulting Fees and/or Grants. All other authors have declared no conflicts of interest.

295. ANKYLOSING SPONDYLITIS: ARE WE DOING ENOUGH TO ASSESS FOR OSTEOPOROSIS AND DOES VITAMIN D MATTER IN THIS PATIENT GROUP?

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Background: AS is a seronegative arthropathy that shows a predilection for young males, primarily causing inflammation of the axial skeleton and resulting in progressive disability. It is recognized that patients with AS are at greater risk of vitamin D deficiency and are also more likely to develop osteoporosis, with the latter being difficult to accurately measure due to the presence of syndesmophytes. Despite these increased health risks, current guidelines do not recommend routine screening for either vitamin D deficiency or osteoporosis. Our aim was to assess the number of patients routinely screened for osteoporosis and vitamin D deficiency in a cohort of patients with AS in an inner city hospital in Manchester.

Methods: Data were collected retrospectively. Patients were identified from the AS clinic database. Data recorded included age, gender and past medical history. The hospital database was used to collect total serum 25-hydroxy vitamin D levels and bone mineral density (BMD) from Dual-energy X-ray absorptiometry (DEXA) imaging of AP spine and hip. WHO definitions of osteoporosis using BMD measured on AP spinal DEXA images and hospital laboratory range references were used to define vitamin D deficiency.

Results: A total of 77 patients were included, with a median age of 44 years (range 23–77); 24 females and 53 males. Of these 79% (61) had DEXA scans completed, 13.1% (8) of whom were identified as having osteoporosis and 49.2% (30) having osteopenia. Of the cohort with osteoporosis, the lumbar spine was affected in 82.6% (3) of cases and the hip affected in 3.2% (2). Serum 25-hydroxy vitamin D levels were tested in 75.3% (58) of all patients and of these, 60.3% (35) had deficient or insufficient levels. Of note, 48.6% (22) of patients aged under 51 years had osteopenia, 48.9% (23) had vitamin D deficiency and 23.4% (11) had both conditions.

Conclusions: AS is known to be an independent risk factor for vitamin D deficiency and osteoporosis and as such, it is imperative to employ strategies to promote bone health and prevent fractures. Despite these recognized health risks, current UK best practice guidelines for management of AS do not suggest routine screening for vitamin D deficiency but make recommendations regarding osteoporosis risk and prevention. It is also important to identify that BMD values may be falsely high due to the presence of syndesmophytes. We demonstrated that <80% of our sample patient group underwent assessment for this; however, a large proportion of the younger patients required vitamin supplement and further assessment for fracture risk. Improving our assessment of the above in routine clinical practice may better inform decisions regarding the clinical relevance of low BMD and vitamin D in those with AS.

Disclosures: The authors have declared no conflicts of interest.

296. TNF INHIBITORS IN AXIAL SPA/EARLY AS: TIME FOR A SHAKE-UP, IS NICE LISTENING?

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Background: TNF inhibitors (TNFi) are highly efficacious and safe in the treatment of AS. In the absence of a head to head comparison with NSAIDs they are the only agents proven to significantly improve the treatment of AS. In the absence of a head to head comparison with New York criteria (mNYC), Treatment efficacy is reported to be better in early disease stages and new treatment recommendations by ASAS recommend the use of TNFi in axial SpA (axSpA) or early AS. In order to ascertain UK rheumatologists’ current practice, we attempted to identify the current prevalence of TNFi prescription in established (mNYC) AS vs axSpA.
Background: There is an unacceptable delay to rheumatology referral for patients with SpA. Previous work has considered screening for SpA in clinics for associated conditions e.g. psoriasis. A specific form of HLA B27 associated acute anterior uveitis (AAU) is the most common extranodal manifestation of SpA and presents primarily to eye casualty departments. Service review elsewhere [1] showed that referral from ophthalmology was infrequent but had a high yield. We aimed to review the feasibility and likely yield of screening for SpA in patients presenting to eye casualty with this type of AAU.

Methods: We devised and piloted a screening questionnaire based on the work of Rudwaeleit [2] to elicit symptoms of SpA and presence of related conditions. After an educational programme including training and posters, the tool was used by eye casualty staff for consecutive patients presenting with AAU over 3 months. Hospital electronic records were used to confirm their ocular diagnosis.

Results: 118 questionnaires were completed in 92 days. 25 (21%) responses were deemed invalid; 17 had the wrong type of uveitis, others mainly for inadequate completion. Of the remaining 93, 24 were already known to have AS and 12 had other relevant conditions. 5 had psoriasis and 7 had IBD (5 Crohn’s disease, 2 ulcerative colitis). For those not already known to have SpA (n=69) the frequency of positive responses to the questionnaire are shown below:

(i) Reported features by patients with AAU, excluding AS patients
(ii) Known comorbidities: psoriasis 5 (7%); Crohn’s 5 (7%); ulcerative colitis 2 (3%)
(iii) Family history: psoriasis 8 (12%); AS 5 (7%); Crohn’s 6 (9%); ulcerative colitis 1 (1%)

Reported symptoms: back pain 34 (49%); radiation of pain to stiffness 10 (14%); joint swelling 18 (26%)

Conclusions: HLA B27 related AAU presents commonly to eye casualty departments. Our results suggest that a high proportion of such patients have symptoms which might indicate an undiagnosed SpA. Further work is needed to determine the specificity of such symptoms. Our work shows that the correct type of AAU is not universally recognized in eye casualty departments by non-specialist staff and so review in specialist uveitis or medical ophthalmology clinics may be required. These results suggest that targeted screening of those presenting with HLA B27 type AAU may identify a significant number of patients likely to have SpA, thereby reducing their referral delay to rheumatology and increasing the rate of prompt appropriate treatment.

Disclosures: L.K., Roche—Advisory Board, Pfizer—Speaker Fees. All other authors have declared no conflicts of interest.

References

298. EXPERIENCE AND EFFECTIVENESS OF EDUCATIONAL PROGRAMMES FOR PRIMARY CARE PHYSICIANS FOR EARLY DIAGNOSIS OF ANKYLOSING SPONDYLITIS IN KAZAN, RUSSIAN FEDERATION

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Background: To evaluate the effectiveness of educational programmes for primary care physicians in AS detection.

Methods: Educational schools on identifying features of inflammatory back pain, diagnosis and treatment of AS were conducted in Kazan (Russian Federation) from January 2009 to December 2010. Training included: AS, SpA and inflammatory low back pain criteria (ASAS), possible clinical picture at the onset of the disease (arthritis, uveitis, enthesitis etc.), the importance of timely assessment of laboratory parameters (ESR, CRP), X-ray evaluation, MRI evaluation, potential effects of disease-modifying therapy at the early stages of AS. The effectiveness of medical schools was evaluated according to an analysis report received from outpatient Municipal Rheumatology Centre in Kazan for 2009-2011 and the following parameters: number of patients consulted with AS, number of primary patients with AS, percentage of differences in diagnosis between rheumatologist and primary care physicians.

Results: The detection of AS improved significantly after training. Mean (±SD) average delay in diagnosis of AS reduced from 8.4 (2.4) years in 2009 to 3.5 (1.7) years in 2011. The share of patients with AS among all patients consulted by rheumatologists at Municipal Rheumatology Centre in Kazan increased to 6.3% (575 patients) in 2010 compared with 2009 (4.5%, 378 patients). The number of newly diagnosed patients with AS increased from 118 (31.2%) in 2008 to 190 (33.05%) in 2010. In 2009, the primary patients with AS were sent to rheumatologist by different doctors with diagnoses other than AS in 78% of cases. In 2010, the percentage difference between diagnosis of AS set up by rheumatologists and referral diagnoses decreased to 20.6%.

Conclusions: Educational programmes for primary care physicians are essential and contribute to early diagnosis of AS, the timely administration of therapy, which can improve quality of life and subsequently lower the percentage of physical disability among AS patients. Particular attention should be paid to the practical use of diagnostic criteria for inflammatory back pain, the importance of determining HLA-B27, and proper MRI and X-ray evaluation training. AS educational activities for primary care physicians in Kazan improved detection of the AS by primary care physicians and timely referral to a rheumatologist.

Disclosures: The authors have declared no conflicts of interest.

299. TNF INHIBITORS IN PSORIATIC ARTHRITIS: EFFECTS ON NAIL DISEASE—AN OBSERVATIONAL STUDY

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Background: Psoriatic nail disease is associated with pain, impaired physical function, cosmetic disturbance and reduced quality of life. There are limited data on the efficacy of TNF inhibitors (TNFi) for nail disease in patients with active PsA.
Background: The BASDAI is the most widely used measure of disease activity in AS and is a critical measure for assessing outcomes of treatment in AS. It relies on patients’ subjective appreciation of their symptoms. Patients’ perceptions of symptoms severe may vary over time irrespective of the efficacy of treatment. Other scoring systems, including measures of function, metrology, quality of life and inflammation are therefore important elements of assessments of disease activity. After observing variation in BASDAI measures in patients otherwise apparently continuing to respond well to TNF inhibitor (TNFi) treatment we reviewed sequential changes in BASDAI and visual analogue scale spinal pain (VAS SP) scores in patients on inhibitor (TNFi) treatment we reviewed sequential changes in BASDAI and visual analogue scale spinal pain (VAS SP) scores in patients on

Methods: A retrospective review of our local AS database was conducted. All patients who had received TNFi medication for over 250 weeks for whom complete datasets were available were included in the study. Patients who had switched biologic treatments within the time period included. BASDAI, BASFI, ASOQL and BASMI scores were recorded, as were ESR and CRP where available. All patients met modified New York Criteria for diagnosis of AS and eligibility for and response to TNFi treatments as defined by NICE.

Results: Data were collected for 26 patients (5 female) with AS. Mean duration of treatment was 370 (range 254–488) weeks. There were taking Adalimumab, 12 etanercept and 8 infliximab. The mean BASDAI score pre-treatment was 6.48 (range 4.16–9.35); this fell by a mean of 4.0 units at 24 weeks of treatment. The mean time to optimal (nadir) BASDAI response was 193 weeks (range 6–373), and mean time to nadir VAS SP scores was 113 weeks (range 6–320). Corresponding changes in acute phase response were seen. Treatment continued in all 11 patients and all reported a sustained symptomatic response.

Conclusions: Tendency of symptomatic clinical measures to revert to the mean is well recognized. This phenomenon, referred to by us as the BASDAI creep, appears to be a significant phenomenon in AS. This is likely to be multifactorial. In some this may reflect changing perception of current symptoms relative to baseline levels. In 5 patients treatment was continued despite failing to meet criteria for ongoing therapy on the basis of continued evident wellbeing and patient choice. If this reflects the reality of long-term treatment of AS the case for adopting more objective measures, such as the ASDAS, is compelling.

Disclosures: The authors have declared no conflicts of interest.

301. SPIRONOLACTONE IMPROVES ENDOTHELIAL DYSFUNCTION IN ANKYLOSING SPONDYLITIS

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Background: Inflammatory change in AS is associated with vascular endothelial dysfunction which leads to accelerated atherosclerosis. Accelerated atherosclerosis probably contributes to the increased cardiovascular mortality in AS. The aim of this study was to determine the effect of spironolactone on endothelial dysfunction in anti-TNF naïve AS patients.

Methods: 20 anti-TNF naïve AS patients (M/F = 15/5) with high disease activity (BASDAI >4) despite treatment with stable doses of conventional DMARDs were investigated. Inflammatory disease activity (BASDAI and BASFI, ESR and CRP levels); serum nitrite concentration, and endothelium-dependent and independent vasodilation of the brachial artery were measured at baseline and after 12 weeks of therapy with oral spironolactone 2 mg/kg/day. Ten healthy subjects matched for age and sex acted as the control.

Results: FMD in AS patients at baseline was significantly impaired as compared with a healthy control group (P < 0.001). After treatment: FMD improved from 11.3 ± 1.70 to 24.69 ± 2.34% (P < 0.001), nitrite concentration reduced from 7.9 ± 0.28 to 4.79 ± 0.19 µmol/l (P < 0.001), ESR from 33.8 ± 4.38 to 15.13 ± 1.30 mm in lst hr, (P = 0.001) and CRP level from 22.39 ± 3.80 to 6.3 ± 1.29 mg/dl (P < 0.001), BASDAI and BASFI reduced significantly (P < 0.001).

Conclusions: The study suggests that in AS endothelial dysfunction is a part of the disease process. This is the first study to show that treatment with spironolactone improves both endothelial dysfunction and inflammatory disease activity in AS.

Disclosures: The authors have declared no conflicts of interest.

302. TIME TO DIAGNOSIS IN AXIAL SPONDYLARTHITIS: A RETROSPECTIVE STUDY OF MILITARY PERSONNEL

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Background: Early diagnosis is the key to the successful management of axial spondylarthritides (SpA). Unfortunately, there is a well recognized delay: the most recent study by Feldtkeller et al (2003) reported an average time to diagnosis of 10 years. Within the military, a specific back pain pathway has been implemented promoting recognition of SpA and early referral to DMRC Headley Court, a specialist centre for the diagnosis and management of SpA. We believe that the time to diagnosis in axial SpA is shorter within the military compared with the general population and devised this study to test the hypothesis.

Methods: Service personnel attending the Axial SpA Inpatient Rehabilitation and Education (ASPIRE) course at DMRC Headley Court from March 2010 to November 2012 were identified. Information regarding age, time to diagnosis, radiological findings and the health care professional who confirmed the diagnosis was retrieved from medical records. In those cases where time to diagnosis was not clear, patients were contacted directly.

Results: Results from 132 patients were retrieved. The mean age of patients was 35.2 years with a male to female ratio of 10:1. 73.5% of patients had a diagnosis of AS, 20.5% undifferentiated axial SpA and 5.3% psoriatic spondylarthritides. The majority of patients received their diagnosis from a consultant (87.1%) and the most common methods of imaging were MRI (78.0%) and X-ray (80.6%). The mean time to diagnosis for all patients was 5.7 years, (range 0–25) from symptom onset. The difference in time to diagnosis between the sexes was marked with SpA being diagnosed on average 3 years later in women. There was no difference in time to diagnosis between patients with AS and axial SpA. Diagnosis was made in 10 years or less in 80.0% of the patients.

Conclusions: Patients in the military are diagnosed with axial SpA on average 4.3 years earlier when compared with an average 10 year delay in the general population. 80% of military personnel who attended rehabilitation at DMRC Headley Court received a diagnosis of axial SpA within this 10 year average. This reflects the increased awareness of military primary care doctors and physiotherapists, the accessibility of radiology resources and a clearly defined care pathway which encourages early specialist involvement.

Disclosures: The authors have declared no conflicts of interest.
303. DOES VITAMIN D STATUS AFFECT DISEASE ACTIVITY OR FUNCTIONALITY IN AS?
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Background: Vitamin D (25 (OH)D) plays an important role in the function of the immune system [1] and in the mineralization of bone [2]. AS is an autoimmune disease, affecting predominantly the axial skeleton, which is associated both with osteoporosis and with proliferative new bone formation; therefore, the level of 25 (OH)D may be important in the pathogenesis. 25 (OH)D deficiency is known to correlate with greater disease activity and disability in patients with RA [3]. We hypothesized that 25 (OH)D deficiency could be associated with greater disease activity and functional impairment in AS patients.

Methods: This was a retrospective cohort study. Electronic AS register was examined for the relationship between 25 (OH)D levels and BASDAI, BASFI and BASMI calculated at the time of blood test or immediately before the replacement of vitamin D. Patients in whom 25 (OH)D levels were not available were not included in the analysis (n = 36). 25 (OH)D deficiency was defined as <30 nmol/l. Total of 70 patients were identified for the study. Results were analysed using excel.

Results: Data from 55 males and 15 females with AS were analysed, of which 63% were HLAB27 positive. 81% were Caucasian and the mean age was 49 years old (range 20–78). 69% patients had AS for >12 years. 37% were in receipt of Biologics. 25 (OH)D deficiency was >36). 25 (OH)D deficiency was defined as <30 nmol/l. Total of 70 patients were identified for the study. Results were analysed using excel.

TABLE 1. Results

<table>
<thead>
<tr>
<th>25 (OH)D level, nmol/l</th>
<th>n=36</th>
<th>%</th>
<th>Mean BASDAI</th>
<th>Mean BASFI</th>
<th>Mean BASMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 (severe deficiency)</td>
<td>9</td>
<td>13</td>
<td>6.86</td>
<td>6.80</td>
<td>4.06</td>
</tr>
<tr>
<td>15–30 (deficiency)</td>
<td>28</td>
<td>40</td>
<td>6.24</td>
<td>5.94</td>
<td>5.87</td>
</tr>
<tr>
<td>&gt;30–50 (insufficiency)</td>
<td>18</td>
<td>26</td>
<td>5.83</td>
<td>5.09</td>
<td>5.04</td>
</tr>
<tr>
<td>&gt;50 (adequate status)</td>
<td>15</td>
<td>21</td>
<td>7.3</td>
<td>6.04</td>
<td>5.94</td>
</tr>
</tbody>
</table>

Conclusions: In AS patients, unlike in RA, no relationship between disease activity, functionality or metrology and level of 25 (OH)D. This was a retrospective cohort study. Electronic AS register was examined for the relationship between 25 (OH)D levels and BASDAI, BASFI and BASMI calculated at the time of blood test or immediately before the replacement of vitamin D. Patients in whom 25 (OH)D levels were not available were not included in the analysis (n = 36). 25 (OH)D deficiency was defined as <30 nmol/l. Total of 70 patients were identified for the study. Results were analysed using excel.

The authors have declared no conflicts of interest.

304. EXPLAINING FATIGUE IN ANCA-ASSOCIATED VASCULITIS
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Background: ANCA-associated vasculitis (AAV) is now considered a chronic disease and so person centred outcomes have become increasingly important. Patients identify fatigue to be the greatest burden of their disease and the principal cause of poor quality of life. Unfortunately there are no interventions which have been shown to alleviate this symptom and this, in part, relates to uncertainty about its underlying determinants. We therefore aimed to identify the determinants of fatigue amongst patients AAV in order to inform future fatigue specific interventions.

Methods: A UK multi-centre cross-sectional study was conducted. Subjects fulfilling the EMEA criteria for granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) were approached according to consecutive clinic attendance and invited to complete a questionnaire assessing fatigue and putative bio-psychosocial determinants of this symptom. Concurrently, potential clinical determinants were recorded. Independent associations of fatigue were identified using forward stepwise logistic regression modelling for which results are expressed as odds ratios (OR) and 95% CI. Their overall impact was further quantified using population attributable risks (PAR).

Results: The majority (74.8%) of participants (n = 410) reported high levels of fatigue which were found to be significantly associated with numerous bio-psychosocial and clinical factors. Sleep disturbance (OR 5.3, 95% CI 2.7, 10.5) and pain (OR 3.8, 95% CI 2.0, 7.3) were the strongest independent associates of fatigue and, on a population level, each more than twice as important as any other putative determinant (PAR: 18.1% and 16.5% respectively). Female gender (OR 2.1, 95% CI 1.1, 4.0), CRP (OR 3.7, 95% CI 1.7, 8.1) and the dysfunctional coping strategies of behavioural disengagement (OR 2.4, 95% CI 1.04, 5.6) and denial (OR 2.4, 95% CI 0.93, 6.7) were also independently associated.

Conclusions: AAV related fatigue is multi-factorial in origin. Sleep disturbance and pain were found to be the most important, although inflammation, as measured by CRP, also has a role. This study has identified potentially modifiable determinants of fatigue which will inform future interventions aimed at alleviating this vexing symptom.

Disclosures: The authors have declared no conflicts of interest.

305. GIANT CELL ARTERITIS: OVER-DIAGNOSED?
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Background: GCA is the most common vasculitis in the western world. It typically affects individuals greater than 55 years of age and has significant morbidity from its pathology and its treatment. There are no recent (after 2001) estimates of the occurrence in the UK. The UK general practice research database (GPRD) reported between 1990 and 2001 an incidence of 22/100,000 aged >55 years in a primary care. The aim of this study was to estimate the occurrence of GCA in the UK.

Methods: All temporal biopsy specimens performed at the Norfolk and Norwich University Hospital between 2003 and 2009 were reviewed. Cases of GCA were included only after careful case notes review with all cases fulfilling 1987 ACR criteria. The general practice GP location was noted for each of the included cases. The GP location was grouped into standard local authority boundaries. In cases where the individual practice population lay on a local authority boundary, the practice was classified into the local authority area which held the majority of the registered patients. The population denominator was calculated from national 2011 census data at 252 400 people. Incidence was calculated for the last 3 years of the study since robust data recording allowed for assured inclusion of cases of GCA with negative biopsy. 95% CI were calculated using the Poisson distribution.

Results: There were 325 temporal biopsies performed at the NNUH between the years 2003 and 2009. Subsequently 134 individuals were diagnosed with GCA (41.2%). The mean age diagnosis was 75.6 years, 97 were women (72.4%). Patients with GCA were significantly older (mean difference 4.1 years CI 1.3 to 6.9, P = 0.001) and had a statistically significant higher ESR (mean difference 44 mm/h, CI 34 to 54, P = 0.001) compared with individuals without GCA who underwent temporal artery biopsy.

There were 78 cases of GCA (15 biopsy negative—19.2%) diagnosed in this period (2007 to 2009). Four cases were excluded as they were from outside the denominator population. Of the remaining 74 cases of GCA came from 42 general practices in five

VASCULITIS

Poster Viewing III

Poster Viewing III

Poster Viewing III

Downloaded from https://academic.oup.com/rheumatology/article-abstract/52/suppl_1/i135/1929007?Basic-Science208-Stem-Cell-Factor-Expression-is
local authority areas. The incidence rate per 100,000 was 9.8 (95% CI 6.4, 14.7) in people aged >50 years and was 17.1 (95% CI 10.7, 25.3) per 100,000 <65 years.

Conclusions: The results reveal an estimate of 9.8 per 100,000 people aged >50 years. This is much lower than the estimate from the GPRD study carried out in 2001. Within the GPRD study only three out of a selection of 45 cases that were reviewed had a positive temporal artery biopsy (6.7%) and 10 cases (22.2%) were diagnosed and managed in primary care alone. These data suggest that in Norfolk at least 50% of cases of GCA are managed in the community without referral for temporal artery biopsy or specialist opinion to confirm the diagnosis before embarking on tocilizumab treatment.

Disclosures: The authors have declared no conflicts of interest.

306. TREATMENT-RELATED DAMAGE IN THE ANCA-ASSOCIATED VASCULITIDES: AN ANALYSIS OF THE EUROPEAN VASCULITIS STUDY GROUP THERAPEUTIC TRIALS

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Background: Granulomatosis with polyangiitis (Wegener’s) (GPA) and microscopic polyangiitis (MPA) are multisystem diseases known collectively as the antineutrophil-cytoplasm antibody associated vasculitides (AAVs). Damage accrued in AAVs can be quantified by use of the Vasculitis Damage Index (VDI), a validated 64 item checklist divided into 11 categories/domains which captures effects of both disease and therapy.

Methods: Data were merged from a long-term follow up questionnaire completed for patients from four European Vasculitis Study Group (EUVAS) therapeutic trials (N=535). 270 patients of the 535 patients from the trials had VDI data at baseline, 6 months, 12 months and long-term follow-up. Treatment related items were defined a priori. Categorical variables are expressed as frequencies with percentages. Chi-squared or Fisher’s exact tests were used to compare groups in terms of change in VDI scores over time.

Results: The length of time of follow up for the 270 patients was 6.94 years (IQR 2.04). The frequency of treatment-related cardiovascular VDI damage items rose significantly over time (Table 1, above). At long-term follow-up, hypertension was recorded in 4.8% (95% CI 3.0, 6.5). At baseline hypertension was recorded in 2.6% (95% CI 1.2, 4.7). Hypertension and diabetes increased over time (P=0.002), and myocardial infarction in 4.4% (95% CI 3.0, 6.0) at baseline increased significantly to 7.4% (95% CI 5.6, 9.3) at 10 years (P<0.001). The frequency of corticosteroid related VDI damage items also rose significantly. At long-term follow-up, osteoporosis was recorded in 14.1% (95% CI 12.1, 15.9). At baseline osteoporosis was recorded in 9.3% (95% CI 7.4, 11.4) with a significant increase over time (P=0.002). The percentage of affected patients at long-term follow-up being osteoporosis increased from 12.6% (95% CI 10.7, 14.6) at baseline to 25.3% (95% CI 22.8, 28.0) at long-term follow-up (P<0.001). At 10 years, 37.4% (95% CI 34.0, 40.9) of the 270 patients had no treatment related damage at long-term follow up, and 24 (23.7%) of the 101 had no VDI items recorded at all long-term follow-up.

Conclusions: In 270 patients with AAV, there is a significant increase in the frequency of treatment related damage items over time, most notably in terms of cardiovascular outcomes, diabetes, osteoporosis and malignancy.

Disclosures: The authors have declared no conflicts of interest.

Table 1: Frequency of recording of VDI items related to treatment over the course of long-term follow-up

<table>
<thead>
<tr>
<th>VDI item</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>LTUFW</th>
<th>% Change at LTUFW from 0 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>13 (4.8)</td>
<td>46 (17.0)</td>
<td>60 (22.2)</td>
<td>112 (41.9)**</td>
<td>+36.7 (30.8, 42.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0</td>
<td>4 (1.5)</td>
<td>12 (4.4)</td>
<td>38 (14.1)**</td>
<td>+14.1 (9.9, 18.2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>34 (12.6)**</td>
<td>+12.6 (8.6, 16.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (1.1)</td>
<td>17 (6.3)</td>
<td>22 (8.1)</td>
<td>28 (10.4)**</td>
<td>+9.3 (5.8, 12.7)</td>
</tr>
<tr>
<td>Angina/bypass</td>
<td>0.7 (0</td>
<td>3 (1.1)</td>
<td>4 (1.5)</td>
<td>22 (8.1)**</td>
<td>+7.4 (4.3, 10.6)</td>
</tr>
<tr>
<td>Cataract</td>
<td>2 (0.7)</td>
<td>5 (1.9)</td>
<td>8 (3.0)</td>
<td>25 (9.3)**</td>
<td>+8.5 (5.2, 11.9)</td>
</tr>
<tr>
<td>Arthro-shield weakness</td>
<td>6 (1.9)</td>
<td>14 (5.2)</td>
<td>16 (5.9)</td>
<td>20 (7.4)**</td>
<td>+5.6 (2.6, 8.5)</td>
</tr>
<tr>
<td>Alopica</td>
<td>0</td>
<td>11 (4.1)</td>
<td>19 (7.0)</td>
<td>23 (8.5)**</td>
<td>+8.5 (5.2, 11.9)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>10 (3.7)**</td>
<td>+3.7 (1.4, 6.0)</td>
</tr>
<tr>
<td>Mucocutaneous ulceration</td>
<td>1 (0.4)</td>
<td>4 (1.5)</td>
<td>5 (1.9)</td>
<td>4 (1.5)</td>
<td>+3.7 (1.4, 6.0)</td>
</tr>
<tr>
<td>Gonadal failure</td>
<td>2 (0.7)</td>
<td>6 (2.2)</td>
<td>8 (3.0)</td>
<td>11 (4.1)**</td>
<td>+3.3 (1.2, 5.5)</td>
</tr>
</tbody>
</table>

LTUFW (n=270). Data are shown as n (% of 270). *P<0.05; **P<0.01; ***P<0.001.

307. FAST-TRACK PATHWAY REDUCES VISION LOSS IN GIANT CELL ARTERITIS

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Background: Analogous to the ‘Time is Brain’ ACT-FAST campaign in stroke, ‘Time is Sight’ in GCA. The key issues in management are urgent recognition and prompt institution of corticosteroid therapy. A retrospective audit in 2009 demonstrated delays from symptom onset to diagnosis, with a high incidence of visual loss. This led to the implementation of a fast track pathway for suspected GCA in our catchment area.

Methods: A fast track referral pathway for suspected GCA was initiated in 2010 with formal agreement of the service between primary and secondary care in 2011. Patients were started immediately on high dose oral steroids by the referring doctor, and seen in rapid access GCA clinic within one working day. In the presence of ischaemia such as jaw pain or eye symptoms, patients were admitted for urgent medical attention and intravenous steroids. We report a retrospective case note audit from 2009 to October 2012 on the effects of the pathway on management with particular reference to ‘time to treatment’ and visual loss. Diagnosis of GCA was confirmed at second visit based on ACR 1990 criteria for GCA.

Results: The percentage of GCA patients presenting with vision loss between 2003 and 2011 varied from 23% to 29% in accordance with reported figures. In contrast, in 2012 only 1/25 (4%) patients presented with vision loss. This single patient was referred from outside the fast-track catchment area. The ‘symptom to steroid time’ decreased from 46.5 days (range 7–224) in 2008 to 23.25 days (range 1–168) from 2011 to date.

Conclusions: To our knowledge, this is the first reported implementation of a fast track GCA pathway. This required agreement between primary and secondary care, professional education, and rapid access GCA clinics with associated services such as urgent ophthalmology review and availability for temporal artery biopsy and ultrasound. Our data demonstrate that visual outcomes can be considerably improved by such a service, with striking decrease in proportions of patients with visual loss. However, although the symptom to steroid time has fallen, there is significant room for improvement. A Department of Health, BSR, RCGP and RCO working group is now evaluating its cost effectiveness and roll out of this fast track pathway across the UK.

Table 1. Visual loss in GCA

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of GCA patients</th>
<th>Number of GCA patients who lost vision (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–2008</td>
<td>60</td>
<td>19 (29)</td>
</tr>
<tr>
<td>2009</td>
<td>17</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>2010</td>
<td>26</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>2011</td>
<td>30</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>2012</td>
<td>15</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

308. SUCCESSFUL PREGNANCY OUTCOMES IN PATIENTS WITH ANCA VASCULITIS

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Background: There are limited data available on the outcomes of pregnancy in women with anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV). Previous publications describe frequent complications including first trimester miscarriages, pre-term birth, premature rupture of membranes and disease relapse resulting in fetal and maternal death. Many of these studies are old and based on isolated case reports. The objective of the current study was to describe recent pregnancy outcomes in women with AAV.

Methods: Retrospective case analysis of all women who became pregnant following a diagnosis of ANCA associated vasculitis in the cohort of patients treated in 3 UK centres.

Results: 10 pregnancies were observed in 8 patients following a diagnosis AAV (granulomatosis with polyangiitis n=7, microscopic polyangiitis n=1). All patients were in clinical remission with low or undetectable serum ANCA titres at the time of conception and had no other risk factors for antenatal complications. Methotrexate was discontinued in all patients with a planned pregnancy. Seven patients were managed with AZA in combination with prednisolone one patient was managed with prednisolone alone. One patient had a first trimester miscarriage following an unplanned pregnancy whilst taking MTX. One patient experienced a second trimester disease relapse which was treated successfully with immunoglobulin G and plasmapheresis and progressed with an otherwise uncomplicated pregnancy. Nine live births were observed with all infants born at full term by normal vaginal delivery with the exception of one patient with twin pregnancy and one patient with breech presentation who underwent an elective Caesarean section. There were no obstetric or neonatal complications and no disease relapse reported in the post-partum period.

Conclusions: Planned pregnancy during remission in ANCA associated vasculitis is safe with a low incidence of fetal and maternal complications. Patients should be on appropriate immunosuppression at conception. Disease relapse can be treated successfully without causing fetal complications.

Disclosures: The authors have declared no conflicts of interest.