Thursday 3 May, 10.30 – 11.30

POSTER VIEWING III

BASIC SCIENCE

232. CERTOLIZUMAB PEGOL PREVENTS PRO-INFLAMMATORY ALTERATIONS IN ENDOTHELIAL CELL FUNCTION

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Background: Cardiovascular disease is a major comorbidity of rheumatoid arthritis (RA) and a leading cause of death. Chronic systemic inflammation involving tumour necrosis factor alpha (TNF) could contribute to endothelial activation and atherogenesis. A number of anti-TNF therapies are in current use for the treatment of RA, including certolizumab pegol (CZP), (Cimzia ®; UCB, Belgium). Anti-TNF therapy has been associated with reduced clinical cardiovascular disease risk and ameliorated vascular function in RA patients. However, the specific effects of TNF inhibitors on endothelial cell function are largely unknown. Our aim was to investigate the mechanisms underpinning CZP effects on TNF-activated human endothelial cells.
Methods: Human aortic endothelial cells (HAoECs) were cultured in vitro and exposed to a) TNF alone, b) TNF plus CZP, or c) neither agent. Microarray analysis was used to examine the transcriptional profile of cells treated for 6 hrs and quantitative polymerase chain reaction (qPCR) analysed gene expression at 1, 3, 6 and 24 hrs. NF-κB localization and IκB degradation were investigated using immunocytochemistry, high content analysis and western blotting. Flow cytometry was conducted to detect microparticle release from HAoECs.
Results: Transcriptional profiling revealed that while TNF alone had strong effects on endothelial gene expression, TNF and CZP in combination produced a global gene expression pattern similar to untreated control. The two most highly up-regulated genes in response to TNF treatment were adhesion molecules E-selectin and VCAM-1 ($q < 0.00005$). This was supported by qPCR analysis at 6 hrs (E-selectin and VCAM-1; 208.5 fold and 40.5, respectively above control) and also at 1, 3 and 24 hrs (E-selectin; 25.6, 93.5, 12.7 fold, respectively) (VCAM-1; 4.7, 47.2, 17.6 fold) ($n = 3$; $p < 0.05$). In contrast, HAoECs treated with TNF in combination with CZP exhibited control levels of E-selectin and VCAM-1 transcript ($p > 0.2$ compared to control; $p > 0.05$ compared to TNF alone). The NF-κB pathway was confirmed as a downstream target of TNF-induced HAoEC activation, via nuclear translocation of NF-κB and degradation of IκB, effects which were abolished by treatment with CZP. In addition, flow cytometry detected an increased production of endothelial microparticles in TNF-activated HAoECs, which was prevented by treatment with CZP.
Conclusions: We have found at a cellular level that a clinically available TNF inhibitor, CZP reduces the expression of adhesion molecule expression, and prevents TNF-induced activation of the NF-κB pathway. Furthermore, CZP prevents the production of microparticles by activated endothelial cells. This could be central to the prevention of inflammatory environments underlying these conditions and measurement of microparticles has potential as a novel prognostic marker for future cardiovascular events in this patient group.
Disclosure statement: Y.A. received a research grant from UCB. I.B. received a research grant from UCB. S.H. received a research grant from UCB. All other authors have declared no conflicts of interest.

233. DEATH RECEPTOR 3 AND TL1A: A DRIVING FORCE IN OSTEOCLAST DIFFERENTIATION AND POTENTIAL TARGET FOR RHEUMATOID ARTHRITIS THERAPY

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Background: Advances in clinical management strategies and the availability of disease-modifying agents for rheumatoid arthritis (RA) means that newly diagnosed patients have a much better prognosis than those 20-30 years ago. However, inflammation-induced bone erosion cannot be prevented, leading to joint deformity, loss of function, pain, distress and eventual mortality in patients and an increased economic burden on society. Studies in a murine model of inflammatory arthritis have highlighted a key role for death receptor 3 (DR3) and its only known ligand TNF-like ligand 1A (TL1A) in regulating osteoclast (OC) differentiation and function, implicating DR3 as a significant regulator in bone (Bull MJ, Williams AS et al. J Exp Med. 2008). We hypothesize that TL1A propagates erosive joint pathology in patients with RA and investigate the potential mechanisms by which DR3/TL1A orchestrate osteoclastogenesis in an in vitro human model.
Methods: Ethical approval was granted by the Bro-Taf Health Authority. Serum samples were obtained from consenting RA patients and TL1A levels measured by ELISA. CD14+ monocytes were obtained from healthy, pre-menopausal, females. Cells were cultured in the presence of macrophage colony stimulating factor (M-CSF) for 7 days on ivory discs and DR3 expression confirmed by flow cytometry. Cells were cultured for a further 7 or 14 days in M-CSF and Receptor Activator for Nuclear Factor κ B Ligand (RANKL) ± TL1A at 10 ng/ml or 100 ng/ml. At termination % osteoclastogenesis and % area of disc resorbed were quantified. Supernatants were collected and levels of chemokine CCL2 measured by ELISA.
Results: TL1A levels were significantly elevated ($p < 0.05$) in serum collected from RA patients over normal healthy individuals. TL1A was also significantly higher in rheumatoid factor-positive RA patients with erosive disease over those who had non-erosive disease.

In vitro: At day 7, % osteoclastogenesis in cultures with TL1A was significantly higher than those without ($p = <0.01$). At day 14, a dose response was observable with % osteoclastogenesis in the 100 ng/ml TL1A cultures greater than both the 10 ng/ml and cultures without TL1A ($p = 0.01$).

At day 14, the % ivory disc resorption also showed a dose response with the greatest observed in the 100 ng/ml TL1A cultures and the least in cultures without TL1A ($p = <0.01$). TL1A significantly induced CCL2, levels of which were increased at day 3 and 7 compared to cultures without TL1A.
Conclusions: Our data supports the hypothesis that DR3/TL1A orchestrates erosive pathology in RA. TL1A has been shown to have a direct effect on the rate of osteoclastogenesis and thus increases the level of bone resorption in a dose dependent manner; through an early increase in CCL2. These findings could have important implications in the treatment of erosive RA, where TL1A levels have been shown to be elevated, via the development of novel DR3/TL1A targeted agents.
Disclosure statement: All authors have declared no conflicts of interest.

234. DISCOVERING CYTOKINE-SPECIFIC GENE EXPRESSION PROFILES IN INFLAMMATORY NEUTROPHILS USING WHOLE TRANSCRIPTOME SEQUENCING

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Background: There is a growing appreciation of the role of the inflammatory neutrophil in inflammatory diseases such as RA and JSLE. Neutrophils respond to inflammatory stimuli through the production of reactive oxygen metabolites (ROS) and proteases, which can damage host tissue if released inappropriately. Neutrophils also drive chronic inflammation via the secretion of inflammatory molecules such as cytokines, chemokines and leukotrienes. The aim of this study was to identify cytokine-specific signalling pathway activation using whole transcriptome sequencing of healthy neutrophils stimulated in vitro with mediators of inflammation.
Methods: Neutrophils were isolated from the venous blood of a healthy donor and incubated in vitro in the absence or presence of inflammatory cytokines (TNF or GM-CSF) for 1 h. RNA was isolated,

enriched for mRNA, fragmented and a cDNA library created. cDNA libraries were size selected for whole transcriptome sequencing on the ABI SOLiD sequencer. A mapping pipeline was developed to optimize mapping of reads to the human genome, using Bowtie and TopHat aligners. Cufflinks software was used to annotate genes and generate gene expression (RPKM) values. Statistical analysis of differentially expressed (DE) genes was carried out using CuffDiff (5% false discovery rate (FDR)) and signalling pathway analysis was carried out using Ingenuity Pathway Analysis software.
Results: The transcriptional profile of the resting neutrophil showed activation of pathways associated with specific neutrophil functions such as ROS production and phagocytosis, as well as more general cellular functions such as RNA processing and protein ubiquitination. 95 genes showed significant DE across the three samples (FDR adjusted q-value < 0.05). Cytokine treatment with TNF or GM-CSF activated transcription of both common and stimulus-specific genes. Genes upregulated by both stimuli included IL1B, ICAM1, BCL2A1, ETS2, PPP1R15A, G0S2, and OSM. Stimulation of neutrophils with TNF activated pathways associated with NF-κB signalling, death receptor signalling and production of chemokines such as CCL3 and CCL4, as well as autocrine production of TNF, whereas GM-CSF treatment activated pathways associated with delayed apoptosis and activation of JAK/STAT signalling.
Conclusions: These data enable us to compile cytokine-specific gene expression profiles for inflammatory neutrophils. These gene expression profiles could potentially be used as a diagnostic tool to measure key cytokines driving inflammatory disease on a patient by patient basis, thus enabling prediction of response to biologic therapies such as anti-TNF, Tocilizumab, Rituximab based on an individual patient's gene expression profile. The next stage of this study will be to measure gene expression profiles of anti-TNF responders and non-responders with a view to compiling a definitive list of genes that can predict response to therapy.
Disclosure statement: All authors have declared no conflicts of interest.

235. BLOCKADE OF CALCITONIN GENE-RELATED PEPTIDE RECEPTORS BY CGRP27-37 INHIBITS RESPONSES OF KNEE JOINT PRIMARY AFFERENTS IN THE MIA MODEL OF OSTEOARTHRITIS

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Background: Peripheral sensitization contributes to pain in knee osteoarthritis (OA). Peripatellar pain thresholds are lowered in human knee OA and knee joint afferents are sensitized to mechanical stimuli in the monosodium iodoacetate (MIA) rat OA pain model. The mechanisms of this sensitization are not well understood. Expression of the neuropeptide calcitonin gene-related peptide (CGRP) in knee afferents is increased in the MIA model. CGRP has a role in neurogenic inflammation and direct excitatory effects on sensory neurones. This study investigated the effects of a modified CGRP27-37 peptide antagonist on mechanical sensitivity of knee joint nociceptors in the MIA model.
Methods: Male Sprague-Dawley rats (242.78 ± 6.04 g) were injected (left knee) with MIA (1 mg/50μl; $n = 15$) or saline (50 μl; $n = 14$). Pain-like behaviour (hind-limb weight bearing and hind paw von Frey withdrawal thresholds) was tested at days 0, 3, 7 and 14 post-injection. 14 days post-injection rats were anaesthetized with sodium pentobarbital (50 mg/kg, i.p) and the external jugular vein, trachea and femoral artery were cannulated. Extracellular recordings were made from knee joint-associated afferents (receptive fields (RFs) over the ipsilateral knee) in response to von Frey stimulation (0.6-15 g, 5 s each / 5 mins). Once stable evoked responses were obtained, CGRP27-37 (5, 10 μg/100μl) ($n = 17$) or vehicle (2×100 μl saline) ($n = 12$) was peripherally injected (close i.a) and effects followed for 60mins. Conduction velocities were estimated (RF electrical stimulation; range = 0.45-13.1 ms-1; A- and C-fibres). CGRP27-37 was modified with proline and phenylalanine at positions 35 and 36, respectively (full sequence: FVPTNVGPFAF-NH2).
Results: MIA injected rats showed pain-like behaviour (reduced ipsilateral hind-limb weighting bearing and lowered ipsilateral von Frey paw withdrawal thresholds) prior to electrophysiology. CGRP27-37 (5 and 10μg) significantly inhibited mechanically evoked responses of knee joint afferents in MIA injected rats. CGRP27-37 also reversed the MIA-induced reduction in mechanical thresholds. CGRP27-37 had no effect on mechanically evoked knee joint afferent responses in saline control rats and did not alter mechanical thresholds. Vehicle had no significant effects on responses in either group.
Conclusions: Acute blockade of CGRP receptors significantly inhibited mechanically evoked responses of knee joint afferents in MIA rats suggesting CGRP may have a role in the maintenance of peripheral sensitization in OA pain. The present study indicates that blockade of the peripheral effects of CGRP with a CGRP antagonist could be a useful therapeutic strategy for modulating peripheral sensitization in OA. Further studies are required to clarify whether CGRP may be a therapeutic target for the treatment of OA pain.
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Disclosure statement: All authors have declared no conflicts of interest.

236. THE EFFECTS OF ACUTE EXPOSURE TO CIGARETTE SMOKE EXTRACT ON T CELL RECEPTOR SIGNALLING

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Background: T cells are important in adaptive immunity to infection, but inappropriate signalling through the T cell receptor (TCR), combined with unwanted responses to self-antigens, promotes development of autoimmune inflammatory diseases. Cigarette smoking is a prevalent environmental risk factor for rheumatoid arthritis, among other inflammatory diseases. However, the mechanisms behind its contribution to disease processes are not understood. Thus we investigated cigarette smoke extract (CSE) as a potential trigger for alterations in TCR signalling, which could promote disease.
Methods: CSE was generated from Marlboro Red cigarettes, and Jurkat T cells or peripheral blood mononuclear cells (PBMC's) were exposed to the diluted CSE for 24 hours, before a range of TCR signalling parameters were measured.
Results: Exposure to CSE caused a reduction in global protein tyrosine phosphatase (PTP) activity, as well as reductions in the activity of specific PTPs, namely CD45 and Lyp. There was reduced signal transduction overall, as demonstrated by decreased Ca2 + mobilization in response to TCR activation. Ca2+ release independent of the TCR remained unaltered. The mechanism by which CSE exerts its effects could be oxidative, as exposure of cells resulted in depletion of the antioxidant glutathione. It is likely that soluble components and particulate matter (PM) play a role, as removal of PM reduced the potency of the CSE.
Conclusions: Overall, acute exposure to CSE alters TCR activation, possibly through oxidation of key signalling proteins. This study shows that smoking can potentially alters T cell responses, which may contribute to impaired regulation of the immune system, thus promoting autoimmune inflammatory diseases.
Disclosure statement: All authors have declared no conflicts of interest.

237. AN ASSESSMENT OF CC CHEMOKINES PRESENT ON THE MICROVASCULATURE OF SYNOVIAL TISSUE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a destructive and chronic autoimmune inflammatory disease. The inflammation of the synovium is associated with the migration of inflammatory cells across the endothelial cells (ECs) of the microvasculature and local pannus invasion of cartilage and bone leading to their destruction via the action of proteinases.

Chemokines are essential factors in immune defence. They are involved in the generation, localization, recruitment and activation of leukocytes in response to inflammatory stimuli such as seen in RA. The CC chemokine family has the first two of four cysteine residues adjacent to each other and are the largest of the chemokine groups. Chemokines have been shown to be bound to the EC surface of the microvasculature. From here they enable leukocyte activation and transmigration from circulating blood into the tissue. A small number of chemokines have been shown to be present at RA synovial endothelial cells. However, the majority of the CC chemokines have not been specifically studied to assess their endothelial presentation and/or

expression in RA. Furthermore, the degree to which these chemokines are up or down regulated in the rheumatoid synovial tissue compared to non-inflamed synovial tissue, and their chemotactic effects have not been assessed. The purpose of this study was to assess which CC chemokines are present on the microvasculature of synovium from patients with RA.
Methods: RA synovial tissue was obtained from patients who fulfilled the American College of Rheumatology criteria for RA and were undergoing joint replacement surgery. Tissue samples were taken from the supratellar pouch or medial gutter. Sections of the tissue (5-6 μm) were cut, then dried before being stored at −80°C. Immunofluorescence histochemistry was used to assess the presence of the CC chemokines in RA synovial tissue. Their presence on the ECs was demonstrated using anti human von Willebrand Factor (vWF) as a pan endothelial marker.
Results: The number of vessels positive for vWF were counted over 4 fields of view (FOV) for each patient (n = 8) to a maximum of 15 vessels per FOV. The number of these vessels which were positive for each chemokine was also counted. A number of the 21 CC chemokines which have currently been assessed have never before been identified in RA ECs. These include CCL7, CCL14, CCL16, and CCL26 which are the most highly represented on the microvasculature of the rheumatoid synovium being seen on 70% 71%, 68%, and 58% of vWF positive vessels respectively.
Conclusions: In conclusion, this study contributes new information to the field with the identification of CC chemokines which have not been identified previously on RA microvascular endothelial cells. Chemokines such as CCL14 and CCL16 merit further investigation to ascertain their functionality in RA. Such information may further promote the understanding of the disease process and offer new therapeutic opportunities.
Disclosure statement: J.M. received a research grant from GlaxoSmithKline, and a consumables grant from Oswestry Rheumatology Association. L.R. received a PhD stipend from GlaxoSmithKline, and a consumables grant from Oswestry Rheumatology Association.

238. INVESTIGATING THE ROLE OF ENDOPLASMIC RETICULUM AMINOPEPTIDASE-1 IN ANKYLOSING SPONDYLITIS

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Background: Recent studies have shown that genetic variation within ERAP1, encoding endoplasmic reticulum aminopeptidase 1, is strongly associated with ankylosing spondylitis (AS). Within the endoplasmic reticulum, ERAP1 is involved in the trimming of peptides to the optimal length for their presentation by major histocompatibility complex (MHC) class 1 proteins, such as HLA-B27 that is also associated with AS. Here, we investigated the role of ERAP1 in AS pathogenesis by comparing the HLA-B27 expression on cell surface between ERAP1 competent and deficient cells.
Methods: ERAP1-siRNAs were generated and tested in transient transfection. The optimal sequence was selected to design ERAP1-shRNA, which was subsequently cloned to a Lentiviral vector for the production of ERAP1-shRNA lentivirus. Using this virus, we tried to stably silence the expression of ERAP1 on several human cell lines expressing HLA-B27, including LCL.721.221.B27, C1RB27 and HeLaB27 cells. Additioned from silencing ERAP1 in human cells, we also used a reverse approach using a ERAP1 deficient murine fibroblasts. The fibroblasts were firstly transduced to express HLA-B27, then we tried to stably express human ERAP1 using lentivirus.
Results: We have achieved more than 90% of ERAP1 silencing using LCL.721.221.B27 and HeLaB27 cells, and approximately 70% on C1RB27 cells. Using the ERAP1 -/- fibroblasts expressing HLA-B27, we also successfully transduced human ERAP1 to a level that is comparable to normal human cells. These cells are being used for functional studies, including the ability to present viral peptide epitopes to T cells.
Conclusions: Comparing immune function and cell surface expression of HLA-B27 between ERAP1 competent and deficient cells will be very informative for the better understanding of the role of ERAP1 in ankylosing spondylitis.
Disclosure statement: All authors have declared no conflicts of interest.

239. NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD+) BIOSYNTHESIS ENZYMES IN RHEUMATOID ARTHRITIS

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Background: Synovial fibroblasts display a 'hyperactive' phenotype in patients with rheumatoid arthritis (RA). NAD+ plays a role in cell metabolism, but may also be a key molecule in maintaining this 'activated' phenotype, in that enzymes that rely on NAD+ to function (e.g. sirtuins, poly (ADP-ribose)-polymerases (PARP), and ADP ribosyl cyclases) have far-reaching consequences on gene expression, apoptosis and Ca2+ signaling. In order to understand the principal pathway of NAD+ biosynthesis during normal synovial development, we investigated the expression of the principal enzymes in synovial tissue of normal and actively developing (i.e., pre-pubescent to adult) subjects. We also compared the expression of these enzymes in synovial tissue retrieved from RA, osteoarthritis (OA) and normal patients.
Methods: Synovial tissue was obtained from patients undergoing joint surgery and was either processed for RNA extraction or synoviocyte culture. Synoviocytes were serum-starved for 24 hours prior to cytokine stimulation. qPCR of Nicotinamide, Quinolinic acid and nicotinic acid phosphoribosyl transferases (Nam-PRT, Na-PRT and Q-PRT), Indoleamine 2,3 dioxygenase (IDO), nicotinamide mononucleotide adenyltransferase (Nmn-AT) 1 & 2 and NAD synthetase (NadSYN) was normalized to 18S, Ubiquitin C (UBC) and Actin β.
Results: Analysis of the enzymes involved in NAD+ biosynthesis were detectable by qPCR both in vivo and in vitro, with the exception of Nmn-AT3. Nam-PRT was highly expressed (RQ value = 15) in normal pre-pubertal subjects, which gradually decreased over time to reach 'normal' levels (RQ value = 1) by adulthood. The other NAD+ biosynthesis enzymes (NaPRT, IDO, QPRT, NMNAT 1 & 2 and NadSYN) showed no significant changes in gene expression relative to age. Synovial tissue retrieved from patients with RA show a subset of patients displaying skewed Nam-PRT expression, compared to normal adults, and patients with OA. Nam-PRT was significantly upregulated in vitro following cytokine (OSM, IFN-γ, IL-1β and TNFα) stimulation, in contrast to the expression of the other NAD+ biosynthesis enzymes. IDO was highly expressed following OSM and IFNγ stimulation
Conclusions: Nam-PRT is highly expressed in synovial tissue of young and actively developing subjects. We believe that Nam-PRT is regulated inappropriately and preferentially in patients with RA due to enhanced cytokine stimulation within these joints. Abnormal Nam-PRT activity may help to maintain an activated phenotype through enhanced NAD+ availability and we are currently investigating this. We have previously shown that a small molecule Nam-PRT inhibitor, APO866, limits arthritis progression in an experimental model of rheumatoid arthritis, thus we believe that manipulating Nam-PRT activity via small molecule inhibition may be a viable and cost-effective therapeutic strategy in RA, with healthy tissues continuing to synthesize NAD+ via alternative pathways (e.g. Nicotinic acid).
Disclosure statement: All authors have declared no conflicts of interest.

240. CHARACTERIZATION OF A PATIENTS' ANTIBODIES TO THE ANTI-CD20 THERAPEUTIC RITUXIMAB

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Background: Over the past three decades, biological therapeutics have come to play an important role in the treatment of cancer and autoimmune disease. However, their effectiveness has been compromised by neutralizing antibodies produced by patients' immune systems. This study used surface plasmon resonance (SPR) to describe the kinetic and thermodynamic characteristics of the anti-drug antibody (ADA) response made in a patient with systemic lupus erythematosus (SLE) following treatment with the chimeric monoclonal anti-CD20 antibody, Rituximab.
Methods: Following an initial good response to Rituximab in a patient with confirmed SLE, a second round of the drug failed to elicit a

response and the presence of ADA was confirmed by SPR analysis using a BIAcore 3000. Immunopurification of the ADA was carried out using affinity chromatography after coupling Rituximab to Sepharose beads. Differential pH fractionation was used to elute potential ADAs of varying affinities. Purity of ADAs was confirmed by Western blotting. Thermodynamic and kinetic analysis of the ADA samples was carried out using a BIAcore analysis. A temperature-dependent, thermodynamic model of the binding behaviour of the ADA-Rituximab complex was constructed with the integrated van't Hoff equation.

Results: Successful immuno-fractionation of the patient's serum produced samples of ADAs with similar, high affinity to Rituximab. The binding behaviour of the ADA to the drug was characterized by fast kinetics of binding (ka) - up to $4.13 \times 10\text{^}4\text{Ms^-1}$ - and a high overall affinity ($KD = 9.48 \times 10\text{^-9}\,M$), indicating a strong binding reaction. Thermodynamic analysis revealed that ADA-Rituximab binding was entropy-driven, with a highly positive entropy value ($T\Delta S = 60.55\text{kJmol^-1}$), and high temperature-dependence.

Conclusions: The results of this study reveal that the antibody response to Rituximab in this patient produced a homogenous family of ADAs that bind to Rituximab with great affinity. Surprisingly we found that this binding reaction is driven by entropy (the alignment of antibody and antigen) - challenging the established theory in which enthalpy (the energy of bond-formation) is said to drive antibody to antigens.

This is one of very few studies to describe the thermodynamic behaviour of human antibodies produced in a natural immune response. Our findings may suggest that previous studies, which have largely used animal responses driven by high levels of antigen and adjuvant may have produced unrepresentative results. There is now growing evidence that our current understanding of antibody-binding, at a thermodynamic level, at least, is incomplete.

The reasons for the very high affinity ADA response in this patient remain unclear but it may be characteristic of SLE patients in whom autoantibody levels are high. Further in-depth studies of ADA may reveal the reasons behind these responses and could be used to improve the clinical effectiveness of Rituximab therapy.

Disclosure statement: All authors have declared no conflicts of interest.

241. FUNCTIONAL AND EXPRESSION ANALYSIS OF COMPLEMENT C5 POLYMORPHISMS ASSOCIATED WITH RHEUMATOID ARTHRITIS

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Background: Complement (C) is a key component of the immune system with a central role of protecting against pathogenic infection. However, C also plays a role in propagating inflammation if activated excessively or inappropriately. Activation of C leads to release of proinflammatory molecules (anaphylatoxins) and assembly of the Membrane Attack Complex (MAC) which directly causes cell activation and tissue damage.

MAC assembly has been linked to pathophysiology of several rheumatological diseases, including Rheumatoid Arthritis (RA). In RA, C activation in affected joints perpetuates inflammation and recruits leukocytes to the site resulting in extensive tissue damage and propagating a 'vicious cycle' of inflammation. The C5/TRAF region has been strongly associated with RA in genome wide association studies. Here we study one polymorphic variant of C5 (rs17611) that has been shown to be overrepresented in the RA population, and investigate this link with pathology. The rs17611 C5 polymorphism is an A/G SNP (AA being the risk haplotype), resulting in the amino acid substitution - V802I. We assess how this variant may lead to differential expression and function of C5. We hypothesize that polymorphic variants in C5 may lead to increased MAC formation and result in exacerbated tissue damage in RA.

Methods: Healthy donors for common RA-associated C5 polymorphisms were identified by genotyping. Novel, in-house antibodies were used to generate a C5 sandwich ELISA. The assay was quality controlled for both intra and inter assay reliability and was shown to have a sensitivity of 40 ng/ml. Haemolytic assays were performed using purified C5 variants, to allow comparison of the rate of MAC formation on target erythrocytes.

Results: We have genotyped a cohort of healthy individuals for the rs17611 polymorphism. In line with previously published data, we observe a population of 54% A:G heterozygotes, 35% G:G homozygotes and 11% A:A homozygotes. The plasma levels of C5 were measured in this cohort using a novel C5 ELISA, and levels were related to polymorphic status. Purification of C5 variants from homozygous donors has been optimized and functional differences have been investigated using haemolysis assays. Add-back haemolysis assays reveal that the functional differences are minor, as would be expected for a common variant, and more sensitive assays are currently being developed to interrogate differential formation of C5b6 and the rate of MAC formation.

Conclusions: C5 is a central C component involved in the formation of the MAC (as C5b) and in promoting inflammation (via C5a). Our preliminary results suggest that the differences in MAC forming capacity of rs17611 variants are minor; therefore the pathogenic link of this SNP may be explained by changes in protein expression and/or other functional effects. RA associated polymorphisms in the C5/TRAF region may substantially affect the expression of C5 and function of the terminal C pathway.

Disclosure statement: All authors have declared no conflicts of interest.

242. HLA-B27 HEAVY CHAIN DIMER EXPRESSION IN SPONDYLOARTHRITIS

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Background: The strong association of human leukocyte antigen HLA-B27 with a group of spondyloarthropathies (SpA), particularly with Ankylosing Spondylitis (AS), led our research group to the discovery of B27 heavy chain dimer (B272) formation. We proposed that these unique molecules may influence immune homeostasis and cause the disease. Generation of a specific antibody to B272 would enable us not only to determine differences in cell surface expression of B272 but moreover to investigate the mechanisms which drive dimer formation.

Methods: HD6 antibody (Ab) was generated by phage display technology. HD6 unlabeled or Alexa Fluor 647 (Invitrogen)-conjugated Abs along with control Abs (ME-1, HC-10, W6/32) were used to determine B272 cell surface expression levels and patterns by flow cytometry of HLA-B27 transfected/non-transfected HeLa cells, human B cell lines LBL721.220 (.220) and LBL721.221 (.221) and AS patient and control peripheral mononuclear blood cells (PBMC). Cytospin and staining with primary HD6, ME-1, W6/32 or Isotype control mAb and secondary anti-mouse Fc-HRP Ab were performed using HLA-B27 transfected/non-transfected .220 cells and analysed by light microscopy. Fluorochrome conjugated antibodies were used for confocal microscopy experiments.

Results: 1) The specificity of HD6 antibody binding to cell surface-expressed heavy chain B27 dimers was confirmed by FACS experiments in both HLA-B27 transfected cell lines and in AS patient PBMCs. 2) The immunohistochemistry .220 HLA-B27 transfected cells with HD6 Ab and control Abs further acknowledged FACS results. 3) Ongoing confocal microscopy experiments will help us to further understand abnormal cell surface and intracellular expression of B272 on live and fixed cells and investigate its role in AS pathogenesis.

Conclusions: Our flow cytometry and immunohistochemistry experiments confirmed HD6

antibody staining of AS patient cells and HLA-B27 transfected cell lines, consistent with B27 heavy chain B27 dimer expression. These findings permit further investigation of the disease mechanisms and open potential novel opportunities for AS treatment. Ongoing confocal microscopy experiments will give us an insight into the dimer formation process, its kinetics and the trafficking of B272 molecules in cell compartments following different stimulatory and environmental factors.

Disclosure statement: All authors have declared no conflicts of interest.

243. ECTOPIC LYMPHONEOGENESIS IN A NOVEL MURINE MODEL OF SALIVARY GLANDS SIALOADENITIS IS CHARACTERIZED BY ASYNCHRONY IN THE LYMPHANGIOGENETIC AND ANGIOGENETIC PROGRAM

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Background: Defective drainage of inflammatory cells from sites of chronic inflammation has been suggested to play a role in the sustenance of the inflammatory process. Secondary lymphoid organs are characterized by concordance in time, function and response to stimuli between the lymphatic and vascular system. Here we use a novel inducible model of resolving ectopic lymphoneogenesis, in adenoviral infected murine salivary glands, to evaluate the relationship between the two vascular systems within developing tertiary lymphoid tissue.
Methods: Whole tissue disaggregation and histological analysis of ectopic lymphoid structures in salivary glands of mice cannulated with 10^8 p.f.u. of lac-Z or luciferase expressing adenovirus was performed at different time points post cannulation (p.c.). FACS sorting was used to identify in digested tissues the lympho/monocyte component (CD45+ cells) and, within the stromal cell compartment (CD45- cells), CD45-EPCAM-CD31+GP38- endothelial and CD45-EPCAM-CD31 + GP38+ lymphatic cells. Immunofluorescence (IF) was used to validate the FACS data and establish the histological relationship between the lymphatic and the vascular system within the inflamed samples.
Results: Data obtained by FACS analysis of salivary gland tissue taken at regular time-points post-infection showed a significant deflection in the percentage of blood endothelial cells (CD45-EPCAM-CD31 + GP38-) in the early phases of the inflammatory process, followed by a progressive return to resting conditions during resolution. A bimodal trend in the number of lymphatic endothelial cells (CD45-EPCAM-CD31 + GP38+) was observed with a significant increase in the early phase, followed by a significant decrease at the peak of the inflammatory process and a drastic increase during resolution. This trend corresponded with the two phases of innate and acquired immune cell infiltration in the glands. Of interest, the inflamed glands were characterized by formation of CD31 + high endothelial venules. A significant change in the number and shape of the lymphatic vessels was observed by immunofluorescence. Small resting lymphatics were engulfed with leukocytes and appear to progressively increase in size during the early phases and peak of inflammation. At resolution a lower number of larger vessels was observed.
Conclusions: In secondary lymphoid organs the homeostatic relationship between lymphatic and vascular system is known to be exquisitely regulated to maintain optimal leukocyte recirculation through the organ. Here we demonstrate that in ectopic tertiary lymphoneogenesis this relationship is altered until resolution occurs. The inability of ectopic lymphoneogenesis to finally recapitulate all physiological programming of secondary lymphoid organs might explain its critical association with the inability to resolve inflammation and lead to disease persistence.
Disclosure statement: All authors have declared no conflicts of interest.

244. COOPERATION OF INNATE AND ACQUIRED IMMUNE SYSTEM DERIVED SIGNALS INDUCES STROMAL CELL ACTIVATION DURING CHRONIC INFLAMMATION AND ECTOPIC LYMPHONEOGENESIS

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Background: Acquisition of lymphoid-like features is a hallmark of ectopic lymphoneogenesis. In lymph nodes, gp38+ fibroblastic reticular cells (FRC) are responsible for lymphoid chemokines/cytokine production and lymphocyte compartmentalization. Gp38 up-regulation on stromal cells has been observed in in cancer and inflammation, suggesting that stroma can acquire lymphoid like features in these conditions. IL-22 and IL-4 are produced by a novel population of innate lymphoid cells (ILCs), similar to lymphoid tissue inducer cells, which have been shown to be critical regulators of stromal cell activation in lymphoneogenesis. The role of ILCs in the context of stromal cell activation in inflammation is unknown.
Methods: We designed a novel inducible model of ectopic lymphoneogenesis, in adenoviral infected murine salivary glands to evaluate the dynamics of gp38 expression and investigate the signals regulating stromal cell activation in different phases of inflammation. Flow cytometry on disaggregated tissue, qRT-PCR and immunofluorescence was performed at different time points post cannulation (p.c.) in WT and knockout mice (IL-4R-/-, IL-22-/-, rag-/-, Lta-/-, LTbR-/-) in order to investigate the role of these molecules in stromal cell activation.
Results: FACS analysis showed that in WT mice stromal cell activation occurs with significant increase in the percentage of FRC (CD45-GP38 + CD31- cells) at day 2 and day 5 with peak of activation at day 8pc. By day 15-18pc. there was full acquisition of lymphoid features with high levels of LTa, LTb and lymphoid chemokine expression. This correlates with acquisition of lymphoid features by the inflammatory aggregates. IL-7 signal increased early in the cannulated animals following the trend of stromal cell activation, which was distinct with other lymphoid cytokines. In absence of IL-22 and IL-4 signals a severe defect in innate immune system activation was observed with lack of gp38 up-regulation at day 2, 5 and 8. Day 15 samples showed a progressive increase of the gp38 component, suggesting that at this stage a critical mass of infiltrating leucocytes is reached, which are able to provide factors to induce stromal cell activation. We confirmed this hypothesis by cannulating RAG, LTa and LTbeta KO mice that showed normal degree of stromal cell activation in the early phases (2-5 days p.c.) but a dramatic decrease in the number of FRCs by day 15. This associates with a significant decrease in lymphoid chemokine/cytokine expression and disorganization of the inflammatory aggregates.
Conclusions: These data suggest that stromal cell activation in ectopic sites results from the coordinated actions of signals derived by both the innate and acquired immune system. While ILC are able to elicit the early maturation of local stroma and gp38 acquisition, later maturation of lymphoid stromal requires leukocytes derived signals and Lta and LTb.
Disclosure statement: All authors have declared no conflicts of interest.

245. INFLAMMATORY CYTOKINES AND BIOENGINEERING STRATEGIES FOR ARTHRITIS: FRIEND OR FOE?

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Background: Despite the development of skeletal or mesenchymal stem cell (MSC) constructs aimed at creating viable cartilage and bone, few studies have examined the effects of the inflammatory cytokines present in rheumatoid arthritis (RA) and osteoarthritis (OA) synovial tissues, or inhibition of these, on such constructs in a reparative context. This work addresses these issues using both in vitro and in vivo approaches and potential ways of overcoming the effects of cytokines on the integrity of bone and cartilage constructs.
Methods: Synovial samples were obtained, with informed consent, from RA or OA (n = 20) patients undergoing primary hip or knee arthroplasty at University Hospital Southampton NHS Foundation Trust with ethical approval. Control bone marrow-derived MSCs obtained from patients undergoing fractured neck of femur repair were cultured in basal (minimum essential medium alpha (alpha MEM) + 10% fetal calf serum) or osteogenic (basal + ascorbate + dexamethasone) conditions. Differentiation towards bone and cartilage was assessed using alkaline phosphatase (ALP) staining, ALP and DNA biochemical assays and real time polymerase chain reaction (qPCR). Exogenous interleukin-1 (IL-1) (10 ng/mL), tumour necrosis factor alpha (TNFalpha) (10 ng/mL) or interleukin-6 (IL-6) (100 ng/mL) was then added and effects on differentiation noted. RA and OA synovial samples were digested, cultured for 48 hours then centrifuged to produce supernatants. Cytokine profiles were determined using ELISA. Supernatants were then added to MSCs and their effects on differentiation assessed.
Results: MSCs cultured in osteogenic media with IL-1 showed an additive osteogenic effect (increased ALP specific activity) on biochemical assays ($p < 0.05$). TNF exerted a less marked and IL-6 no apparent effect on osteogenic differentiation. Critically, this effect was maintained out to passage five. Human fetal cell cultures from three patients were used as a positive control and replicated these findings. In addition, molecular studies using qPCR showed corresponding increases in ALP gene expression in the presence of IL-1. Addition of synovial supernatants at a 1:10 dilution to MSC cultures produced a marked osteogenic profile, with increased ALP specific activity. This was IL-1 and TNFalpha concentration dependent, correlating with lower supernatant dilutions on initial ELISA analysis.
Conclusions: This study indicates that exogenous IL-1 and TNFalpha modulate the osteogenic phenotype in MSCs in vitro and that OA and RA synovial supernatants affect skeletal cell differentiation. Variations in cytokine profiles between supernatants require analysis for potential

confounders. Current studies are in progress across larger patient numbers using immunoselected skeletal stem cells (Stro-1 + ve cells). The effects of cytokines on skeletal cell differentiation on commercially available scaffolds both in vitro and in an in vivo murine model of bone formation will also be assessed.
Disclosure statement: All authors have declared no conflicts of interest.

BIOLOGY OF BONE, CARTILAGE AND CONNECTIVE TISSUE DISEASE

246. THE EFFECTS OF CANNABINOIDS ON IL-1 INDUCED MATRIX METALLOPROTEINASE EXPRESSION

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Background: A key feature of osteoarthritis and rheumatoid arthritis is the loss of articular cartilage. Cartilage breakdown is mediated by complex interactions of proinflammatory cytokines such as interleukin 1 (IL-1), inflammatory mediators including nitric oxide and prostaglandin E2 and proteases including matrix metalloproteinases (MMPs) and aggrecanases such as ADAMTS-4 and -5. The *Cannabis Sativa* plant is the source of 60 different cannabinoids. Cannabinoids have been shown to reduce joint damage in animal models of arthritis. They have also been shown to prevent IL-1 induced matrix breakdown of collagen and proteoglycan, suggesting a chondroprotective effect of these compounds. We have studied the effects of the synthetic cannabinoid WIN-55, 212-2 (WIN-55) on IL-1- induced MMP -3 and -13 and ADAMTS-4 gene expression in primary human chondrocytes in high density monolayer and 3D culture systems of cell pellets and alginate beads.
Methods: Primary human chondrocytes were obtained from patients undergoing total knee replacements. Chondrocytes were investigated in high density monolayers and in 3D pellet and alginate cultures following 4 weeks of culture to induce re-differentiation to a chondrocytic phenotype. Cells in 3D culture and monolayer were treated with cannabinoid WIN-55 with and without IL-1 stimulation for 48 h. RNA was extracted using TRIZOl reagent, reverse transcribed and real time qPCR was used to investigate the expression of matrix degrading enzymes MMP-3, -13 and ADAMTS-4 following WIN-55 and IL-1 stimulation.
Results: IL-1 treatment of primary human chondrocytes induced MMP-3, -13 and ADAMTS-4 gene expression. Stimulation with IL-1 in combination with WIN-55 showed inhibition of the IL-1 induced MMP-3, -13 and ADAMTS-4 gene expression.
Conclusions: The results suggest that WIN-55 can inhibit the catabolic actions of IL-1 in primary human chondrocytes. IL-1 is a well known mediator of cartilage degradation, thus the inhibition of IL-1 induced expression of MMPs and ADAMTS-4 shown here suggests that cannabinoids could provide a model for the development of novel therapeutic agents for arthritis.
Disclosure statement: All authors have declared no conflicts of interest.

CELL RECEPTOR–LIGAND INTERACTION, SIGNALLING, ACTIVATION AND APOPTOSIS

247. INTRACELLULAR SIGNALLING MECHANISMS INDUCED BY IL-1 IN HUMAN NUCLEUS PULPOSUS CELLS

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Background: Intervertebral disc (IVD) degeneration is a major cause of lower back pain. Evidence suggests that inflammatory cytokines produced by chondrocyte-like cells within the IVD during degeneration are integral in the pathogenesis of this disease, with a particular role for IL-1 hypothesized. Targeting intracellular signalling mechanisms of IL-1 could provide a mechanism to inhibit multiple catabolic cytokines simultaneously. Many cytokines share intracellular signalling pathways and thus inhibiting signalling rather than direct receptors could prevent compensatory actions occurring. However a complete understanding of the multitude of signalling pathways activated by catabolic cytokines is essential to enable such an approach.
Methods: Human nucleus pulposus (NP) cells were extracted via collagenase digestion and expanded in monolayer culture. Cells were treated with IL-1 in monolayer to investigate NFkB activation or cultured in alginate bead culture for 2 weeks to induce differentiation. Cells were treated with IL-1 (0,1,10,100 ng/ml) from 10 minutes up to 6 hrs. Following stimulation in alginate activation of pERK, pP38 MAPK and JNK were investigated using BD phosflow techniques, NFkB activation was investigated via dual IkB/NFkB immunofluorescence and R&D proteome array used to identify alternative signaling pathways.
Results: Activation of ERK1/2, P38 MAPK and AKT signalling pathways were detected using BD phosflow techniques with maximal responses seen following 30 minutes IL-1 stimulation. Activation of the NFkB pathway, with decreased expression of the inhibitory protein (IkB) enabling the translocation of NFkB to the nucleus was also seen following IL-1 stimulation. R&D proteosome arrays enabled the investigation of 46 signalling molecules simultaneously following 10 ng/ml IL-1 stimulation for 5 and 20 minutes, following 5 minutes no signalling molecule was seen to be activated, however following 20 minutes a number of key signalling molecules were activated evidenced by upregulation of the phosphorylated protein.
Conclusions: The catabolic cytokine IL-1 has been implicated in the pathogenesis of IVD degeneration which leads to low back pain. Here we identify a number of signalling pathways activated by IL-1. Elucidation of which of these pathways are specific to catabolic processes is essential to identify potential new targets for IVD regeneration therapies, and new methods of modulating the catabolic response.
Disclosure statement: All authors have declared no conflicts of interest.

248. THE ROLE OF HLA-B27 KIR3DL2 INTERACTIONS IN THE PATHOGENESIS OF SPONDYLOARTHRITIS

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Background: Ankylosing Spondylitis (AS), the commonest spondyloarthropathy, is genetically associated with HLA-B27 (B27) and genes involved in regulation of IL17 production, including the IL23 receptor. Previously we have shown that B27 can be expressed at the surface of antigen presenting cells (APC) both as classical β2microglobulin-associated heterotrimeric and β2microglobulin-free disulphide-bonded heavy chain homodimers (termed $B27_2$. Ligation of KIR3DL2 by $B27_2$ promotes the survival of KIR3DL2 CD4 T cells. KIR3DL2 + expressing CD4 T cells are expanded in the peripheral blood of individuals with AS and are an important source of IL17 production. Since KIR3DL2 can also bind to other class I including HLA-A3 we investigated whether stronger binding of $B27_2$ to KIR3DL2 could promote enhanced survival of KIR3DL2-expressing leukocytes and might explain the differential association of HLA-B27 with AS compared with other ligands.
Methods: Binding of $B27_2$ and other class I to KIR3DL2-expressing cells was investigated by tetramer competition and FACS staining. KIR3DL2Fc binding to cells transfected with HLA-B27 and control HLA- class 1 was also assessed. We studied activation and survival of Jurkat T cells transduced with KIR3DL2 and KIR3DL2CD3ε constructs. We compared proliferation, survival and cytokine production of CFSE-labelled KIR3DL2+ T cells from AS patients and control peripheral blood mononuclear cells (PBMC) or cells stimulated with APC expressing $B27_2$ or control HLA class I by FACS analysis and ELISA.
Results: $B27_2$ tetramers bound more strongly to KIR3DL2 transfectants and competed more effectively for binding to KIR3DL2 than HLA-A3. KIR3DL2Fc FACS stained HLA-B27 transfected 221 cells more strongly than cells transfected with HLA-A3. KIR3DL2-expressing Jurkat T cells stimulated with superantigen presented by $B27_2$ expressing APC survived more compared to stimulation with control

APC. $B27_2$-expressing APC stimulated greater production of IL-2 by KIR3DL2CD3ε transduced T cells compared to stimulation with control APC (resting 15.06+/-2 pg/ml: +$B27_2$ 813+/-54 pg/ml; +HLA-A3 192+/-24 pg/ml; HLA-B35 65+/-3 pg/ml; mean+/-SD). Peripheral blood KIR3DL2 expressing T cells but not T cells expressing other KIR expanded more than T cells from healthy and rheumatoid arthritis controls in response to superantigen presented by syngeneic APC. KIR3DL2 interactions with B27 were inhibited by B27 dimer and heavy chain antibodies and recombinant LILRB2 protein which binds strongly to B27 dimers.

Conclusions: The enhanced survival of KIR3DL2-expressing leukocytes in AS patients could result from increased avidity of interaction with $B27_2$ compared with other HLA class I ligands. We propose that $B27_2$ KIR3DL2 interactions drive the expansion of proinflammatory NK and CD4 T cells in disease. Targeting these interactions could provide new therapeutic avenues for the treatment of AS disease.

Disclosure statement: All authors have declared no conflicts of interest.

CYTOKINES AND INFLAMMATORY MEDIATORS

249. CONVENTIONAL THERAPY FOR EARLY INFLAMMATORY ARTHRITIS DOES NOT MODIFY PERIPHERAL BLOOD CYTOKINE PROFILES

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Background: Prognosis of patients with early inflammatory arthritis (EIA) is highly variable. We compared levels of cytokine expressing cells in EIA, established rheumatoid arthritis (RA) and healthy controls (HC), and followed EIA patients over 1 year to correlate with changes in disease activity and peripheral blood cytokines and chemokines.

Methods: Peripheral blood mononuclear cells from HC (n = 30), patients with EIA (n = 20) or RA (n = 38) were stimulated with PMA/Ionomycin for 3 hours then stained for cell markers and cytokines. Serum cytokines and chemokines were measured by luminex. Patients with EIA were reassessed at 6 and 12 months.

Results: The percentage of IL-17 + CD4+ T cells, but not the %IFNγ+CD4+ T cells or %TNFα+ monocytes, was increased in RA (median 0.59; IQR 0.38, 1.55) and EIA (0.81; 0.15, 1.46) vs. HC (0.40; 0.24, 0.65; $p = 0.0043$ by Kruskal-Wallis test, $p < 0.05$ for RA and EIA vs. HC by Dunn's post test). Serum IL-17, IL-1β, MIP-1α, IL-15, TNFα and IL-2 were increased in RA and EIA vs. HC, and IL-1Ra and IL-8 were increased in EIA vs. HC. IL-6 was increased in RA but not EIA vs. HC.

In EIA, %IL-17+CD4+ T cells at baseline was positively correlated with both RF titre ($r = 0.587$, $p < 0.01$) and HAQ ($r = 0.574$, $p < 0.03$) at 12 months, and %IFNγ + CD4+ T cells was negatively correlated with initial patient global assessment ($r = -0.673$, $p < 0.01$) and baseline CRP ($r = -0.573$, $p < 0.01$). Baseline %IL-6 + monocytes was correlated with CRP at 12 months ($r = 0.603$, $p < 0.01$), but baseline %TNFα+ monocytes was negatively correlated with both ESR ($r = -0.66$, $p < 0.01$) and TJ ($r = -0.52$, $p < 0.03$) at 12 months.

Mean DAS28 in EIA patients at baseline was 5.3 vs. 4.5 after 12 months despite use of DMARDs ± steroids, similar to data from the methotrexate monotherapy arm in a large clinical trial involving patients with early RA1. There were no significant changes in cytokine expressing CD4 + T cells over time, although %IL-6 + monocytes increased.

Conclusions: DMARDs, with or without steroids do not impact significantly on the presence of inflammatory cytokine producing T cells and monocytes in peripheral blood from patients with early inflammatory arthritis. This was accompanied by incomplete clinical response, suggesting that more intensive therapy is required early in the disease process.

TABLE 1 Serum cytokines in patients with EIA, RA and healthy controls

	EIA (baseline)	RA	HC
IL-17 pg/ml	23 (20, 60)*	26 (18, 48)*	18 (25, 20)
IL-1β pg/ml	53 (35, 56)**	56 (59, 129)**	24 (20, 31)
IL-2 pg/ml	22 (18, 32)*	24 (15, 43)*	15 (14, 19)
MIP1α pg/ml	39 (35, 65)**	41 (32, 61)**	30 (29, 35)
TNFα pg/ml	36 (29, 46)	45 (33, 98)*	28 (24, 32)
IL-8 pg/ml	114 (61, 184)*	102 (76, 139)	23 (17, 49)
IL-15 pg/ml	37 (33, 74)**	31 (27, 53)	27 (24, 30)
IL-6 pg/ml	31 (16, 53)	67 (30, 105)*	23 (17, 49)

Data expressed as median with inter-quartile range; **$p < 0.01$; *$p < 0.05$ vs. HC (Kruskal-Wallis with Dunn's post test).

Disclosure statement: All authors have declared no conflicts of interest.

Reference

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250. SAFETY AND PHARMACOKINETICS OF CDP6038, AN ANTI-IL-6 MONOCLONAL ANTIBODY, ADMINISTERED BY SUBCUTANEOUS INJECTION AND INTRAVENOUS INFUSION TO HEALTHY MALE VOLUNTEERS: A PHASE 1 STUDY

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Background: CDP6038 is a potent anti-interleukin-6 (IL-6) monoclonal antibody that selectively blocks the final assembly step of the IL-6 signalling complex, which is important in rheumatoid arthritis (RA) pathogenesis. CDP6038 is in phase 2 development for the treatment of moderate to severe RA. This phase 1 study evaluates the safety and pharmacokinetics (PK) of intravenous (iv) and subcutaneous (sc) CDP6038 in healthy volunteers.

Methods: This single-centre, double-blind, placebo (PBO)-controlled, dose-escalation study comprised 11 treatment groups. Six healthy males per group were randomized 1:1 to receive either 1 of 8 single iv doses of CDP6038 (ranging from 0.001 to 10.0 mg/kg) or PBO, or 1 of 3 single sc doses of CDP6038 (0.3, 1.0 or 3.0 mg/kg) or PBO. The primary endpoint was the safety of CDP6038 over 14 wks. Plasma concentrations of CDP6038 were measured for PK analysis.

Results: 67 subjects were randomized (CDP6038 n = 33; PBO n = 34, including 1 per-protocol replacement). No deaths or serious treatment-emergent adverse events (TEAEs) were reported. The overall incidence of TEAEs was higher with PBO compared to CDP6038 (52.9% vs 33.3%). The incidence of vomiting was higher with CDP6038 (6.1% vs 0%). The incidence of TEAEs did not increase with increasing CDP6038 dose. Most TEAEs were Grade 1 using CTCAE v3.0 and 4.0 criteria except a Grade 4 rise in creatinine kinase level and a Grade 3 rise in aspartate aminotransferase level in 1 subject (CDP6038 0.3 mg/kg iv group; both events transitory after intense exercise) and 2 Grade 3 events of toothache (1 subject each on iv PBO and CDP6038 1.0 mg/kg sc); none of these were considered related to study drug. Two subjects had Grade 1 headache (iv PBO and CDP6038 0.3 mg/kg iv groups) considered possibly related to the study drug; all other TEAEs were considered unrelated. Reductions in neutrophil and leukocyte counts and slight increases in alanine aminotransferase levels were obwith CDP6038, with no apparent dose dependency. Increases in bilirubin levels in higher CDP6038 dose groups (3 mg/kg sc and iv and 10 mg/kg iv) were not associated with elevations in liver enzymes. Lipid levels were unaffected by CDP6038 use. No post-dose anti-CDP6038 antibodies were detected. AUC and C(max) increased linearly with increasing doses of CDP6038 (iv and sc). Median half-life iv and sc was 31.1 days (range 11.371.2 days) and appeared to be independent of dose. The absolute bioavailability after sc administration of CDP6038 ranged from 84% (3 mg/kg sc group) to 92% (1 mg/kg group).

Conclusions: CDP6038 was tolerated at single doses of up to 3 mg/kg sc and 10 mg/kg iv exhibiting a median half-life of 31.1 days, absolute bioavailability of 8492% and no apparent target-mediated clearance. These findings support the ongoing clinical evaluation of CDP6038 for RA treatment.

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an employee of UCB. S.S. is an employee of UCB. All other authors have declared no conflicts of interest.

251. DEVELOPMENT OF A HIGH FIDELITY SIMULATION FOR THE TRAINING AND TEACHING OF THE IDENTIFICATION AND MANAGEMENT OF INFUSION REACTIONS TO BIOLOGIC AGENTS

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Background: There has been a dramatic expansion in the use of biologic therapies for rheumatic diseases over last decade. Several of these therapies are given by infusion which can induce immunological adverse reactions, which can be fatal. Early recognition and treatment of these reactions is vital.

We examined:

The incidence of biologic infusion reactions in our Rheumatology Day Unit.

The nature of these reactions for different biologics.

Whether an infusion reaction could be simulated using a LaerdalSimMan3G, and modified as an education/training tool for both students & staff.

Methods: Retrospective & prospective analysis of patients ($n = 258$) receiving a biologic infusion ($n = 2460$) in our unit was carried out. An infusion reaction was deemed to have occurred if the infusion was stopped due to a medical reason and the subsequent pathway of care was followed and recorded. Information from patients having reactions was used to develop scenarios for assessment on a LaerdalSimMan3G on our simulation suite with the operator & observers in a separate room. Experienced nursing staff was used to validate the simulation as an infusion reaction and medical students to evaluate its usefulness as a teaching tool in conjunction with lectures on adverse reactions.

Results: A significant number of patients (13%) treated with biologics had an infusion reaction during their course of therapy, with no statistically significant difference between Infliximab & Rituximab ($p > 0.05$). However, further analysis showed the incidence of reactions per infusion was markedly less with a statistically significant difference between Infliximab (0.9%) & Rituximab (3.4%) ($p < 0.05$).

Reactions to Rituximab infusions were predominantly after the first infusion (90%) whereas majority of infusion reactions to Infliximab occurred on subsequent infusions (70%). Difference in the symptoms was also observed with itching of ears/head & sore itchy throat being noticeable for Rituximab, and flushing & dizziness in case of Infliximab.

Evaluation of the simulation showed that the reaction was readily identifiable by both experienced nurses (VAS 88, SEM 5.4) and medical students (VAS 90, SEM 1.8). Similar results were seen when asked if they were able to treat appropriately. However, when asked on how they assessed their ability to respond, a marked difference was seen between the nurses (VAS 87, SEM 3.3) and the students (VAS 69, SEM 3.7).

Conclusions: A significant number of patients (1 in 8) that receive a biologic infusion experience a reaction, although similar for the 2 biologics we studied, there was difference statistically in the incidence/infusion and symptoms experienced by the patients.

Patient driven simulations of reactions to biologic infusions have been developed that can be readily recognized & treated, and used as a teaching/training tool for students and staff.

Disclosure statement: All authors have declared no conflicts of interest.

252. CYTOKINE AND CHEMOKINE EXPRESSION PROFILE IN HUMAN INTERVERTEBRAL DISC DEGENERATION

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Background: Tissue homeostasis in the normal intervertebral disc (IVD) is maintained by the chondrocyte-like cells. In degeneration these cells adopt a catabolic phenotype that leads to progressive functional failure of the IVD. The initiating factors for this disregulated cellular function remain unknown. Cytokines and chemokines regulate diverse cellular functions in many tissue environments. Within the IVD IL-1 has been shown to regulate cellular processes associated with IVD degeneration[1,2]. Here, cytokine and chemokine expression profiles from non-degenerate and degenerate IVDs are compared to investigate whether an altered cytokine and chemokine expression profile is associated with IVD degeneration.

Methods: Human IVD tissue from 3 non-degenerate and 3 degenerate IVDs was used to generate gene expression profiles by cDNA low density array of 91 target cytokine and chemokine genes. Real-time RT-PCR and immunohistochemistry was used to validate array data on additional human IVD samples.

Results: Expression of 78 cytokine, chemokine, receptor, accessory protein and activating enzyme genes were identified, including a number previously unreported within the IVD. Comparative analysis of non-degenerate and degenerate groups indicated 30 genes that exhibit altered gene expression profiles including the cytokines; IL-1, IL-6, IL-16, IL-17D, IL-18, IL-20, TNF, LIF and OSM, and the chemokines; CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CXCL1, CXCL2, CXCL3, CXCL8 and CX3CL1. Immunohistochemistry has confirmed localization of several of these cytokines and chemokines to the chondrocyte-like cells.

Conclusions: This study demonstrates expression and production of a number of cytokines and chemokines within the IVD that have not been shown previously. This suggests a role for these cytokines and chemokines in IVD homeostasis or in the pathogenesis of IVD degeneration.

Disclosure statement: All authors have declared no conflicts of interest.

253. THE ROLE OF CYTOKINES AND CHEMOKINES IN HUMAN INTERVERTEBRAL DISC DEGENERATION

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Background: The unique mechanical properties of the Nucleus Pulposus (NP) depend on the composition and organization of its extra-cellular matrix (ECM). NP ECM is synthesized, maintained and highly regulated by the cells within it. Adverse changes to the NP ECM, as seen in intervertebral disc (IVD) degeneration, are mediated by disturbances in the biology of these cells. Within the avascular IVD the NP cells are considered primary effectors capable of autologus regulation, via the secretion of soluble factors that act through autocrine or paracrine signalling circuits, to effect tissue homeostasis. Previously it has been shown that IL-1 is involved in NP ECM remodelling[1] and that the normal IL-1 homeostatic mechanism is replaced by a positive feedback loop in IVD degeneration[2]. Here, cytokines and chemokines that we have previously identified within the human IVD are investigated as to their regulatory potential on each other to address the hypothesis that regulatory inter-relationships exist between the cytokines and chemokines of the IVD.

Methods: Primary human NP cells were subjected to 48 hour treatment with IL-1beta, IL-16, CCL2, CCL3, CCL7 and CXCL8. RNA extracted from these cultures was used in qRT-PCR gene expression analysis to determine the effects of treatment on cytokine, chemokine, ECM components and ECM degrading enzyme expression.

Results: mRNA expression of IL-16, CCL2 and CXCL8 was confirmed in cells derived from all human disc samples and expression of CCL2 and CXCL8 was upregulated by IL-1beta treatment. IL-1beta and CCL3 were not expressed in all samples however, their expression was induced by IL-1beta treatment.

Conclusions: This study demonstrates the regulatory potential of a number of cytokines and chemokines within the IVD that have not been shown previously. This suggests a role for these cytokines and chemokines in the regulation of NP cell biology and possibly the pathogenesis of IVD degeneration.

Disclosure statement: All authors have declared no conflicts of interest.

RHEUMATOID ARTHRITIS: AETIOPATHOGENESIS AND ANIMAL MODELS

254. DEFECTIVE CD8 + CD28: REGULATORY T CELL SUPPRESSOR FUNCTION IN RHEUMATOID ARTHRITIS IS DUE TO SOLUBLE MEDIATORS AND REDUCED SENSITIVITY OF RESPONDER CELLS

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Background: Rheumatoid arthritis (RA) is due to the inability of regulatory mediators to suppress inflammation. We have shown that in RA patients treated with methotrexate; RA(MTX), CD8 + CD28-Tregs in the peripheral blood (PB) are functionally defective compared to RA patients treated with a TNF inhibitor; RA(iTNF) which mediate suppression. This study examines the underlying defects of CD8 + CD28-Tregs in RA.
Methods: CD8 + CD28-Tregs were isolated by negative selection (>97%) with magnetic beads and placed in co-culture with autologous peripheral blood mononuclear cells (PBMC) at 1:1 in the presence of anti-CD3 antibody. For cross over co-culture assays, CD8 + CD28-Tregs were co-cultured with autologous or allogeneic T cells from HC or RA(MTX) and stimulated with CD3/CD28 beads. Cultures were up to 72 hours and pulsed with tritiated thymidine to determine cell proliferation. For blocking experiments, an anti- TGF- β antibody was added to 1:1 cultures. To examine cell responsiveness, a TNF inhibitor was added in vitro to RA(MTX) cultures. FlowCytomix Technology was used to determine IL-10 levels and IL-10R expression was investigated by flow cytometry.
Results: Cross over co-culture experiments showed HC CD8 + CD28-Tregs significantly suppressed autologous T cell (20017 ± 3375 cpm, T cells vs 10508 ± 3821 cpm, 1:1, $p = 0.0366$), allogeneic HC T cell (13133 ± 1545 cpm, HCT cells vs 7054 ± 1817 cpm, 1:1, $p = 0.004$) but not allogeneic RA(MTX) T cell proliferation (15183 ± 3198 cpm T cells vs 12957 ± 4230 cpm, 1:1). In contrast, RA(MTX) CD3 + CD8 + CD28-Treg failed to suppress autologous T cell (7197 ± 841 cpm, PBMC vs 7674 ± 228 cpm, 1:1), allogeneic HC T cell (9246 ± 1787 cpm, T cells vs 8465 ± 822 cpm, 1:1) and allogeneic RA(MTX) T cell (4122 ± 344 cpm, T cells vs 4843 ± 1401 cpm, 1:1) proliferation. In RA(MTX) cultures, in vitro addition of a TNF inhibitor increased suppression of PBMC proliferation (20522 ± 3261 cpm, PBMC alone vs 21449 ± 3401 cpm, 1:1 vs 14088 ± 2126 cpm, 1:1 + TNF inhibitor, $p = 0.0113$). HC cultures in the presence of an anti-TGF-β antibody showed reduced suppression of PBMC proliferation compared with control IgG (21535 ± 7266 cpm, 1:1 + isotype IgG ($p = 0.0394$) vs 28484 ± 8494 cpm, 1:1 + TGF-β Ab). Cytokine analysis of anti-CD3 antibody stimulated RA(MTX) CD8 + CD28-Tregs showed higher levels of IL-10 compared with HC (1013 ± 231 pg/ml, RA(MTX) vs 271 ± 69 pg/ml, HC, $p = 0.0072$) but RA(MTX) responder T cells had lower expression of the IL-10R than HC.
Conclusions: This novel study demonstrates defective CD8 + CD28-Treg suppressor function is due to intrinsic defects and reduced sensitivity of RA(MTX) responder T cells to suppression. TGF-β and reduced IL-10R expression on RA(MTX) responder T cells suggest suppression is mediated predominantly by soluble factors. In conclusion, CD3 + CD8 + CD28-Tregs may be part of the deficient immunoregulation which drives the pathogenesis of RA.
Disclosure statement: All authors have declared no conflicts of interest.

255. PROTEINASE-ACTIVATED RECEPTOR-2 MODULATES IL-17 GENERATION IN COLLAGEN INDUCED ARTHRITIS

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Background: Proteinase-activated receptor-2 (PAR-2) is a member of a subfamily of G protein-coupled receptors activated by a novel mechanism involving proteolysis of the N terminus by serine proteinases, thereby exposing a tethered ligand. PAR-2 has been identified on a number of cell types known to regulate innate immune responses but its role in adaptive immunity is uncertain. This study investigated the extent to which adaptive immune responses were modulated by collagen induced arthritis (CIA) in wild-type compared to PAR-2 deficient mice.
Methods: CIA was induced in C57Bl/6J mice using modification of a previously described protocol (Inglis et al 2008). Arthritis severity was assessed by paw scoring, histological analysis of joint damage and a novel index of paw hyperaemia using laser Doppler imaging (Moor Instruments Ltd, Axminster, UK). Cytokine and chemokine generation from lymph node cells in response to collagen was analysed by Luminex.
Results: The progression of CIA, assessed by arthritic score and histological assessment of joint damage, was significantly ($P < 0.0001$) abrogated in both PAR-2 deficient mice and in wild-type mice administered a PAR-2 antagonist (ENMD-1068), the latter also showing reduced paw hyperaemia. Lymph node derived cell suspensions from PAR-2 deficient mice were found to produce significantly less IL-17 ($P < 0.02$) in ex vivo recall collagen stimulation assays compared to wild-type littermates (300 ± 184 and 1119 ± 130 pg/ml respectively, mean ± SEM, $n = 8$). Interferon gamma was also significantly lower ($P < 0.001$) in PAR-2 deficient mice compared to wild-type (281 ± 114 and 4173 ± 1428 pg/ml respectively) as were TNFα, IL-6, IL-1β and IL-12, along with chemokines GM-CSF and MIP-1α.
Conclusions: These data support an important role for PAR-2 in the pathogenesis of CIA, and suggest an immunomodulatory role for this receptor in an adaptive model of inflammatory arthritis. By yielding insight into possible triggers of breach of tolerance, this finding may prove key in advancing our understanding of autoimmune joint diseases.
This work was supported by Arthritis Research UK (18306).
Disclosure statement: All authors have declared no conflicts of interest.

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256. CIGARETTE SMOKING HISTORY IS MORE STRONGLY ASSOCIATED WITH VERY STRONGLY POSITIVE RHEUMATOID FACTOR RATHER THAN VERY STRONGLY POSITIVE ANTI-CITRULLINATED PROTEIN ANTIBODY POSITIVITY WITHOUT VERY STRONGLY POSITIVE RHEUMATOID FACTOR IN RHEUMATOID ARTHRITIS

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Background: Debate continues as to whether smoking is associated with the pathogenesis of rheumatoid arthritis (RA) by means of anti-citrullinated protein antibody (ACPA) production (current theory) or by rheumatoid factor (RF) production. The strong association between cigarette smoking and RF positivity is well recognized. Despite studies showing a similar association with ACPA levels no studies to date have compared the smoking history of RA patients with very strongly positive RF levels to RA patients with very strongly positive ACPA levels without very strongly positive RF levels.
Methods: We defined very strongly positive RF levels as >30 fold the upper range of normal (0-10iu) i.e.>300iu. Very strongly positive ACPA levels (measured using a 2nd generation assay) were also defined as >30 fold the upper range of normal (0-17iu) i.e.>500iu.

We reviewed all serological testing undertaken at our hospital from 2009-2010 and selected a random sample of 40 RF strongly positive patients, all had a definite diagnosis of RA with RF > 300. In addition, we selected a random sample of 40 ACPA strongly positive patients without strongly positive RF levels, all had a definite diagnosis of RA with RF <60iu and ACPA > 500iu. The age, age of presentation, gender and smoking history was compared between the 2 groups.
Results: Gender differed between the groups with a predominance of males in the RF very strongly positive group, 22 (55%) vs 16 (40%), $p = 0.2$. The median age in the RF very strongly positive group was 64.5 (SD 13.4) yrs vs 59.5 (SD 14.6), $p = 0.14$. The median age of presentation in the RF very strongly positive group was 56.5 yrs (SD 14.5) vs 52.5 yrs (SD 15.4), $p = 0.26$.

The smoking history differed significantly with ever smokers being significantly more prevalent in the RF very strongly positive group, 36 (90%) vs. 27 (68.5%), $p = 0.03$. The median pack years smoked were

markedly raised in the RF very strongly positive group, 22 (SD 19) vs. 5 (SD 17). On closer analysis it is noteworthy that since 2009 5 of the 40 RF very strongly positive patients have died from smoking related diseases.

Conclusions: Smoking history is significantly increased in RA patients very strongly positive for RF compared to RA patients very strongly positive for ACPA without very strongly positive RF levels. This raises the important question as to whether the production of high levels of RF and ACPA are driven by the same pathogenic process in these different patient groups.

Disclosure statement: All authors have declared no conflicts of interest.

257. THE PATHOBIOLOGY OF EARLY ARTHRITIS COHORT: A PRELIMINARY ANALYSIS CORRELATING HISTOMORPHOLOGY AND DISEASE ACTIVITY

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Background: There is ample evidence to indicate that the synovitis load drives disease progression, joint damage and disability in RA. It is also becoming clearer that synovitis is a heterogeneous process with some tissues heavily infiltrated by a myeloid cellular component with very few B cells while others rich in B cells lead to the formation of ectopic lymphoid aggregates. Many observations have suggested that these structures are immunologically competent and can support chronic inflammation. However their role as predictors of disease severity and/or response to treatment remains controversial. The aim of this study was therefore to evaluate the correlation between synovial lymphoid aggregates and disease activity at baseline and after 6 months of treatment in early inflammatory arthritis.

Methods: A cohort of 73 disease-modifying antirheumatic drug-naïve consecutive patients (55% female) with early inflammatory arthritis (<12 months duration) was recruited at Barts and The London, as part of a multi centred MRC-funded Pathobiology of Early Arthritis Cohort (PEAC) http://www.peac-mrc.mds.qmul.ac.uk/. Patients underwent ultrasound (US) guided synovial biopsies and were stratified according to a diagnosis of rheumatoid arthritis (RA) using 1987 ACR criteria and undifferentiated arthritis (UndA). All patients were started on DMARDs therapy (including Methotrexate, Sulfasalazine and Hydroxychloroquine) in monotherapy or in combination, according to diagnostic and prognostic categories.

Disease activity was assessed at baseline (T0) and after 6 months of treatment (T6) utilizing DAS28.

The histological grading of tissues and degree of lymphoid organization was assessed by immunohistochemical staining of sequentially cut sections of RA synovial tissue. The number of lymphocytic aggregates was counted in each section and graded according to a validated, previously published grading system.

Results: Preliminary results from this cohort show:

1. The pattern of synovitis is stable over 6 months in the majority of patients (78%).

2.Lymphocytic aggregates are more frequent in RA (40%) vs non-RA (18%) patients at baseline [OR: 3.5, 95% CI (1.02-14.2)]

3.The number of B cells and plasma cells are closely associated in early RA [$R = 0.89$], suggesting in situ differentiation.

4.Aggregate synovitis, B cells and macrophage sublining grading are positively associated with increased DAS and ESR at baseline [$p < 0.05$].

Conclusions: A synovial lymphocyte aggregate pattern correlates with provisional diagnosis and disease activity at baseline in early inflammatory arthritis. Further studies are needed in order to establish to what extent the presence of lymphocyte aggregates could serve as a biomarker for clinical response to treatment.

Disclosure statement: All authors have declared no conflicts of interest.

CASE REPORTS

258. HYPOPHOSPHATAEMIC RICKETS AND ANKYLOSING SPONDYLITIS-LIKE FEATURES ASSOCIATED WITH AN INACTIVATING ENPP1 MUTATION, A NOVEL PATHOGENETIC LINK

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Background: Hypophosphataemic rickets are rare disorders of phosphate handling and may result from mutations in PHEX (most commonly), FGF23 and DMP1, presenting as X-linked recessive, autosomal-dominant and autosomal-recessive patterns respectively. All three mutations are associated with elevated FGF23 levels, which inhibits renal phosphate reabsorption and 1,25-dihydroxyvitamin D synthesis, resulting in hypophosphataemia and inappropriately low 1,25(OH)2D. ENPP1 is emerging as the fourth gene associated with hypophosphatemic rickets.

Methods: We present a 42 year old Caucasian female with a 10 year history of polyarthralgia and progressive back pain and stiffness. She was diagnosed with hypophosphataemic rickets in childhood and had received intermittent vitamin D and phosphate replacement until aged 20 years. She was borne of non-consanguineous parents, with no family history. Clinical examination revealed severe restriction of all spinal movements.

Results: Biochemical analyses were consistent with hypophosphataemic rickets. Radiographs demonstrated complete ossification of the anterior spinal ligament, as well as iliosacral ligament calcification and Baastrup's disease. Mutations were not found in the PHEX, FGF23 and DMP1 genes. Sequence analysis of the ENPP1 gene identified two variants: a previously unreported missense variant, p.Thr319Arg (c.956 C>G), in exon 9, which is predicted to be disease-causing and was found to be paternally inherited and a heterozygous nonsense mutation, p.Arg782X (c.2344C>T), in exon 23, which was found to be maternally inherited and created a premature stop codon at 782. The finding of these mutations in trans strongly suggest that these variants are pathogenic and causative of the features in our patient.

Conclusions: ENPP1 generates inorganic pyrophosphate (PPi), an essential physiologic inhibitor of calcification. ENPP1 knockout ('tiptoe walking') mice exhibit ossification of spinal ligaments and articular cartilage calcification. ENPP1 inactivating mutations in humans have been extensively described in generalized arterial calcification of infancy. There have been 9 recent reports of hypophosphataemic rickets associated with ENPP1 mutations. None of these patients exhibited vascular calcification and only one of these patients was similar to ours and resembled the murine phenotype with ligamentous ossification. Both our patient and the recently reported case were previously presumed to have X-linked heritability, which highlights the importance of genetic analysis. The mechanism that balance arterial calcification and bone mineralization and the effect of treatment is unclear. We support the emerging concept that ENPP1 is the fourth candidate gene associated with hypophosphatemic rickets, emphasize that this may manifest as spinal ligament ossification, similar to the ENPP1-knock out mouse model and encourage genetic screening of probands and their families.

Disclosure statement: All authors have declared no conflicts of interest.

259. REACTIVE ARTHRITS AND TRISMUS POST INTRAVESICAL BCG IMMUNOTHERAPY FOR BLADDER CARCINOMA

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Background: Intravesical BCG immunotherapy is used with efficacy and safety in the treatment of patients with intermediate and high risk superficial bladder carcinoma. Reactive arthritis(ReA), post BCG immunotherapy is a rare but well recognized complication. Osteoarticualr side effects are seen in 0.5-1% of patients. Chronic arthritis is very rare. Trismus and temporomandibular joint (TMJ)

involvement is not well described in literature. We report a case of ReA with associated trismus, post intravesical BCG therapy.
Methods: She was started on intravesical BCG immunotherapy, receiving 6-weekly instillations in May and June 2010, followed by 3-weekly instillations in August 2010, to complete induction therapy. Early in September 2010, she developed a sudden onset of pain in the right TMJ. Restricted mouth opening and hence chewing, limited oral intake to a soft diet. A few weeks later, she developed a painful swollen right wrist, knee and foot. Clinical examination revealed prominent synovitis in the right wrist, knee and ankle with signs of right sided plantar fasciitis and Maxillofacial surgeons confirmed trismus.
Results: Bloods revealed raised inflammatory markers (ESR 63, CRP 39) with a positive HLA B27. The remaining routine blood tests were normal with negative serology. Synovial fluid from the worst affected joint (right knee) was negative for gram stain and culture with no crystals detected. An OPG was normal. Swollen joints were injected with steroids and was she was started on NSAIDs and a reducing dose of Prednisolone. Joint symptoms improved but not the TMJ pain. By January 2011, worsening right sided trismus and reduced mouth opening to 18 mm, had resulted in weight loss. MRI showed effusion and synovitis, leading to an arthrocentesis and steroid injection in April 2011. This markedly improved the trismus/TMJ pain. By June 2011, she was eating and drinking normally with mouth opening of 2.5 cm.
Conclusions: Reactive arthritis is an uncommon but recognized complication, post-intravesical BCG immunotherapy, although TMJ involvement is not well described. The literature reports only one case of trismus which, as with our patient, did not respond to conventional systemic treatment of ReA. A reactive arthritis of TMJ, post-intravesical BCG, though uncommon, when suspected should be investigated and treated early, as it may not respond to generalized treatment of ReA and may require more targeted therapy.
Disclosure statement: All authors have declared no conflicts of interest.

260. IT REALLY CAN'T BE GOUT: WHAT IS IT? CRYOPYRIN-ASSOCIATED PERIODIC FEVERS: A DELAYED DIAGNOSIS

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Background: A 23 year old female nurse was referred to Dermatology in 2005 with an urticarial rash. This was familial, and she was offered treatment for chronic idiopathic urticaria. The Dermatologists noted a history of arthralgia, so referred her to Rheumatology, who discharged her without a diagnosis. She was referred back to Rheumatology a year later with pain and swelling affecting the left metacarpophalangeal joint. Serum urate was slightly elevated, there was a paternal history of gout, and she was treated as such with allopurinol and NSAIDs, from which she gained little relief. In February 2011 a second Rheumatologist elicited a history of urticarial rash since infancy, worse in the evenings and fading by morning. She had intermittent arthralgia with synovitis, recurrent kerato-conjunctivitis and episodes of feeling profoundly cold. All symptoms abated when in warmer climes. The proband's sister, mother, maternal aunt and maternal grandmother all had similar symptoms. The patient was referred to the clinical geneticist, and tested positive for a mutation in NLRP3, confirming the diagnosis of a Cryopyrin Associated Periodic Syndrome (CAPS).
Methods: Not applicable.
Results: Cryopyrin-associated periodic syndromes form a spectrum of autoinflammatory disorders which are coded by the NLRP3 gene. They are similar to periodic fevers such as tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) which are characterized by inappropriate activation of antigen-dependent inflammatory mechanisms. In CAPS, a gain of function point mutation promotes formation of defective inflammasomes, leading to inappropriate overproduction of Interleukin-1β (IL-1β). Incidence of CAPS is estimated at one in a million.

The mildest form is Familial Cold Autoinflammatory Syndrome (FCAS), characterized by an urticarial rash in response to cold air, fever, conjunctivitis and arthralgia. Muckle-Wells syndrome presents similarly, along with progressive sensorineural hearing loss. Both are autosomal dominant. Neonatal onset multisystem inflammatory disorder (NOMID) leads to neurological abnormalities, growth retardation and premature death. NOMID arises spontaneously. All are associated with secondary amyloidosis and nephropathy. Diagnosis is centred on a thorough history, measurement of inflammatory markers including serum amylase A, skin biopsy and genetic testing. Treatment was limited until recent breakthroughs in IL-1β inhibition, which leads to effective symptomatic and serological response. Patients should be offered genetic counselling and referral to specialist centres.
Conclusions: Cryopyrin-associated periodic syndromes are an important, albeit rare, set of diseases which are easily missed due to their low prevalence. Our patients' family have been seeking a unifying diagnosis for their rash, ocular symptoms and arthralgia for three generations. Awareness needs to be raised to prevent such delayed diagnosis.
Disclosure statement: All authors have declared no conflicts of interest.

261. SYSTEMATIC LUPUS ERYTHEMATOSUS, MOLLUSCUM CONTAGIOSUM AND HUMAN IMMUNODEFICIENCY VIRUS

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Background: We present a case of a woman fulfilling ACR criteria for SLE. We describe how this patient developed molluscum contagiosum and 2 respiratory tract infections whilst on immunomodulatory drugs, which alerted clinicians to test her HIV status.
Methods: Not applicable.
Results: A 46 year old Jamaican female was referred to rheumatology with a high ESR and arthralgias. There was no history of Raynaud's, photosensitive rashes, paraesthesiae, weight loss or fevers. She denied recreational drug use and had no history of sexually transmitted disease. There was tenderness over several joints but no synovitis and other systems examinations were unremarkable. Her ESR was 108 mm/hr, she had a positive ANA (1:640, homogeneous pattern), raised dsDNA antibody of 57 IU/l (normal range 0-30), a polyclonal gammopathy and a low C4 concentration. Her vitamin D level and lymphocyte counts were also low. At her 4 week review, she had a malar rash involving her cheeks and nose. A diagnosis of SLE was made for which she was commenced on corticosteroids. In the next 4 months, prednisolone was increased to 15 mg/day and hydroxychloroquine (400 mg) added. Her joint symptoms dramatically improved but her rash persisted. Azathioprine was commenced after 6 months to a maintenance dose of 150 mg. Her dsDNA and ESR returned to normal. At this time she developed facial molluscum contagiosum and had 2 lower respiratory tract infections requiring hospitalization. Due to persistent infections, the patient was tested for HIV. She tested HIV positive with a CD4 count 57% and viral load 29000 copies/ml. Azathioprine and hydroxychloroquine were discontinued, prednisolone was weaned to a low dose and she was commenced on anti-retroviral therapy. A favourable HIV prognosis was given and her SLE remained stable.
Conclusions: Our case highlights the finding of HIV in a patient with SLE. Although false-positive ANA/dsDNA are observed in HIV, the duration of symptoms, response to immunomodulatory drugs and improvement in dsDNA titres post-treatment highlights that our patient had concomitant SLE and HIV. Although there are no formal recommendations regarding HIV testing before commencing immunomodulatory drugs, it is suggested that patients undergo HIV testing before commencing certain drugs e.g. anti-TNF therapy. The Centers for Disease Control and Prevention (CDC) already recommend HIV testing as part of routine screening in all healthcare settings between the ages of 13-64 regardless of perceived risk (2). We recommend establishing the HIV status in all patients with rheumatic diseases, particularly those considered for disease-modifying drugs, since HIV status has a significant impact on future management.
Disclosure statement: All authors have declared no conflicts of interest.

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262. POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME ASSOCIATED WITH TOCILIZUMAB

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Background: PRES is a combined clinical and radiological syndrome characterized by headaches, encephalopathy, seizures and visual disturbance with radiological evidence of posterior cerebral oedema. It has been associated with a wide range of conditions including acute

hypertension, renal failure, sepsis and autoimmune conditions. In addition it has been associated with numerous immunosuppressant treatments including rituximab, infliximab, methotrexate, corticosteroids, cyclophosphamide and ciclosporin. This is the first reported case of PRES occurring after treatment with the IL-6 receptor antagonist tocilizumab.

Methods: A 66 year old Caucasian woman developed occipital headaches two days following her first infusion of tocilizumab for the treatment of RA. She had a 30 year history of RhF/ACPA positive RA for which she had previously had MTX, LFN and four courses of rituximab. Co-morbidities included chronic inflammatory demyelinating polyneuropathy (CIDP), Graves ophthalmopathy (treated with radio-iodine), ischaemic heart disease and OA. At initiation of tocilizumab she was taking concurrent LFN 10 mg daily.

Her headaches persisted for three weeks before developing a rapid increase in pain, new visual blurring and subsequent coma over the space of a few hours. On admission to hospital she suffered four tonic-clonic seizures in short succession requiring intubation and admission to ITU for intravenous phenytoin and aggressive blood pressure control.

Results: There was no evidence of sepsis or acute kidney injury, and CT head revealed no intracranial bleed. CSF cell counts were normal, with no pathogen detected either on bacteriology or viral PCR. Magnetic resonance imaging (MRI) of her brain revealed high T2 signal in the left posterior parietal lobe and in both frontal lobes confirming the suspicion of PRES.Her headaches slowly resolved and she had no further seizures upon the gradual withdrawal of anticonvulsant medication. Repeat MRI one month after admission showed complete resolution of the original signal changes. She was subsequently recommenced on LFN and a small dose of oral prednisolone.

Conclusions: The diagnosis of PRES is based on the combination of clinical features (headache, encephalopathy, seizures and visual disturbance) with radiological evidence cerebral oedema affecting the parietal-occipital lobes. However, atypical presentations are recognized, with less than 50% of patients having visual symptoms, and neuroimaging frequently showing either unilateral changes or predominant involvement of frontal lobes.

The mechanism of PRES is unclear, although one theory is an imbalance between systemic blood pressure and cerebral autoregulation of blood flow, leading to vasogenic cerebral oedema. Management of PRES requires aggressive blood pressure control combined with cessation of seizure activity. The syndrome is typically reversible and long term anticonvulsants are not usually required.

Written consent was obtained for this publication.

Disclosure statement: All authors have declared no conflicts of interest.

263. DIFFUSE OSTEONECROSIS IN ANTI-PHOSPHOLIPID SYNDROME MANIFESTING WITH HIGH BONE MINERAL DENSITY

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Background: The finding of high bone mineral density (h-BMD) while interpreting dual x-ray absorptiometry (DXA) scans is not uncommon. In most cases it reflects localized bone sclerosis as in spinal facet joint osteoarthritis, though all-site h-BMD can indicate sclerosing bone dysplasia requiring investigation.We report a case of diffuse osteonecrosis diagnosed through the investigation of h-BMD phenotype,in a patient with longstanding APLS.

Methods: A 54year old woman was diagnosed with APLS by the haematology team after a 31 year history of APLS-related features.

These included: 2 episodes of intrauterine fetal death at weeks 20 and 27 in consecutive pregnancies; pregnancy complications including pre-eclampsia, disseminated intravascular coagulation, deep venous thrombosis and intra uterine growth retardation owing to placental insufficiency.

Later she developed episodic neurological symptoms including dizziness, memory impairment and complex partial seizures,and she was found to be heterozygous for factor V Leiden. Finally, diagnosis of APLS was made with the demonstration of lupus anticoagulant with high titer IgG anti-cardiolipin (ACL) and β2 glycoprotein (β2GPI) antibodies. (IgG ACL 39 u/ml [0-10]; IgG β2GPI 77U/ml [0-10])

Anticoagulation treatment was started with enoxaparin and then warfarin,however due to better control of her cognitive symptoms with enoxaparin it was reintroduced.

Then, owing to thoracic back pain, a thoracic spine radiograph was performed revealing a T7 vertebral deformity reported as a 'wedge fracture'.

Results: Given concern about enoxaparin induced osteoporosis DXA scan was requested,simultaneously with MRI scan of the thoracic and lumbar spine.

DXA showed multiple site h-BMD. (table)

MRI was reported as "thin vertical hyperintense clefts with sclerotic rims on T2 weighted images in T7,T8,L3,L4,S1 vertebral bodies, with increased signal in L3,L4 vertebral bodies on T1 weighted images".The aetiology could not be identified.

DXA report, in light of clinical,and radiographic findings raised the possibility of osteonecrosis associated with APLS contributing in part, or exclusively to the vertebral deformities and h-BMD. Subsequently a trans-iliac undecalcified bone biopsy showed diffuse areas of cortical osteonecrosis associated with small blood vessel ischaemia. Further review of MRI images concluded that they were consistent with osteonecrosis.

Conclusions: In light of generalized h-BMD, it is reasonable to conclude that the biopsy results may be representative of the pathology through the skeleton.

To our knowledge this is the first report of diffuse skeletal osteonecrosis associated with APLS presenting as h-BMD. The potential extent of the findings may reflect the severity and duration of untreated APLS.

TABLE 1.

Site	T-score	Z-score
Femoral neck	5	5.9
Spine(L1-L4)	0.6	1.5
Forearm	1.8	2.7

Disclosure statement: All authors have declared no conflicts of interest.

264. AN UNUSUAL CASE OF CHILDHOOD DERMATOMYOSITIS RECURRING HALF A CENTURY LATER

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Background: A 62-year old female presented with malaise, lethargy, proximal muscle weakness and an erythematous macular rash over the anterior chest wall.

Methods: In 1956, aged 8, she presented with a 5 week history of proximal muscle weakness, fever, malaise and arthralgia. The ESR was 105 mm/hr. A muscle biopsy was inconclusive, however, corticosteroids were commenced for a presumptive diagnosis of inflammatory myositis. She made a good recovery and was discharged on a reducing regime of corticosteroids. The patient relapsed in 1957, presenting with proximal muscle weakness and calcinosis cutis. The clinical and histopathological findings were consistent with juvenile dermatomyositis (DM). The patient was treated with corticosteroids for several months, only to develop another relapse in 1958, although the relationship with steroids was unclear. On this occasion she was given a prolonged course of oral Prednisolone, leading to remission. At the age of 40 she was diagnosed with malignant melanoma, treated with local excision and radiotherapy. After this, she remained well for 22 years until November 2009, when she had a relapse of DM occurring over 2-3 weeks.

Results: During her current admission, initial investigations showed a CPK of 18,319 U/L, ESR 95 mm/hr, CRP 36.5 mg/L. ANA and ANCA were negative. An OGD (performed following complaints of dysphagia), colonoscopy and computer tomography of the thorax, abdomen and pelvis were normal. The muscle biopsy confirmed inflammatory myositis, with the distribution of the lymphocytic infiltrate (largely perivascular & perifasicular with B-lymphocytes) being suggestive of DM. The patient was treated with 3 pulses of intravenous Methylprednisolone (500 mg) followed by oral Prednisolone (30 mg) and Methotrexate (20 mg weekly). The CPK normalized within 3 weeks of treatment (CPK 50 U/L, ESR 20 mm/hr), dysphagia improved and there was gradual improvement in muscle strength. She is currently in remission on Prednisolone 8 mg & Methotrexate 12.5 mg/week.

Conclusions: This is a case of DM relapsing after 51 years of remission. The association between malignancy and DM is well recognized, with malignancy often detected within the first year of DM [1] although, as our case suggests, there can be exceptions. This case is unusual because of the very late relapse of myositis and also the presentation of malignancy at least 20 years after childhood presentation and prior to recurrence in adulthood. A report by Touton described 2 cases of childhood DM with recurrence in adulthood after 30 & 21 years of remission [2]. In another report by Martini [3], the patient had a polyphasic course with recurrences separated by long remission periods. We report a recurrence period of 51 years after complete remission of DM, the longest remission interval

of DM reported in the literature. We conclude that although relapses of DM are uncommon, they can occur at late stages, raising issues concerning maintenance therapy.

Disclosure statement: All authors have declared no conflicts of interest.

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265. INEXPLICABLE IMMUNOLOGY? NEW-ONSET RHEUMATOID ARTHRITIS IN A RENAL TRANSPLANT PATIENT ON TRIPLE IMMUNOSUPPRESSIVE THERAPY

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Background: Development of rheumatoid arthritis (RA) after renal transplant is an extremely rare phenomenon, with only one report internationally. Patients in receipt of cadaveric renal transplant require life-long immunosuppression to prevent graft rejection. Most transplant centres utilize triple therapy with cyclosporin (Cyc), mycophenolate mofetil (MMF) and prednisolone. With such potent immunosuppression, using agents that have proven efficacy in the treatment of RA, it would seem impossible for de novo RA to arise.

Methods: A 48 year old woman presented with a 6 month history of inflammatory polyarthritis. She had been taking prednisolone 5 mg daily, MMF 750 mg twice daily and Cyc 100 mg/75mg twice daily for 4 years following a cadaveric renal transplant for ischaemic nephropathy. There were no features of chronic infection, latent malignancy or connective tissue disease. There was no significant family history and alcohol consumption was minimal. Examination revealed symmetrical synovitis of the MCPJ and PIPJ of the hands and wrists. Laboratory and radiological investigations were consistent with a diagnosis of seropositive RA (see Table 1).

Results: Low-dose MTX methotrexate (MTX) was added to her treatment regime. A major concern was MTX toxicity and the increased risk of malignancy, especially since RA, immunosuppressive agents and renal transplant are all independently associated with an increased incidence. However, the severity of her symptoms outweighed this risk. Biochemical indices, including Cyc levels, were monitored fortnightly and short-term results of MTX therapy have been favourable.

Conclusions: Why should RA develop whilst on triple immunosuppression? Both the patient and donor are HLA-DR4 positive and the patient is shared-epitope (SE) positive (HLA-DRB*01:01, DRB1*04:01). HLA antigens from the donor may have induced RA via matching of HLA DR alleles, similar to a case of transmission of psoriatic arthritis to a patient via bone marrow transplant. Alternatively, the patient may have had RA for several years but symptoms were initially masked by pre-transplant uraemia, and later by high dose immunosuppressives. To the authors' knowledge, we have described the only known case of new-onset RA post renal transplant in the UK and the second such case internationally. We encourage clinicians to report similar experiences, as a case series may delineate the immunological mechanisms of RA pathogenesis in such patients.

The patient provided written consent for publication.

Table 1 Relevant Investigations

Investigation	Result
Hb (haemoglobin 11.5 - 16.0 g/dL)	14
ESR (erythrocyte sedimentation rate 1-12 mm/hr)	38
Creatinine (60-120 umol/l)	92
CRP (C-reactive protein 1-6 mg/l)	17
Urate (100 - 430 umol/l)	246
RF (rheumatoid factor 0-20 IU/mL)	85
Anti-CCP (anti-cyclic citrullinated protein antibody 0-7 U/ml)	314

Disclosure statement: All authors have declared no conflicts of interest.

266. DOES RHEUMATOLOGY HAVE A ROLE IN IDIOPATHIC RETROPERITONEAL FIBROSIS?

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Background: The mainstay of treatment of RPF is the relief of urinary tract obstruction by stents or surgery. Medical therapies such as glucocorticoids, immunosuppressives and tamoxifen are usually adjuncts. Because of the association of RPF with high IgG4 levels and probable increased B cell activity, we report on the use of rituximab in RPF.

Methods: The report concerns a 48 year old man with diabetes who first attended rheumatology in 2006 and a review of treatment options for RPF.

Results: A diagnosis of RPF was established following the development of obstructive uropathy with associated malaise and acute phase reaction. Retroperitoneal tissue biopsy confirmed the diagnosis. Despite insertion of ureteric stents and prednisolone therapy, abdominal, back & testicular pain continued. He was monitored at clinic visits by renal function, ESR, CRP and abdominal MRI. Azathioprine failed as a steroid sparing agent and progressive leg swelling developed because of pressure on inferior vena cava. He required bilateral hip replacement for avascular necrosis and then refused further steroids. Azathioprine was replaced by mycophenolate, and then combined with tamoxifen. Finally iv cyclophosphamide was tried; all proved unsuccessful with enlarging tissue mass on imaging. In spring 2011, following starting rituximab, MRI showed reduction of the retroperitoneal mass; he no longer needs nephrostomy tubes and the eGFR is now stable at around 40ml/min (lowest at 10 ml/min in February 2011). The response has been associated with a fall in IgG4 level from 1.68 to 0.99 g/l. (reference range 0- 1.3) after two 1g doses of iv rituximab.

RPF involves chronic inflammation, fibroblast proliferation, and excessive extracellular matrix deposition. Nearly 90% patients respond to glucocorticoids. In refractory cases the use of immunosuppressives (eg. methotrexate, mycophenolate, azathioprine or cyclophosphamide) is recommended.

Case reports suggest tamoxifen may improve RPF. The balance of growth factors may change and therefore inhibit fibroblast proliferation. Tamoxifen's antiangiogenic property may also contribute.

RPF may be a manifestation of IgG4-related sclerosing disease. Rituximab therapy has resulted in prompt clinical improvement and rapid decline of serum IgG4 levels in IgG4-related diseases such as

Table 1.

N0	Age and sex	Background disease	Indication	Clinical response	Side effects	Evidence of pulmonary hypertension
1	68 F	SSc	Severe RP + gangrene	Good, skin improvement	No	Severe
2	81 F	SSc	Severe RP	Good	No	No
3	75 M	SSc	Severe digital ischaemia	Good	No	Moderate
4	85 F	SSc	Severe RP	Stop as SE	Flushing, headache, dizziness	Mild
5	47 F	L SSc	RP + digital ulcer	Good, regression of calcinosis	No	No
6	46 F	L SSc	RP with digital ischaemia	Good	No	No
7	80 F	L SSc	SevereRP	Good	Dairrhoea, pervaginal bleeding	Moderate
8	64 F	RP + Sjogrens syndrome	Severe RP	Good	No	No
9	44 F	SLE,APLS + RP	RP + gangrene	Good	Sweating	No
10	69 F	RP ACLA positive	RP + gangrene	Good	No	No

SSC = Systemic sclerosis L SSC = Limited systemic sclerosis RP = Raynaud's phenomenon

sclerosing cholangitis, autoimmune panreatitis, & lymphoplasmacytic aortitis.
Conclusions: This case report demonstrates a response to B cell suppressive therapy in IgG4-associated RPF. Rituximab may be a logical immunosuppressive for RPF where it is refractory to or the patient is intolerant of steroids. Determining the concentration of serum IgG4 may be helpful in assessing response to therapies in RPF.
Disclosure statement: All authors have declared no conflicts of interest.

267. TADALAFIL: A NOVEL TREATMENT FOR VASCULAR MANIFESTATIONS OF SYSTEMIC SCLEROSIS AND OTHER CONNECTIVE TISSUE DISEASES

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Background: Tadalafil, a long-acting 5 phosphodiesterase inhibitor (PDE5) is a smooth muscle relaxant and its use is associated with vasodilatation. Systemic sclerosis (SSc) related vasculopathy, as manifested by Raynaud's Phenomenon (RP) and digital ulcers (DUs), carries a significant impact on quality of life. Despite advances in the management of pulmonary hypertension (PAH), current therapies for severe digital ischaemia are not optimal. We present our experience of tadalafil in the management of patients with SSc and other connective tissue diseases.
Methods: Case records of ten patients treated with tadalafil 20 mg alternate days were reviewed. All parameters in relation to digital ischaemia, skin disease and PAH were recorded. We also made note of other therapeutic options used by these patients for Raynauds and digital ulcers.
Results: Ten patients were treated with mean follow up of 10 months (range 2-34 months). All of the 10 patients had severe Raynauds. Tadalafil was well tolerated except in 3 patients who experienced side effects (diarrhoea, per vaginal bleeding, flushing, headache, dizziness, sweating)- one of whom was able to continue on lower doses of the drug at 2.5 mg daily. All patients noticed remarkable improvement in their RP and following 2 patients reported improvement in skin thickening and calcinosis.

Case 1 (68 yr old woman with SSc with PAH) responded dramatically with complete resolution of RP, DU and reduction of PAH and skin thickening.

Case 2 (SSc, interstitial lung disease, RP not controlled by nifedipine and iloprost infusion) had a remarkable response in term of RP as well as lung function.
Conclusions: Raynaud's Phenomenon, Pulmonary Hypertension and skin thickening in systemic sclerosis are associated with frequent sustained arteriolar constriction and Tadalafil is postulated to reduce ischaemia and prevent proliferation of skin fibroblasts. Sustained PDE-5 inhibition with tadalafil is a promising therapeutic approach in such patients and appears to be well tolerated. Our case series supports use of tadalafil as useful addition to the therapies currently available and further larger scale RCTs of the drug are required.
Disclosure statement: All authors have declared no conflicts of interest.

268. HARLEQUIN SYNDROME: A CASE REPORT AND REVIEW OF LITERATURE

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Background: Harlequin syndrome (HS) is a rare condition characterized by unilateral facial flushing typically induced by stress or exercise. The clinical features occur as a consequence of disruption of the sympathetic outflow to one half of the face. The absence of flushing is the abnormality. We present an unusual case of HS with hypertension, Adie's pupils and exercise-induced pallor of the ipsilateral hand.
Methods: We present a case of Harlequin syndrome and review of literature.
Results: A 41 year-old female was reviewed in the rheumatology outpatient clinic with a 2 year history of unilateral facial flushing and relative coldness of the ipsilateral hand after vigorous exercise. The patient had also described having unequal pupils on several occasions. She had a past history of hypertension that was diagnosed at the same time as the facial flushing. The blood pressure was normal and equal in both arms. Neurological assessment was a normal and no pupillary abnormalities were noted. MRI of her neck, thoracic outlet and chest was normal. A diagnosis of HS was made clinically. The patient was offered thoracic sympathectomy but declined any intervention.

HS, first described by Lance et al in 1988, results from disruption of sympathetic fibres at or distal to the sympathetic chain ganglia at the level of T2/T3. A total of 93 cases have been reported in English language literature. In these reports, a structural lesion was seen in 16% of patients and an iatrogenic cause in a further 12%. In some patients there appears to be a generalized disorder of the autonomic nervous system. There is only one other reported case describing coldness of the ipsilateral arm suggesting multifocal involvement of the autonomic nerves. Table 1 enumerates the various conditions associated with HS. Treatment is limited to improving the cosmetic aspect of the condition with disruption of the T2/3 thoracic ganglion on the normal side having been found to be beneficial.
Conclusions: Although rare, HS may present to a rheumatologist. Knowledge of this condition therefore is important in any patient presenting with the characteristic features. In addition to HS, our patient described coldness of the ipsilateral arm. This has only been reported once in the literature in association with HS. In addition the history of hypertension and pupil abnormalities (possibly Adie's pupils) would suggest more widespread involvement of the autonomic nervous system the nature of which has yet to be elucidated.

TABLE 1 Conditions associated with the development of HS

Mediastinal tumours
Cervical cord tumours/syringomyelia
Apical lung tumours
Thyroid artery aneurysm
Carotid artery dissection
Paravertebral thoracic blocks
Neck mass resection
Jugular vein catheterization

Disclosure statement: All authors have declared no conflicts of interest.

269. SUCCESSFUL USE OF TOCILIZUMAB IN A CAUCASIAN PATIENT WITH RELAPSING POLYCHONDRITIS COMPLICATED BY SWEETS SYNDROME

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Background: A 68 year old Caucasian male was diagnosed with relapsing polychondritis (RP) following a six month history of recurrent episcleritis, bilateral non-erosive ankle arthritis, hoarse voice, swollen nasal bridge and inflamed right ear pinna. In addition he had experienced fevers, night sweats, weight loss of one stone and fatigue. His inflammatory markers were elevated at CRP 25 mg/L and ESR 44 mm/hr. Having satisfied the McAdam et al criteria [1] prednisolone 40 mg daily was commenced.
Methods: Initial clinical response was good with a reduction in CRP and ESR of 1.4 mg/L and 14 mm/hr respectively. Prednisolone was tapered and methotrexate 10 mg weekly commenced with titration to 20 mg weekly. Despite this and switching methotrexate to azathioprine 100 mg daily, our patient suffered three relapses of his condition on attempted reduction of prednisolone. Adalumimab 40 mg fortnightly was commenced. Following the first dose of Adalumimab our patient developed a widespread erythematous pustular rash with left hand swelling and rigors. Adalumimab was discontinued and a skin biopsy arranged. Biopsy revealed an acute neutrophilic dermatosis consistent with Sweets Syndrome. Prednisolone was increased to 30 mg daily continued with azathioprine 100 mg daily and the rash settled.

Despite treatment this gentleman continued to have active RP and Etanercept was commenced. A bone marrow biopsy confirmed the presence of myelodysplasia, accounting for his mild pancytopenia and cytogenetic testing was negative. Following an initial response, Etanercept failed to suppress his disease activity even at an increased dose of 75 mg weekly. It was discontinued and Tocilizumab commenced at 8 mg/kg monthly.
Results: Our patient had a dramatic response following his first infusion of Tocilizumab. His CRP dropped to 7.1 mg/L from 214 mg/L and ESR 99 mm/hr to 69 mm/hr. Our patient continues to do well on Tocilizumab in conjunction with azathioprine 100 mg and is on a reducing dose of prednisolone. His latest inflammatory markers are an ESR of 29 mm/hr and CRP <1 mg/L.
Conclusions: Relapsing polychondritis is a rare autoimmune condition with recurrent inflammation of cartilaginous structures resulting in destruction and potentially life threatening complications. Treatment predominantly involves the use of corticosteroids and immunosuppressive therapy. There have been numerous case reports of the use of anti-TNFalpha and anti IL-1 therapies in resistant disease. The

successful use of Tocilizumab has been described in two Japanese patients who had, like our patient, failed conventional treatment including anti-TNF alpha therapy [2]. We believe this to be the first reported case of a Caucasian with RP complicated by Sweets syndrome to be successfully treated with Tocilizumab.
Disclosure statement: All authors have declared no conflicts of interest.

270. A PRECIOUS METAL: COPPER DEFICIENCY PRESENTING AS MYELONEUROPATHY

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Background: Copper deficiency is a rare cause of haematological and neurological disease. We describe a case of copper deficiency mimicking subacute combined degeneration of the cord.
Methods: A 65 year old woman presented with leg weakness, poor balance and paraesthaesia in her hands and legs. She was known to have coeliac disease and B12 and folate deficiency, with erratic compliance with B12 injections. There were no features of inflammatory joint or muscle disease, or of an underlying autoimmune connective tissue disorder. Neurological examination revealed normal tone and power with brisk reflexes. She had a sensory level at mid-thigh, with proprioception reduced to the ankles and vibration sense absent up to the hips. Sensory ataxia and a positive Romberg's test were demonstrated.

Her clinical picture suggested combined myeloneuropathy. In view of her medical history, actual or functional B12 deficiency was suspected.

MRI spine and nerve conduction studies showed no specific changes. Blood tests, including B12, folate, inflammatory markers and autoimmune profile were normal. However, copper studies were abnormal, with serum copper level low at 2.3 [normal range 11-20], caeruloplasmin 0.1[NR 0.2-0.6], and zinc 6.1 [NR 11-24].

She was diagnosed with copper deficiency. With oral copper supplementation, her symptoms have improved.
Results: Copper deficiency is recognized as a cause of myelopathy in humans and other animals, particularly ruminants. Copper chelators are used in animal models to model demyelination and neurodegenerative phenomena. In humans, it has been seen following gastric bypass surgery or after excessive use of zinc-containing denture adhesives, although many cases are idiopathic. The disease may mimic subacute combined degeneration of the cord, optic neuropathy, or myelodysplasia with refractory anaemia and other cytopenias.

Copper deficiency myelopathy is commoner amongst women, peaking in the 5th and 6th decades. This picture is not seen in Wilson's disease, but in cases of clinical doubt, copper deficiency can distinguished by demonstrating low levels of urinary copper. Spinal MRI may show increased T2 signal in the posterior cervical and thoracic cord.

It is unclear how copper deficiency causes neurodegeneration, or why it appears similar to other deficiency related neurodegenerative conditions. Dysfunction of cytochrome oxidase, and of the methylation process involved in the synthesis of the myelin protein, may explain both the pathogenesis and the similarity between the phenotypes.
Conclusions: Copper deficiency is a rare cause of neurodegenerative symptoms that may mimic other conditions. A combination of myelopathy and cytopenia is particularly suspicious. Clinicians should be alert to this possibility, especially in patients with risk factors such as malabsorption, bariatric surgery or megadoses of zinc. After treatment, cytopenias usually resolve, but neurological recovery is often incomplete.
Disclosure statement: All authors have declared no conflicts of interest.

271. REMISSION OF RESISTANT LIFE-THREATENING NON-RENAL WEGENER'S GRANULOMATOSIS WITH RITUXIMAB AND MYCOPHENOLATE MOFITIL

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Background: A 15 year old female was referred with a 5 week history of multiple deep skin ulcers, fever, weight loss, malaise, arthralgias and nasal congestion with bloody rhinorrhoea.
Methods: The ulcers were pyoderma gangrenosum (PG) clinically and histologically. Clinical examination revealed facial swelling, nasal collapse, profound lethargy and 6 deep skin ulcers. She was hypotensive, pyrexial and urinalysis was clear. CXR was normal. CT sinuses showed opacification of the sinuses, bone mottling and some erosive changes. Nasal biopsy showed lymphocytic infiltrates around blood vessels. PR3-ANCA was 44.3 IU/ml. Wegener's granulomatosis (WG) was diagnosed.
Results: Topical nasal antiseptics, 500 mg IV methylprednisolone, 1 mg/kg oral prednisolone (pred), and 15 mg/kg IV cyclophosphamide (Cyc) were started in the vasculitis regime. Within 6 weeks of treatment all of the ulcers had healed. She rapidly gained over 40 kg in weight and became cushingoid in appearance. The nasal symptoms persisted and she developed evidence of subglottic disease. Cyc was therefore continued for a further 4 pulses. However she rapidly deteriorated culminating in an admission in respiratory distress. HRCT showed complete collapse of the left upper lobe. The left upper lobe bronchus was occluded. There was a 5 cm lobulated mass in the left lower lobe. There was also marked stenosis of the left main bronchus which measured 2 mm diameter. She received two 1 gram rituximab infusions, a further pulse of IV Cyc and escalation back to 60 mg of pred. 2 grams of mycophenolate mofitil (MMF) was then added. She was amennorheaic for over a year following initial Cyc, however periods restarted as she went into remission. Bronchial balloon dilatation was planned to treat both dyspnoea and noisy breathing, however this became unnecessary as her disease remitted. Pred has been slowly reduced and she has lost the weight she initially gained. The pressures of nasal deformity, peer exclusion, periods of hospitalization, refusal of a college course on spurious medical grounds and potent medication became too much for her as she turned 18, and she started taking excessive alcohol. Fortunately this phase passed and she is now in employment. She is seeking plastic surgery to remove excess skin at the abdomen and breasts, and has had no problems detected at clinical psychology review. As her condition remains in remission further plastic surgery to correct the nasal deformity is being considered. Photos of PG ulcers are available.
Conclusions: This case demonstrates an unusual presentation of WG, and the life-threatening nature of aggressive non-renal disease. Remission was not truly achieved until she received rituximab and MMF. This regime may be considered for aggressive or non-responsive disease, especially when exposure to increasing doses of Cyc is a concern for long-term fertility. Close liaison between ENT and respiratory services was vital in this outcome.
Disclosure statement: J.S. received travel expenses from GSK and Merck (both fees donated to charity). All other authors have declared no conflicts of interest.

272. ANTIPHOSPHOLIPID ANTIBODY SYNDROME PRESENTING AS HEMI-CHOREA IN SECOND TRIMESTER PREGNANCY

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Background: Anti-phospholipid antibody syndrome (APS) is characterized by recurrent pregnancy loss and thromboembolism due to a pro-coagulant state conferred by the presence of anti-phospholipid antibodies. Involvement of the central nervous system most often presents as a stroke or transient ischaemic attack, however chorea is rare in both primary and secondary APS. Currently, the underlying pathophysiology is poorly understood and not thought to be exclusively explained by a hypercoagulable state.
Methods: A 25yo Bangladeshi lady was referred to neurology because of a three-month history of involuntary movements of her right arm, associated with loss of power. There was progression to the right leg and she subsequently developed episodes of slurred speech and blurred vision. At the time of presentation, she was 12 weeks pregnant and the symptoms had started at conception. There was no relevant past medical history apart from one first trimester miscarriage and no significant family history suggestive of a hereditary neurological condition. A working diagnosis of chorea gravidarum was made. MRI of the head revealed no abnormalities but serology showed positive anti-nuclear antibodies (ANA) at a titre of 1/400, and a rheumatology opinion was sought. No other features of connective tissue disease were present when she was seen in clinic.
Results: Further investigations revealed negative ds DNA and ENA antibodies, normal compliment C3 but reduced C4 levels. Anti-cardiolipin antibodies were strongly positive (> 120), and positive lupus anti-coagulant test.

The patient had a second miscarriage at 19 weeks gestation strengthening the possibility that the chorea was related to anti-

phospholipid antibody syndrome and she was started on a reducing dose of Prednisolone 40 mg daily and aspirin 300 mg daily which was substituted for hydroxychloroquine 200 mg daily because she developed an urticarial rash.

Six months following her presentation she had complete resolution of neurological symptoms but remained strongly positive for anti-phospholipid antibodies.

Conclusions: There are several reports of chorea as a feature of anti-phospholipid syndrome, but no clear consensus on underlying pathophysiology. The published literature is inconclusive about the possible mechanism of injury. Cervera et al., in their review of 50 patients found that 35% of the cohort were found to have CT and/or MRI evidence of cerebral infarcts although most patients had SLE, where a vascular pathogenesis is more likely. A possible non-vascular mechanism of chorea in APS is that antigen/antibody complexes bind phospholipids in the basal ganglia and cause direct damage to neurons or supportive tissues.

Chorea should be considered as a possible manifestation of APS in young patients and prompt investigations that may reveal primary or secondary APS. Early diagnosis allows for appropriate treatment to minimize complications.

Disclosure statement: All authors have declared no conflicts of interest.

273. CASE PRESENTATION OF INFLAMMATORY MONO-ARTHRITIS TREATED WITH INTRA-ARTICULAR INFLIXIMAB

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Background: We present a case of 29 year old man with inflammatory mono-arthritis affecting the left knee. He has had swelling of the left knee since the age of 16 years. His initial treatment was with the orthopaedic department and was managed with repeated intra-articular steroid injections. Three years ago he was referred to the rheumatology department of Trafford Healthcare NHS Trust with a large left knee effusion. He had a history of psoriasis but no past history or family history of iritis, colitis or ankylosing spondylitis. He was HLA B27 positive and had evidence of unilateral sacroiliitis on plain radiograph. He was treated with sulphasalazine for 12 months with little effect followed by methotrexate which also did not have much effect. He had to stop the methotrexate after three months due to intolerance. Over a period of two years he required eight intra-articular kenalog injection mostly of a dose of 80 mg. He then had an arthroscopic synovectomy in January 2011. On review two months later he had developed a large effusion again. Treatment with yttrium was considered. However he was treated with a single dose of 100 mg infliximab given intra-articularly in May 2011. Since then he has had a small effusion but needed no further aspirations or intra-articular steroid injections. He has subsequently developed back pain and stiffness and a diagnosis of ankylosing spondylitis was made. He was recently started on adalimumab with clinical improvement in his spinal symptoms.

Methods: The case was compiled by reading through the electronic records for historic data and a review in the clinic.

Results: See conclusion.

Conclusions: There is some experience in the use of intra-articular infliximab in the treatment of inflammatory arthritis. It has previously been used in refractory rheumatoid arthritis1, 2 and with spondyloarthropathies3. A study by Conti F et al looked at efficacy and safety intra-articular infliximab in rheumatoid arthritis and psoriatic arthritis in patients refractory to steroids and disease-modifying drugs, some of whom were on infliximab or other anti-TNF agents. There was ultrasound evidence of improved synovitis. A second intra-articular injection of infliximab was sometimes required for complete remission (4). Resistant monoarthritis can be a difficult management problem. Synovectomy either chemical or surgical is still considered the definitive treatment. There are currently only few centres in the UK that perform yttrium synovectomy. Arthroscopic synovectomy is more commonly performed. This patient is an example of the severity of synovitis seen in some patients with spondyloarthropathy. We can conclude that for some patients with resistant monoarthritis, a trial of intra-articular infliximab may be an option.

Disclosure statement: All authors have declared no conflicts of interest.

274. A CASE OF ANTI-SYNTHETASE SYNDROME THAT RESPONDED TO RITUXIMAB TREATMENT

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Background: A 39 year old man was referred to the rheumatology department with painful hands and wrist of five weeks duration. He had a history of upper respiratory tract infection six weeks prior to the onset of arthralgia. Nonsteroidal anti inflammatory drugs and intra-muscular steroids (Kenalog 40 mg) from his GP were unhelpful. He had a history of a photosensitive rash in 2005 suggestive of SLE. On examination he was found to have diffuse swelling of the fingers and showed resemblance of mechanics hands. Investigations revealed he was rheumatoid factor positive (1/64) but anti CCP antibody negative, ANA positive with ENA positive for Ro, La and Jo-1. Repeat examination confirmed that he did not have muscle weakness and the creatinine kinase (CK) was not raised (69 IU/L) and both chest x-ray and pulmonary function tests were normal. He was treated with a repeat dose of Kenalog 80 mg followed by methotrexate and most of his articular symptoms settled. He was unable to tolerate higher dose of methotrexate and remained on 10 mg weekly. Nine months later he was finding it difficult to get out of the chair unaided and had stopped playing football. His CK which was raised to 2997 IU/L. HRCT showed subpleural fibrosis in both lower lobes. MRI scans of the thighs showed extensive inflammatory changes in the muscles. EMG showed myopathic changes. The histopathological appearances were consistent with an inflammatory myopathy. He was treated with two doses of rituximab 1 gm 2 weeks apart and an increased dose of oral steroids. He had a dramatic clinical improvement and the CK gradually dropped to 90 IU/L over 6 months. He is clinically in remission and has returned to playing football.

Rituximab has been used in a small series to indicate promising outcomes when treated in patients with resistant dermatomyositis and polymyositis. Levine et al showed in an open labelled study that rituximab dosed at 375 mg/m2 weekly for four weeks had achieved an improvement of muscle strength. (1) Two patients had Jo-1antibodies and anti-synthetase syndrome. These patients experienced an improvement in the forced vital capacity in 12 weeks. Another case report also showed a good response to rituximab treatment (2 doses of 1 g) in a patient with the anti-synthetase syndrome.(2) The regime used in rheumatoid arthritis was used in our case has also been tried in a previously case study.(3) In our patient we noted that the response was slower than that observed on other patients with Jo-1 -ve polymyositis treated in our unit.

Methods: The case was compiled by reviewing the electronic case notes.

Results: See above.

Conclusions: Rituximab seems a sensible option for patients having anti-synthetase syndrome who are refractory to steroids and azathioprine. This case illustrates the effectiveness of rituximab in treating patients with Jo-1 positive myositis with the the anti-synthetase syndrome. Dosing regimes and short and long term outcomes will hopefully be established in further studies.

Disclosure statement: All authors have declared no conflicts of interest.

275. HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PATIENT WITH WEGENER'S GRANULOMATOSIS

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Background: A 26 year old woman with Wegener's Granulomatosis, on long-term Azathioprine and Prednisolone, presented with fevers, myalgia, epigastric pain and diarrhoea 3 weeks after returning from the Dominican Republic.

Methods: While extensive investigations were performed, the patient was treated with antibiotics and anti-fungals on the advice of the Hospital for Tropical Diseases. She continued spiking temperatures and became progressively pancytopenic, with splenomegaly and coagulopathy. She became hypotensive and tachycardic with type I respiratory failure and was admitted to ITU for mechanical ventilation and haemofiltration.

Results: The 'septic screen' produced multiple negative blood, urine and stool cultures, as well as negative tests for ova, cysts and parasites in the stool, norovirus, Dengue, West Nile Virus, Yellow fever, Malaria, Mycoplasma, HIV, Hep B&C, EBV and HTLV-1. Amoebic and Rickettsia serology were negative. An abdominal/pelvic ultrasound found no collections or liver lesions and no vegetations were seen on echocardiography. The CRP of 87 made bacterial infection less likely. Ferritin was markedly raised (20946) and a diagnosis of

Haemophagocytic Lymphohistiocytosis was considered. A bone marrow aspirate confirmed this diagnosis and the trephine biopsy was hypocellular with no evidence of lymphoma. She was treated for HLH with Methylprednisolone, Cyclosporine and Etoposide. The CMV PCR was high (19000) and was considered to be the likely causative agent; prompting the discontinuation of Cyclosporine and treatment with Foscarnet and later Gancyclovir. Due to bone marrow suppression, she was also given Meropenem, Caspofungin and G-CSF.

A CT showed pulmonary infiltrates and signs of intra-peritoneal bleeding from a large mass within the liver, felt to be a pseudoaneurysm. The bleeding stopped with Novo 7, but unfortunately she did not recover from multi-organ failure and died following an acute myocardial infarction.

Conclusions: This case highlights the difficulty in diagnosing a patient whose non-specific symptoms, history of recent potential exposure to tropical diseases, an underlying inflammatory disorder and immune-suppression from medication creates a wide differential diagnosis. HLH is not a common complication of Wegener's, but is likely to have been caused by CMV infection secondary to immunosuppression.

Current BSR guidelines for Azathioprine caution against treating patients with localized or systemic infection including Hepatitis B or C, or a history of tuberculosis. There have been several case reports of HLH in patients taking Azathioprine for a variety of gastroenterological and rheumatological indications. Given the prevalence of CMV in the general population, it may not be appropriate to screen for previous exposure prior to starting Azathioprine. However, the possibility of HLH with underlying viral infection or re-activation should be considered in immunocompromised patients presenting with fevers and cytopenia.

Disclosure statement: All authors have declared no conflicts of interest.

276. ANTI TA/MA2 ANTIBODIES IN BRAINSTEM VASCULITIS WITHOUT MALIGNANCY

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Background: Anti Ta/Ma2 antineuronal antibodies are associated with paraneoplastic neurological syndromes. (Hoffmann et al, 2008). We have previously reported a single case (no:3) with cerebral vasculitis only (Mehta etal 2009).

Methods: We now describe three cases of Brain Stem Vasculitis with anti-Ta/Ma2 antibodies and no known malignancy at more than three years from diagnosis.

Results: Case 1 - 45 year old wheelchair dependent lady with morbid obesity and type 2 DM presented with severe headaches, right hemiparesis, dysarthria, swallowing deficit and foot drop. MRI showed multiple vascular lesions in bilateral cerebral hemispheres and MRA circle of Willis (MRA COW) showed irregularities consistent with vasculitis. Autoimmune screen, ANCA and thrombophilia screen was negative. Lumbar puncture was unsuccessful. Anti Ta/Ma2 antibodies were positive on Western Blot. No malignancy was found. She was treated for cerebral vasculitis with IV and oral steroids and Mycophenolate mofetil. Her headaches resolved and speech and swallowing and power improved though she remained wheelchair dependent as before. She died from abdominal sepsis three years later without any evidence of neoplasia.

Case 2 - 51 year old lady with persistent debilitating headaches over several years and sicca symptoms had speckled ANA 1:640, ENA negative. MRI Brain shows multiple small foci of high signal intensity within white matter of both cerebral hemispheres, Pons and Medulla. MRA COW showed pathological reduction in size of right anterior cerebral artery. Oligoclonal bands (OCB) were present in the CSF. Anti Ta/Ma2 was positive. She responded to Prednisolone and IV cyclophosphamide / MMF therapy. At 3+ years she has no evidence of malignancy.

Case 3 - A previously reported (Mehta 2009) 61 year old female with Sjogren's syndrome presented with a posterior inferior cerebellar artery syndrome. She had positive ANA, Ro, La, rheumatoid factor and hypergammaglobulinaemia. Lupus anticoagulant and anticardiolipin antibodies were negative. MRI brain shows high signal intensities in the frontal lobes, left medulla and cerebellar hemispheres. MRA COW revealed left vertebral artery occlusion and narrowing of the right vertebral artery suggestive of vasculitis. OCB were present in CSF. Anti Ta/Ma2 was strongly positive and there is no evidence of malignancy. She was treated with cyclophosphamide with virtual recovery of all neurological signs besides mild ataxia. At 4+ years she has no evidence of malignancy.

Conclusions: Anti- Ta/Ma2 in neurological syndromes are commonly seen with testicular germ cell tumours but also in lung and breast cancer. Headaches and brainstem features in our three cases suggest there are non-paraneoplastic mechanisms for production of these autoantibodies, and recommend anti-neuronal ab screen in all cerebral vasculitides

Disclosure statement: All authors have declared no conflicts of interest.

277. USE OF RITUXIMAB TO TREAT RHEUMATOID ARTHRITIS AND FOCAL SEGMENTAL GLOMERULAR SCLEROSIS

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Background: Rituximab, a B cell depleting antibody, has been successfully used for Rheumatoid Arthritis (RA) and post renal transplant to prevent recurrent FSGS. Recent findings suggest the action of rituximab in FSGS may be through modulating podocyte function in the kidney.

Methods: We present 2 cases of difficult to treat rheumatoid arthritis (RA) and FSGS successfully treated with rituximab.

Results: Case 1: A 48 year old lady with a background of bronchiectasis with recurrent chest infections and long standing, erosive seropositive RA on methotrexate (MTX), developed FSGS with nephrotic syndrome. Her kidney disease was stable with persistent proteinuria on prednisolone and ciclosporin (CPN) which was subsequently withdrawn. She deteriorated in 2007 with active RA, anaemia, neutropenia and mild splenomegaly. MTX was withdrawn and she required erythropoietin and GCSF injections for a presumptive diagnosis of Felty's syndrome. She was treated with four weekly infusions of rituximab (RTX) following a standard haematology protocol.

Her haemoglobin and white cell count normalized within 3 infusions and GCSF and erythropoetin injections were stopped. Her creatinine and albumin normalized and proteinuria resolved. Four months after RTX her RA improved enabling a reduction in steroid dose, but a year later flared requiring the reintroduction of MTX.

Case 2: A 42 year old man with a 12 year history of FSGS and nephrotic syndrome presented with new onset sero-negative RA in 2007. Past treatment for renal disease included prednisolone and CPN. CPN was stopped prior to commencing MTX to treat his RA. His proteinuria recurred and he was treated with 2 cycles of RTX 12 months apart whilst continuing Prednisolone only. MTX was stopped.

Six months following the first RTX cycle his joint symptoms improved significantly with reduction in clinical and ultrasonographic synovitis. Levels of proteinuria continued to fluctuate but following the second RTX cycle his urine albumin:creatinine ratio and total protein:creatinine ratio remain at lowest levels seen since diagnosis of FSGS. His renal function remains stable.

Conclusions: To our knowledge, these are the first cases in which RTX has been used to induce remission for patients with both RA and FSGS. Our second patient was able to stop both MTX and CPN, thus the burden of immunosuppressant therapy was reduced. We suggest that RTX be considered early in the treatment of inflammatory rheumatic disease complicated by FSGS.

Disclosure statement: All authors have declared no conflicts of interest.

EDUCATION RESEARCH

278. CAN PEER ASSISTED LEARNING DELIVERED BY MEDICAL STUDENTS BE USEFUL IN TRAINING SENIOR COLLEAGUES IN USE OF REMS TECHNIQUE FOR MSS EXAMINATION? A PILOT STUDY

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Background: In 2008 training in musculoskeletal system (MSS) examination at Glasgow University changed from the Gait, Arms, Legs and Spine technique to Regional Examination of Musculoskeletal System (REMS). Vocational Studies Tutors (VSTs), mainly general practitioners, and hospital consultants who supervise MSS training for medical students in years 2 and 3, asked for extra training in REMS before teaching students the new technique. Peer-assisted-learning (PAL) programmes delivered by senior medical students have been effective in providing additional tuition for younger students (1). As yet

no studies have assessed the benefit of student-led teaching with PAL techniques to senior colleagues. Here we have address whether medical students can effectively use PAL techniques for training senior colleagues.
Methods: Glasgow VSTs attend an annual Teaching and Learning Event (TALE) designed to equip the tutor with the skills needed to facilitate effective student learning. Since its introduction 1 of the 8 workshops has been devoted to training VSTs in the use of REMS. In a pilot study, 8 trained medical students used PAL techniques to train 23 VSTs in use of REMS for lower limb examination. Students demonstrated the REMS techniques on each other to groups of up to 6 VSTs, and then volunteered to give the VSTs an opportunity to practice the examination on them, while helping provide constructive feedback on the technique. VSTs were asked to evaluate each session for value using a 4 point Likert scale, complete a course evaluation questionnaire and provide free text comments.
Results: All VSTs (100%) agreed or strongly agreed that student-led REMS teaching had met their expectations, achieved the stated aims and been engaging, relevant and interesting. A single concern was raised by a VST during knee examination but review confirmed the student technique to be correct. Free text comments were submitted by 13/23 (57%). 7 (54%) commented on the good quality of the session and 4 (31%) on the positive impact for their future teaching. One VST stated that the student demonstration were better than many delivered by clinicians. 10 VSTs (77%) perceived an improvement in their confidence to examine the MSS in patients. 3 made no comment and the remaining 2 stated that they had already been using the REMS techniques being demonstrated. Overall the REMS session rated highest of all eight TALE workshops.
Conclusions: Student-led PAL style teaching can support learning for students and senior colleagues and may benefit patient care by improving VST confidence in MSS examination.
Disclosure statement: All authors have declared no conflicts of interest.

279. DRUG KNOWLEDGE IN PATIENTS ESTABLISHED ON LONG-TERM TREATMENT WITH METHOTREXATE

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Background: Methotrexate (MTX) is the most frequently prescribed DMARD for inflammatory arthritis. Knowledge of the drug is essential for patients to take it safely and effectively and this is recommended by the PSA. Patients routinely receive this education on commencement of the drug with the intention of improving understanding to optimize patient concordance and safety. Little is known of the effectiveness of this interaction. Patients may be on the drug for many years and in our units, no formal reinforcement is delivered. We were interested to explore the knowledge of long term Methotrexate users as a prelude to studying the educational interaction.
Methods: Fifty two consecutive patients who had been on MTX for at least 2 years and were on no other conventional DMARDs were recruited from outpatient clinics. They were asked to complete a MTX knowledge questionnaire (MKQ) which was based on the ARUK information sheet.
Results: The population was mainly RA (89%) with some psoriatic arthritis and 1 gut associated. Average age was 59yrs (Range 24-84) with average duration of MTX of 6.2yrs (Range 2-15).

The average score on the MKQ was 12.9 out of 18 (72%) (Range 6-18). All but one patient knew how to take the drug, but there was much less certainty about how long it takes to work.

There was a range of knowledge of vaccinations which was in line with the total score. Knowledge of expected side effects was somewhat less. 12 patients (23%) did not identify shortness of breath as a significant side effect. Blood monitoring requirements were well known.

8 (15%) patients thought it was OK to get pregnant while on MTX, with 13 (25%) offering no answer. 12 (23%) thought it was OK to take antibiotics with the MTX while only 4 (8%) thought that there was no limit to alcohol consumption.
Conclusions: While 72% may be a good result in an public exam, if the subject is core safety knowledge then it is better viewed as 28% wrong. As expected in established patients they knew how to take MTX and about monitoring. The poor knowledge of vaccinations may lead to sub optimal immunization. The substantial minorities not knowing about shortness of breath; pregnancy and antibiotics is more worrying and suggests that further input is required.
Disclosure statement: All authors have declared no conflicts of interest.

280. OPEN ACCESS MUSCULOSKELETAL ONLINE EDUCATION: VIRTUAL PATIENTS LEADING THE WAY

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Background: Virtual patients (VPs) are an approach in e-learning that use web based clinical representations of realistic clinical cases. They can be used to complement the teaching of a range of competencies including clinical reasoning skills. Unfortunately, musculoskeletal e-learning resources are often restricted to individual institutions, and created using bespoke information technology systems which are not easy to edit, share, update or expand. Open access VP cases represent one potential solution to this problem, in that they are created to an accepted technical inter-operability standard. They have the potential to cost effectively broaden the undergraduate exposure to core musculoskeletal (MSK) problems.
Methods: Following institutional ethics approval, we have developed a series of VP cases that focus on core MSK problems (large joint degenerative arthritis, back pain, polyarthritis, connective tissue disease). Each case has been developed using an open access approach to e-learning resources. All case content (text, clinical images, radiography, pathophysiology images, feedback) are taken from appropriate sources or have been created for the project. All use a Creative Commons attribution-share-alike licence. As a consequence, all media in the VP case including over 120 images, investigation results, photographs, and annotated images will be freely available for any educator to use, modify, and re-publish either in any format.
Results: The study has already enrolled students from three centres in the United Kingdom. By the end of the academic year 2011-2012, over 650 students from a single year group in Birmingham, Keele, and Warwick Medical schools will have been provided with access to the MSK education cases in the context of a research study. Students are using cases in both time-tabled teaching sessions, and self-directed study time. Following the end of the study period, the cases will form a freely accessible MSK education resource for students, which can be distributed to undergraduates using existing IT infrastructure. Furthermore individual educators can modify and adapt cases to local requirements, with no associated licencing cost.
Conclusions: The use of online resources in undergraduate MSK education is likely to increase. VPs can be an attractive, free, evidence-based teaching resource that can be widely distributed to all MSK undergraduates in the United Kingdom at low cost, if materials are published under an open access licence. Although producing, maintaining, and updating such resources remains a challenge, open access VP cases funded by national bodies are likely to promote collaboration between institutions, increase student exposure to core MSK problems, and assist in formative and summative assessments of undergraduates.
Disclosure statement: All authors have declared no conflicts of interest.

281. CHOOSING A CAREER IN A MUSCULOSKELETAL SPECIALTY: HOW POPULAR ARE RHEUMATOLOGY AND ORTHOPAEDICS AMONG MEDICAL STUDENTS AND WHAT FACTORS ARE RELEVANT IN THE CHOICE?

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Background: Musculoskeletal conditions affect at least 25% of the population at any point in time. As the population ages, more musculoskeletal morbidity is inevitable. Most medical students receive a basic grounding in rheumatology and orthopaedics at medical school but little is known about what influences them to choose these careers long-term.
Methods: All fourth year medical students in one of the new medical schools were surveyed about their career aspirations and what they felt might influence their future career choices. Detailed information was collected about factors which may have shaped career preferences alongside personal characteristics such as team skills and practical aptitudes.
Results: 87 completed questionnaires were returned (71%). All respondents had heard of Rheumatology and Orthopaedics with 91% and 86% respectively stating they knew what these specialities involved. From the whole range of career options, 6/87 (7%) defined Rheumatology as their main aspiration and a further 25 (29%) thought

they might be interested. 7/87(8%) selected Orthopaedics as their main aspiration and 18 (21%) stated they might be interested. No student described both rheumatology and orthopaedics as a 'main' aspiration. Students expressing a main aspiration for Orthopaedics were significantly more likely to be male (6/7, $p < 0.0001$), whereas Rheumatology was the main choice of 3 men and 3 women. 16/25 interested in orthopaedics and 19/31 interested in Rhuematology had an intercalated or other degree.

A key influence cited by students for choosing Rheumatology was that of role models. For aspiring orthopaedic surgeons, medical student experiences were cited as key. Among the personality traits, students interested in Rheumatology were more likely to say that understanding people was important and that they enjoyed problem solving and sharing their ideas with others. Being a practical person was associated with a main career aspiration for Orthopaedics, along with being a person who needed to have proof. Similar numbers of students with a main aspiration for either Rheumatology or Orthopaedics indicated that they like to know how things work but that they find it hard to 'step into someone else's shoes'.

Conclusions: By the fourth year of medical school, the majority of students have developed preferences for particular specialities. Career decisions are influenced by many factors and our results demonstrate that gender, personal characteristics, role models and medical school experiences are among the determinants for choosing a career in Rheumatology and Orthopaedics. Future research is needed to see how many graduates maintain these aspirations and whether they are ultimately successful.

Disclosure statement: All authors have declared no conflicts of interest.

282. DELIVERING THE RHEUMATOLOGY CURRICULUM: A REVIEW FROM THE TRAINEE AND TRAINER PERSPECTIVE

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Background: The Royal College of Physicians holds responsibility for training curricula and assessment systems, but deaneries and local education providers are responsible for delivering suitable training programmes.

Methods: Curriculum delivery was reviewed by structured interview of both rheumatology trainees and trainers to assess current posts met JRCPTB/GMC general standards for training. Two 'expert' Rheumatology trainers were asked to define knowledge, skills and attitudes required of Rheumatology trainees at 3 levels (ST3, ST4-5, ST6-7) in a Designing a Curriculum (DACUM) process. Finally two trainees logged their clinical experience, and the case-mix mapped to core topics in the 2010 curriculum.

Results: Learning opportunities were available in both outpatient clinics and inpatient ward-rounds, including demonstration of practical procedures, with exposure to a wide range of rheumatological conditions. Formal instruction in basic science and pharmacology as well as modern rheumatology practice was achieved through deanery training days and an MSc in Rheumatology. All posts provided opportunities for audit, and many also provided research experience.

The DACUM process identified generic and specialty skills across both rheumatology and general internal medicine, with progression of competencies during training.

Workplace based assessments were felt to be useful by both trainees and trainers if performed correctly. However, trainees reported variation in the execution of these assessments, raising concerns over their reliability.

Mapping of case-mix to core topics in the curriculum showed a broad coverage of core topics with little difference in case-mix between DGH and teaching hospital settings (Table), demonstrating the importance of experiential learning to rheumatology specialty training.

Conclusions: Successful completion of specialty training is now based on acquiring competencies rather than a pre-ordained time within training posts. Mapping of individual cases to core topics demonstrates accrual of relevant experience, and identifies areas of the curriculum that are less well covered during training, guiding personal and professional development plans to meet individual training needs.

TABLE 1 Cases seen by rheumatology trainees matched to curriculum topics

	District hospital 12 months 50% Rheum n (%)	Teaching hospital 4.5 months 100% Rheum n (%)
Musculoskeletal problems and soft-tissue rheumatism	41 (7.3)	53 (11.8)
Osteoarthritis and related conditions	64 (11.4)	30 (6.7)
Crystal-associated pathologies	24 (4.3)	15 (3.3)
Rheumatoid arthritis	119 (21.3)	84 (18.8)
Spondyloarthropathies	67 (12.0)	55 (12.3)
Juvenile idiopathic arthritis	0 (0)	4 (0.9)
Autoimmune connective tissue disorders	204 (36)	160 (35.7)
I CTD II GCA/PMR III APS IV Vasculitis	136 (24.3) 23 (4.1) 14 (2.5) 31 (5.5)	86 (19.2) 29 (6.5) 5 (1.1) 40 (8.9)
Bone disorders	23 (4.1)	8 (1.8)
Metabolic, endocrine and other disorders	4 (0.7)	4 (0.9)
Infection and arthritis	6 (1.1)	10 (2.2)
Neoplastic disease	4 (0.7)	5 (1.1)
Miscellaneous disorders	4 (0.7)	20 (4.5)

Disclosure statement: All authors have declared no conflicts of interest.

283. BENEFICIAL EFFECTS OF OMEGA-3-POLYUNSATURATED FATTY ACIDS ON SF-36 SCORES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is the archetypal autoimmune disease, with a wide range of clinical manifestations. Among the clinical challenges of SLE, one of the most compelling is the high incidence of atherosclerosis in young women that is not fully explained by the incidence of traditional Framingham risk factors. Supplementation with omega-3 polyunsaturated fatty acids (PUFAs) improves conditions associated with atherosclerosis, and we have previously shown a beneficial effect on endothelial function and disease activity in patients with SLE following a 24 week clinical trial. The MOS Short Form 36 (SF-36) is a measure of functional health and is useful in comparing the relative burden of disease across populations and in assessing the cost-effectiveness of different treatments. It includes thirty-six questions covering eight domains which relate to the patient's perception of pain, fatigue, physical and mental health. We here report the impact on SF-36 scores of patients with SLE before and after treatment.

Methods: A total of 60 patients who fulfilled the ACR diagnostic criteria for SLE were selected and entered the randomized double-blind placebo-controlled trial. The patients were randomized to take either 3 grams of Omacor (n3-PUFAs: 1.8 grams Eicosapentaeinoic acid & 1.2 grams Docosahexaenoic acid) or placebo for a total of 24 weeks and all subjects were asked to complete the SF-36v2 health questionnaire at week 0 (baseline) and week 24. Continuous data were then analysed using paired t-tests where normally distributed and the Wilcoxon rank test where not normally distributed.

Results: At baseline, patients with SLE showed significantly lower values in all eight domains of SF-36 compared with United Kingdom and Northern Ireland population means. There was no statistical significance between the baseline scores (at week 0) for the placebo group or treatment groups. After unblinding, the placebo treatment arm showed no difference in any of the eight domains of the SF-36 scores at week 0 and week 24, whilst the treatment arm showed statistically significant differences in domains relating to emotional well-being (role emotional) and social function with p-values of 0.01 and 0.04 respectively. Pain and general health scores in the treatment group improved, but did not reach statistical significance.

Conclusions: SLE patients have significantly reduced health status measured with SF-36. This study demonstrates that 24 week dietary supplementation with Omacor significantly improves SF-36 health status domains of emotional well-being and social functioning.

Disclosure statement: All authors have declared no conflicts of interest.

284. MEDICAL STUDENTS PERCEPTION OF RHEUMATOLOGY AS AN OPTION DURING FOUNDATION TRAINING: RESULTS FROM OPEN RESPONSES OF A NATIONAL SURVEY

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Background: In a survey taken place in 2009 among medical students in which 256 students from 11 medical schools responded, Rheumatology was among the bottom 3 specialities of choice from a total of 21 to be considered useful for foundation year 1 (FY1) and foundation year 2 (FY2) training.
Methods: Aiming to assess the rationale behind 4th, 5th and 6th (where applicable) year medical students' views on having Rheumatology as part of their foundation training, we analysed the open responses of those provided and grouped them in subcategories according to their content. The following subcategories were developed: 1) Fascinating area, 2) overlap with other specialities/limited exposure/lack of ward patients, 3) not sure/don't know/don't mind, 4)small speciality/very specialized/not interested and 5)other/ irrelevant.
Results: A total of 49 open responses were obtained from the 254 medical students (19.2%). Two students out of 49 regarded Rheumatology a fascinating area (4%); 16 students (32.6 %) were unclear because they either considered it overlapping with other specialities (7 of 16; 43.7%); or they felt they had been offered limited exposure (4 of 16; 5%);or due to the lack of dedicated ward beds (5 of 16; 31.2%). Seven (7) of 49 students (14.2%) had no preference or did not think about it, while 8 of 49 (16.3%) considered it ''very specialized'',''small'',''niche'' speciality of no interest. Another 7 students (14.2%) provided comments irrelevant to the question on the rationale behind it, by either commenting on the structure of the survey, the bias related to exposure they had experienced, or offering suggestions i.e for non clinical specialities. Looking at those (24 of 256; 9.37%) who had chosen Rheumatology as part of FY1/FY2 rotation, they were 7 males and 17 females (M:F = 1:2.4) Most were aged 22-28 years (23 of 24; 95.8 %) (1 was in 36-42 age group). 6 were attending 4th year (25%), 15 attending 5th year (62.5%) and 3 were attending 6th year (12.5%). 21 were undergraduates (87.5) and 3 (12.5%) were from graduate entry programs (GEPs). Ten of 24 (41.6%) responded the rationale behind their choices as follows: 5 students (50%) wanted Rheumatology because it is required in their chosen career path (3 of those aiming for general practice and 2 for orthopaedics). 3 students wanted Rheumatology in FY1/FY2 training to enable exposure and aid them in future career decision-making; 2/10 wanted it as they planned a career in Rheumatology.
Conclusions: Medical students consider Rheumatology a small ''niche'' speciality having considerable overlap with other specialities, particularly Medicine and Orthopaedics. This does not provide knowledge needed for foundation years training. The lack of in-patients' dedicated beds contributes to it, making it more of an 'outpatient' specialty. Many medical students consider their time spent in Rheumatology during theirl training years as 'rheuma-holiday'.
Disclosure statement: All authors have declared no conflicts of interest.

285. THE INFORMATION AND SUPPORT NEEDS OF PEOPLE LIVING WITH RHEUMATOID ARTHRITIS

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Background: A UK national helpline received 43,338 contact enquiries from 2007-10. There were 6,377 [14.7%] calls from people self-reporting RA. We have examined the information needs of this group at first contact.
Methods: Every helpline contact is logged anonymously onto a secure confidential database complying with the UK Data Protection Act. Demographic Data is routinely recorded with the reason(s) for contact selected from drop-down menus. Analysis was made of all first time contacts from adults [≥18 years] with self-reported RA.
Results: Over the study period, the helpline received 6,377 contacts reporting RA, of which 3,792 (59%) were first time contacts. A new diagnosis had recently been made in12%. Forty six percent lived in southern England.

The majority of subjects were female 81% and 67% of working age. Forty eight percent were aged 45-54 years old, 33% over 65 years old, 17% 26-44 years old, and 2% 18-25 years old. Of these 9.6% enquired about benefits. Of those in work, 8% reported problems with their employers.

Contacts reported an additional form of arthritis in 14% with 11% noting osteoarthritis. Fibromyalgia, polymyalgia rheumatica and gout were also described. Co-morbidities were reported in 10%, with osteoporosis being the most frequent, followed by coronary heart disease and hypertension.

The commonest issues raised were RA disease knowledge (45%) and pain control (45%). A further 40% asked about drugs, of which 55% needed explanation of specific treatments. Where pain was raised as a problem, 80% asked for specific information to take back control and manage themselves better.

Twenty seven percent of contacts had emotional needs. The majority of these people [86%] preferred to talk about their problems ''one to one'' rather than receive written information. A small number (4%) feeling lonely, isolated and depressed.

Nineteen percent asked for information about exercise [720] and a similar number about diet and healthy eating [712]. There were 284 enquiries about self management programmes with 72% of these requested more information. Ten percent [370] talked about mobility problems and of these 72% required signposting information. Nine percent reported referral difficulties to secondary health care.
Conclusions: We identified the key information needs as understanding their disease, pain control, drug information and emotional issues. Contacts with emotional needs [27%] were able to utilize a professional counselling service to help them cope with living with RA.

Most contacts were from people of working age and 8% experienced employment problems.

People with RA have information needs requiring personal telephone contact. This may represent a need for independent advice or a shortfall in their local primary or secondary care service.
Disclosure statement: All authors have declared no conflicts of interest.

286. ARE MEDICAL STUDENTS INTERESTED IN SELECTING MUSCULOSKLEETAL MEDICINE (RHEUMATOLOGY AND ORTHOPAEDICS COMBINED) AS A FOUNDATION YEAR TRAINING ROTATION?

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Background: Rheumatology has been found to be of less interest amongst medical students for FY training, attracting only 9% and being the 3rd speciality from the bottom among the 21 specialities of choice. One of the reasons for this was that Rheumatology is taught in most medical schools combined in a medical or orthopaedic rotation. The aim of this analysis was to assess whether Rheumatology and Orthopaedics comprising musculoskeletal medicine (Msk) are of any interest to medical students for FY training.
Methods: The online questionnaire in 2009 consisted of 10 questions (designed on www.surveymonkey.com) that targeted 4th, 5th and 6th (where applicable) year students. The survey was a service evaluation and therefore exempt from ethical approval. Responses obtained were treated confidentially.
Results: The 6 most preferred specialities amongst medical students were: acute medicine, emergency medicine, surgery, general practice and paediatrics, with the 6th preference varying according to the medical school. The total group preferred Cardiology; Queen Mary's group were inclined towards respiratory medicine while the Oxford group were interested in Neurology.

In the total group, 68 of 254 students (26.7%) expressed an interest for Msk medicine to be part of the FY program. From those 44 (17.3%) expressed a desire to do Orthopaedics [(M:F = 19:25; 40/44 were at the 22-28 age range; 16 were 4th year, 26 were 5th year, 2 were 6th year; 41 were undergraduates and 3 were GEP] and 24 (9.4%) wanted to do Rheumatology [[M:F = 7:17; 23 /24 were at the 22-28 age group; 6 were 4th year, 15 were 5th year, 3 were 6th year; 21 were undergraduates and 3 were GEP.]

A total of 25 open-ended responses (15 from the 44 students willing to have Orthopaedics and 10 of 24 students willing to have Rheumatology) were collected; 13 of 25 would like exposure to Msk specialities as it would be useful for their career choice. The other 12/ 25 want more exposure/teaching to support their career choice (General Practice, Trauma, Forensic Medicine, Paediatrics)

When we analysed responses from only 5th year students belonging to the 2 medical schools that supplied us with the highest response rate (Queen Mary's (n = 43) and Oxford (n = 36), we identified

that 11/43 (25.5%) from the QM students and 9/36 of OX students (25%) expressed an interest for musculoskeletal medicine.
Conclusions: One in 4 medical students are willing to have some form of training in musculoskeletal medicine (orthopaedics and/or rheumatology) in FY. Msk medicine taken together is placed 10th in the ranking of specialities needed for FY training. These 2 specilaities, however, when taken individually are placed further down with orthopaedics being 14th and Rheumatology being 19th out of 21 in the ranking.
Disclosure statement: All authors have declared no conflicts of interest.

287. SUN EXPOSURE AND THE USE OF SUNSCREEN AMONG INFLAMMATORY ARTHROPATHY PATIENTS RECEIVING ANTI-TNF THERAPY

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Background: Exposure to the sun and getting sunburned have been well documented as causative factors for development of skin carcinoma. Findings from the British Biologics Register suggests an increased risk of such carcinomas among RA patients on DMARD therapy, while there has long been a question surrounding the risks of carcinoma development secondary to the use of biologic therapies. From a Rheumatology perspective vasculitis patients are very aware of the risk of sunburn and skin cancer, and actively use sunscreen. Little is known about inflammatory arthropathy patients, especially those receiving biologic therapies, regarding sun exposure or the use of sunscreen. Our aim is to explore this area.
Methods: All patients with a diagnosis of an inflammatory arthropathy being treated with anti-TNF therapy attending the Rheumatology Services at our hospital were eligible for inclusion, with 276 randomly selected for a telephone survey. The survey focused on sun exposure and use of sunscreen. It was carried out during June 2011. Patients under 18 yrs old and those no longer receiving/deceased were omitted from the study. Patients not contactable after two attempts were also excluded. Data was analysed using the statistical package SPSS.
Results: A total of 276 patients were telephoned with 155 contactable and 150 willing to take part (97% response). 40% (n = 60) were male and 60% (n = 90) female with a mean age of 54.3yrs and all Caucasian. 117 had RA, 14 PsA, 1 SNA and 18 AS. The mean length of diagnosis was 11.22yr (range: 1-30yr) with a mean of 3.64yrs (range: 1month - 10yrs) receiving anti-TNF therapy and 106 patients receiving concurrent MTX (17 via SC injection). 73% (n = 110) go on sun holidays and 20% (n = 30) have a sunbed use history. 65% (n = 98) use sunscreen when exposed to the sun, 87% (n = 131) report previous sunburn and 5% (n = 7) report ever receiving advise regard sun exposure/sunscreen use. 6% (n = 9) report a skin cancer diagnosis with 1% (n = 2) awaiting consultants for mole assessment. Of those with a skin cancer the mean age was 63yrs, none received prior sun advice but all use sunscreen, they had a 4yr history of anti-TNF therapy with all cancers after commencement of ant-TNF therapy, 6 use concurrent MTX orally, 3 use sunbeds (male ×1, female ×2) and 6 report previous sunburn.
Conclusions: Patients need to be educated regarding sun exposure, its risks and prevention measures, along with the facts of skin cancer. It is questionable if we should follow up patients, at time intervals, after commencing anti-TNF therapy for skin cancers.
Disclosure statement: All authors have declared no conflicts of interest.

288. EVALUATION OF THE FIRST BSR TEACHING THE TEACHERS COURSE

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Background: Is it suggested that Rheumatology trainees and AHP's receive training in teaching skills. Often courses are run locally through a deanery and provide generic teaching skills. This does not answer some of the needs specific of Rheumatology teaching. In September 2011 we set up and ran the 1st BSR course 'teaching the teachers' and present course evaluation below.
Methods: The aim was to deliver practical and meaningful teaching skills specific to AHP's and Rheumatology trainees. The course involved overviews in areas of learning theory, lesson planning, giving feedback, educational research and small group teaching. The focus on day one was also in teaching the clinical skills of GALS and REMS. This was delivered in a way previously validated in primary care (1). This involved each delegate taking on the role of student and then teacher giving the opportunity to incorporate and reflect on new skills. Day two workshops focused on preparing a lesson plan for a teaching event. These were focused on likely scenarios such as teaching medical students about DMARDS. This allowed delegates to develop lesson plans mapped to learning theory and different student learning styles.
Results: In a specific questionnaire survey of the 16 delegates (Likert scale 1-5, poor to excellent), the aims and objectives of the course were considered to have been achieved. Overall the course was rated highly at 4.19 with 100% of delegates stating it would change their practice in teaching. The practical teaching of GALS and REMS and the lesson planning workshops recorded the highest feedback (4.5 and 4.75). Qualitative feedback asked for more time given to clinical teaching and the practice of skills (GALS and REMS). Delegates appeared to enjoy the opportunity of practicing teaching in a non-threatening environment.
Conclusions: Often the acquisition of teaching skills is on an 'ad hoc' basis but perhaps a more structured development route in Rheumatology can be attained. We would suggest that this would lead to better teaching outcomes for individuals and help to raise the profile of Rheumatology amongst students. Although this further evaluation work needs to be carried out. Overall satisfaction with this 1st course has been excellent suggesting a need for further events. These could include further modules on assessment skills, evaluation methods and program design.
Disclosure statement: All authors have declared no conflicts of interest.

Reference

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EPIDEMIOLOGY

289. PREDICTORS OF LOW BONE MINERAL DENSITY IN MEN AND WOMEN UNDER 50 YEARS OF AGE

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Background: Little is known regarding the therapeutic options and prognosis in patients diagnosed with osteoporosis when under the age of 50. This study set out to identify the predictors of a low bone mineral density (BMD) in this age group for both men & women.
Methods: Patients under 50 years of age attending for a DXA scan at the Royal Lancaster Infirmary from 1992-2010 were included in the analysis. Factors influencing Gross Total mean hip BMD and Spine L1-L4 BMD data were assessed independently using univariate and multivariate linear regression adjusting for possible confounders, males and females were analysed separately. Factors included: Gender, age at scan, height, weight, BMI, index of multiple deprivation (IMD) score, rheumatoid arthritis, family history of fractures, age of menopause (females), number of indications for scan, previous fracture, any tobacco use, any steroid use, and any alcohol excess.
Results: There were 3872 patient's data analysed in the study, with a mean age of 42.4 years (SD = 6.91). 3348 were female, 86.5% of the total population. Significant predictors identified using the multivariate linear regression model analysis are shown in Table 1.
Conclusions: The study found the predictors of a low BMD in the under 50's varied according to anatomical location and sex, with the only consistent predictor the number of indications for scan. Further study is needed to expand upon this knowledge and assess the utility of using these predictors in clinical practice for the identification of high risk individuals.

TABLE 1 Significant predictors of low BMD according to multivariate linear regression analysis

Predictors	Coefficient	95% Confidence interval	P value
Female total mean hip BMD data			
Weight	.0050	.0040 to .0060	<0.001
BMI	−.0030	−.0070 to -.0003	0.032
Number of indications for scan	−.0200	−.0260 to -.0140	<0.001
Family history of fracture	.0170	.0020 to .0310	0.026
Female L1L4 BMD data			
Height	.0020	.0005 to .0030	0.010
Weight	.0040	.0020 to .0050	<0.001
Indicies of multiple deprivation score	−.0004	−.0008 to -.0001	0.019
Number of indications for scan	−.0270	−.0330 to -.0210	<0.001
Family history of fracture	.0180	.0013 to .0350	0.035
Age at scan	.0010	.0003 to .0020	0.006
Male total mean hip BMD data			
Number of indications for scan	−.0280	−.0470 to -.0081	0.006
Male L1L4 BMD data			
Height	.0140	.0040 to .0230	0.004
BMI	.0330	.0020 to .0640	0.037
Number of indications for scan	−.0290	−.0460 to -.011	0.001
Any tobacco use	.0480	.0050 to .0900	0.028

Disclosure statement: All authors have declared no conflicts of interest.

290. CHRONIC WIDESPREAD PAIN, CO-MORBID DEPRESSION AND FATIGUE IN OLDER PEOPLE

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Background: In people aged ≥ 65 years fatigue is associated with increased morbidity and mortality. Chronic widespread pain (CWP) increases the risk of developing clinically significant fatigue. Whether depression, a common CWP comorbidity, is associated with a further increased risk is unclear. The aim of this study was to test the hypothesis that among older people with CWP co-morbid depression would significantly increase the risk of fatigue.
Methods: A cross-sectional study was conducted. Subjects were 765 individuals aged 66-99 years who had participated in the Ageing and Cognitive Performance Research Centre Study, a long-term prospective cohort study conducted in the North of England. All subjects were mailed a questionnaire that assessed the presence, distribution and duration of pain. Using their pain reports subjects were classified as ''CWP'' using the criteria in the ACR classification for fibromyalgia, ''some pain'' were subjects with pain that did not satisfy the criteria for CWP, or ''no pain''. Depression was classified using the Hospital Anxiety and Depression (HAD) scale as ''non-case'' (score 0-7) or ''borderline/definite case'' (≥ 8). The outcome was the Chalder Fatigue Scale (CFS), score range 0-11, categorized as ''None'' (score 0), ''Moderate'' (1-3), ''Clinically significant'' (4-11) fatigue. The questionnaire also assessed sociodemographic factors (age, sex, number of children, age left education, marital status) and gastrointestinal symptoms (Irritable Bowel Syndrome (IBS), Rome II criteria). Multinomial logistic regression was used to quantify the relationship between CWP, depression and the combined effects of CWP and depression, with CFS scores. Subjects with no pain were the referent category. Results are presented as relative risk ratios (RRR) with 95% confidence intervals (CI).
Results: A total of 537 (70.2%) subjects returned a questionnaire and provided complete data. The median age of subjects was 84 years (IQR 80-88) and 411 (76.5%) were female. Of the 537 participants 117 (21.8%) had CWP, 224 (41.7%) reported some pain, and 196 (36.5%) reported no pain. 57.3%, 46.0%, and 29.6% of those subjects respectively were depressed. After adjusting for age and sex the RRR of clinically significant fatigue among those with some pain was 2.5 (95% CI 1.4, 4.3) and CWP 4.3 (2.2, 8.9). Depressed subjects were almost 8 times more likely to report clinically significant fatigue, 7.5 (4.3, 13.1). These associations were attenuated after adjustment for sociodemographic factors, HAD anxiety, and IBS although all associations remained statistically significant. The presence of comorbid depression in subjects with some pain or CWP was non-multiplicative (0.8 (0.2, 2.7) and 0.96 (0.2, 4.4) respectively).
Conclusions: CWP and co-morbid depression did not significantly increase the risk of fatigue over and above the additive effects of the individual disorders. Whether CWP and co-morbid depression predicts increasing or more severe fatigue over time should be examined.

Disclosure statement: All authors have declared no conflicts of interest.

291. LEAN MASS IS POSITIVELY ASSOCIATED WITH HIP STRENGTH AND GEOMETRY IN CHILDHOOD: FINDINGS FROM THE SOUTHAMPTON WOMEN'S SURVEY

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Background: We have previously shown that poor growth early in life is associated with an increased risk of hip fracture in older adulthood, and that this might be mediated through altered proximal femoral geometry. It is not clear, however, whether factors such as body composition during childhood might further influence hip geometry. We therefore evaluated the cross-sectional relationships between body composition and bone size, density and indices of hip strength using DXA in a population cohort of six year old children.
Methods: 499 children were recruited at six years old from the Southampton Women's Survey. Bone size and density at the total hip site, together with body composition, were assessed by DXA (Hologic Discovery, Hologic Inc., Bradford, MA, USA). Additionally, femoral neck geometry and strength were estimated using hip structural analysis. Height, weight, diet (by questionnaire) and physical activity were also assessed.
Results: After adjustment for the child's age, height and sex, there were statistically significant positive associations between total body lean mass (in standard deviations (sd)) and total hip bone area ($\beta = 0.96 cm^2$/sd, $p = <0.001$), bone mineral content ($\beta = 1.30$ g/sd, $p = <0.001$), areal bone mineral density ($\beta = 0.04$ g/cm^2/sd, $p = <0.001$) and bone mineral content adjusted for body size ($\beta = 0.14$ g/sd, $p = 0.002$). Furthermore total lean mass was positively correlated with femoral neck cross sectional area ($\beta = 0.15 cm^2$/sd, $p = <0.001$), cross-sectional moment of inertia ($\beta = 0.11 cm^4$/sd, $p = < 0.001$) and cortical thickness ($\beta = 0.009$ cm/sd, $p = <0.001$). These associations persisted after adjustment for maternal social class and child's total fat mass, milk intake and physical activity.
Conclusions: We have demonstrated that childhood total lean mass is positively related to proximal femoral size, shape, density and strength, independently of fat mass. These findings suggest that hip geometry, an independent risk factor for osteoporotic fracture in later life, might be partly determined by muscle strength in childhood, and thus potentially amenable to modification through lifestyle intervention.
Disclosure statement: All authors have declared no conflicts of interest.

292. DOES DEPRESSION AFFECT RESPONSE TO ANTI-TUMOUR NECROSIS FACTOR THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS? RESULTS FROM THE BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER

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Background: Depression is widely reported in RA, with prevalence estimates at 14-46%. Some studies have suggested that RA patients with persistent depression have poorer response to anti-TNF therapy.

The aims of this analysis were to investigate the effects of depression status at baseline in patients with RA on (1) response to anti-TNF therapy at 6 months, and (2) survival rates on first anti-TNF drug.
Methods: 8899 patients with RA starting their first anti-TNF in the BSRBR were included in this analysis. Data were collected via the hospital (including the 28 joint count disease activity score (DAS28)), comorbidity, anti-rheumatic drug use (start and stop dates and reasons for discontinuation) and current medication use) and the patients (Health Assessment Questionnaire (HAQ)) at baseline, 6-monthly for three years. Depression was defined at baseline as no history (ND), depression history without current medication (D), or depressed with current medication (CM).

Response at 6-months was defined using (1) EULAR response criteria (none versus moderate or good) and (2) achieving >0.22 improvement in HAQ score. Multivariate logistic regression was used to study the effect of depression on response. Anti-TNF drug survival

was compared using Cox Regression to determine survival on anti-TNF.

Results: Depressed patients were younger, comprised more female with similar disease severity (Table 1). There was no difference in DAS28 response between the groups. However, patients were less likely to achieve a clinically significant improvement in HAQ with a history of depression alone OR 0.79 (95% CI 0.68, 0.92) or with medication OR 0.74 (95% CI 0.62, 0.89). Survival rates on drug were not affected by baseline depression.

Conclusions: Patients with baseline depression were less likely to achieve a clinically important improvement in HAQ at 6 months, with no difference in DAS28 response, suggesting it may be more subjective measures of disease and ultimately response that are affected by patient depression. Drug survival was not affected by depression suggesting that anti-TNF therapy is still effective in these patients.

TABLE 1.

	No depression	Depression without medication	Current medication
Subjects (n)	7292	967	640
Age ± SD	57 ± 12	56 ± 11	56 ± 12
Gender, % female	76	81	84
DAS28, mean ± SD	6.5 ± 1.0	6.6 ± 0.9	6.6 ± 1.0
HAQ, mean ± SD	2.0 ± 0.6	2.1 ± 0.5	2.1 ± 0.5
DAS responders, n (%)	5099 (70)	673 (70)	445 (70)
HAQ responders, n (%)	3737(51)	457(47)	300(47)
OR DAS response[a] (95% CI)[b]	ref	1.03 [0.85, 1.25]	0.90 [0.73, 1.13]
OR HAQ*	ref	0.79 [0.68, 0.92]	0.74 [0.62, 0.89]
HR failure on 1st anti-TNF[a]	ref	1.01 [0.92, 1.12]	1.00 [0.88, 1.13]

[a]Adjusted for age, gender, disease duration, year of entry into study, DAS, HAQ, ethnicity, steroids at baseline, NSAID at baseline, previous DMARDs, current methotrexate, selected co-morbidities smoking status. [b]95% confidence interval.

Disclosure statement: O.B. received research grants from Abbott, Merck, Pfizer, Roche, Swedish Orphan Biovitrium and UCB. All other authors have declared no conflicts of interest.

293. INITIAL TRIPLE DMARD THERAPY PREDICTS ACR EULAR REMISSION IN AN EARLY RHEUMATOID ARTHRITIS INCEPTION COHORT

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Background: ACR EULAR remission in rheumatoid arthritis (RA) represents absence of disease activity and is difficult to achieve with disease-modifying anti-rheumatic drug (DMARD) therapy in a clinical setting. Our aim was to identify predictors of this remission in a cohort of early RA (eRA) patients.

Methods: eRA patients (defined as a clinical diagnosis of RA with symptom duration ≤1year) treated in an early arthritis clinic (EAC) with a stratified DMARD remission induction protocol were examined. At diagnosis anti-CCP antibody & or rheumatoid factor positive (seropositive) patients with erosive disease were initiated on triple DMARD therapy (methotrexate, sulfasalazine & hydroxychloroquine), all others were started on mono/dual DMARDs. DMARDs were escalated monthly until either:1) DAS28 ≤2 .6 & or 2) Doppler ultrasound remission was achieved or 3) patients completed 6 months treatment in EAC. ACR EULAR remission criteria were applied at this time point. After 1 year from diagnosis these remission rates were reassessed. Baseline age, gender, smoking status, symptom duration, seropositive status, DAS-28 ≥ 5.1, presence of erosions and initial triple DMARD therapy were examined to see whether they predicted ACR EULAR remission at the 2 time points using multivariate logistic regression.

Results: 186 patients completed 1-year of follow up in the study. At baseline, mean age was 58 years (SD 15.8 years), 61% female, 30% current smokers, 45% had symptoms ≤ 3 months, 77% were seropositive and 25% had erosions. Triple therapy was initiated in 22 (11.8%) patients. Steroid bridging therapy was used at time of diagnosis. 34 (18.3%) patients achieved ACR EULAR remission in ≤ 6 months. After 1 year of follow-up from diagnosis, 35 (18.3%) achieved ACR EULAR remission with 14 (7.5%) being in sustained remission (remission at both time points). Final multivariate models predicting: remission at 1) ≤ 6 months, 2) ≥ 1 year and 3) sustained remission are shown in table 1.Compared to initial mono/dual DMARD therapy, triple therapy increased the odds of achieving ACR EULAR remission at both time points and was strongly associated with sustained remission. A high baseline DAS28 ≥ 5.1 was inversely associated with ACR-EULAR remission.

Conclusions: This study shows that in eRA, initial triple DMARD therapy increases the likelihood of remission, even in patients with poor prognostic features. It remains to be seen whether this translates into better radiographic and functional outcomes.

An interesting finding was that disease activity appears to be set early in the disease process and high baseline disease activity is in itself a poor prognostic indicator.

TABLE 1 Final multivariate model predicting ACR EULAR remission during first year of follow-up (FU)

Baseline variables	≤ 6 months FU OR (95%CI)	≥ 1 year FU OR (95%CI)	Sustained remission OR (95%CI)
Mono/dual therapy	1.0	1.0	1.0
Triple therapy	2.95 (1.05, 8.31)	2.75 (0.99, 7.64)	8.38 (2.15, 32.59)
DAS-28 ≥ 5.1	0.38 (0.17, 0.84)	0.42 (0.19, 0.92)	0.15 (0.04, 0.63)

Disclosure statement: C.E. received a research grant for an ultrasound fellow from Wyeth and funding for an ultrasound machine from Abbott. All other authors have declared no conflicts of interest.

294. ASSOCIATION BETWEEN PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS IN A LARGE CHINESE COHORT: FINDINGS FROM THE GUANGZHOU BIOBANK COHORT STUDY

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Background: There is increasing interest in the role of periodontal disease in the aetiology of inflammatory diseases, including rheumatoid arthritis (RA). Periodontal bacteria, including Porphyromonas gingivalis, may generate citrullinated peptides which trigger anti-citrullinated peptide antibodies; and in susceptible people break tolerance to citrullinated proteins.

Methods: Using data from the Guangzhou Biobank Cohort Study we examined the association between RA and periodontal disease. RA was defined based on at least two from the following: reporting physician diagnosis of RA, pain and swelling in at least 3 joints (including the wrist), positive rheumatoid factor, reporting morning stiffness, or swelling or tenderness of small hand joints on examination. Presence of periodontal disease was defined as reporting bleeding gums on tooth brushing. Logistic regression was used to adjust for age, sex, smoking history and frequency of tooth brushing.

Results: Data was available for 29,991 individuals (72.4% female), with mean age 62 years. RA was present in 2.5% and gum bleeding was reported by 25.8%. After adjusting for other factors, people with RA were significantly more likely to report bleeding gums (adjusted OR 1.33; 95% CI 1.01-1.75).

Conclusions: These data provide epidemiological support for an association between gum/periodontal disease and RA in a large cohort of middle-aged and elderly Chinese people. Persistent infection could provide a continuing stimulus to the inflammatory process in susceptible individuals.

Disclosure statement: All authors have declared no conflicts of interest.

295. OBESE EARLY RHEUMATOID ARTHRITIS PATIENTS HAVE A REDUCED RESPONSE TO DMARD THERAPY DURING THEIR FIRST YEAR OF TREATMENT

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Background: The effect of obesity on rheumatoid arthritis (RA) disease outcomes is controversial, with some studies reporting more favourable radiographic outcomes associated with increased body mass index (BMI). However, excess adiposity may be associated with impaired physical function and elevated inflammatory indices. Previously, we reported that obese early (e)RA patients present with higher disease activity scores (DAS28). It is not clear whether treatment response is influenced by BMI status.

Study aim: To explore whether baseline obesity is associated with DAS28 response during the first year of DMARD treatment.

Methods: An inception cohort of eRA patients (defined as a clinical diagnosis of RA with symptom duration <1 year) were identified from

an early arthritis clinic. At the baseline assessment, symptom duration, DAS28 and its separate components, rheumatoid factor (RF) and anti-cyclic citrullinated protein antibody (ACPA) status were recorded. BMI was calculated at baseline and the cohort was divided into 3 categories: 1) normal $<25\,kg/m^2$, overweight 25-29.9 kg/m^2 and obese $\geq 30\,kg/m^2$. All were treated with DMARDs following a targeted treatment protocol. Associations between baseline BMI category and DAS28: 1) at baseline; and 2) after 1 year of DMARD treatment, were explored using logistic regression, adjusting for age, gender and smoking status. At 1 year, associations between obesity and change from baseline DAS28 were assessed using the EULAR response criteria.

Results: 212 eRA patients with 1-year follow-up data were identified. At baseline, the mean age was 57.7 years (SD 15.3), 60.1% were female and 71.2% were ACPA positive. The median BMI was 27.5 [IQR 24.3, 31.8] and 34% of the cohort were obese. The median baseline DAS28 was 5.1 [IQR 4.3, 6.1]. After 1 year of treatment, 51% were in DAS28 remission (DAS28<2.6) and 58% had achieved good EULAR response.

A trend for association was seen between obesity and high baseline DAS28 (defined as DAS28>5.1) (OR_{adj} 1.7 [95%CI 0.9, 3.1]), which was stronger in the ACPA positive subgroup (OR_{adj} 2.0 [95%CI 1.0, 4.0]).

After 1 year, obesity was inversely associated with: 1) DAS28 remission (OR_{adj} 0.51 [95%CI 0.28, 0.93]), and 2) good EULAR response (OR_{adj} 0.6 [95%CI 0.3, 1.0]). This inverse association between obesity and good EULAR response was strongest in female patients (OR_{adj} 0.4 [95%CI 0.2, 0.8]). Obese and non obese patients had similar DMARD/biologic treatments during their first year after diagnosis.

Conclusions: Obese eRA patients appear to have increased disease activity at presentation and are less likely to be in DAS28 remission after 1 year of follow-up, despite similar treatment. This persistence of elevated disease activity during the first year of treatment is likely to result in adverse long-term outcomes for RA patients presenting with obesity.

Disclosure statement: All authors have declared no conflicts of interest.

296. OBESITY IS ASSOCIATED WITH HIGHER HAQ SCORES IN PATIENTS WITH EARLY INFLAMMATORY POLYARTHRITIS: RESULTS FROM THE NORFOLK ARTHRITIS REGISTER

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Background: Functional disability, usually measured using the Health Assessment Questionnaire (HAQ), is a key outcome in patients with rheumatoid arthritis (RA). It is not clear whether an abnormal body mass index (BMI) at the time of initial presentation is associated with later disability. With the rising prevalence of obesity in the general population, any such association will be increasingly important when trying to achieve optimal outcomes for RA patients. The aims of this study were i) to describe the prevalence of obesity at baseline in patients with early inflammatory polyarthritis (IP) registered with the Norfolk Arthritis Register (NOAR) and ii) to investigate the association between BMI and HAQ scores.

Methods: Patients with IP ($\geq$ 2 swollen joints for $\geq$4 wks) recruited to NOAR from 2004-8, were assessed at baseline and one year later. Patients completed the HAQ at each visit, and the research nurse administered a standard questionnaire including details co-morbidities and smoking status; examined the joints, and measured height and weight. Blood samples were taken at the initial assessment to measure rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-ccp) antibodies. BMI was grouped according to the WHO classification as normal/underweight (<25), overweight (25-29.99), obesity class I (30-34.99) and obesity classes II&III ($\geq$35). HAQ scores were categorized as low (0-1) or high (>1) disability. Univariate and multivariate ordinal regression analyses were applied to investigate the influence of initial BMI on HAQ at baseline and 1 year. The multivariate model adjusted for gender, age, smoking status, HAQ, co-morbidities, autoantibodies, and tender and swollen joint counts, all measured at baseline.

Results: 803 patients with IP had baseline BMI recorded. 523 (65%) patients were female, mean age was 56 (sd14.7) years and 547 (68%) were RF and/or anticcp antibody positive. At baseline, 32% (108/523) of women and 22% (61/280) of men were obese; the median HAQ score was 1.000 (IQR 0.375-1.625). There was no association between obesity and baseline haq score in the cross-sectional multivariate analysis. Obesity (but not being overweight) was significantly associated with 1 year HAQ score in the univariate analysis and this was maintained in the fully adjusted multivariate model.

Conclusions: This study shows that a high proportion of patients presenting with IP are obese, and that obesity at baseline is associated with an increased likelihood of disability (HAQ >1) one year later. This relationship should be taken into consideration when interpreting HAQ scores in RA patients.

TABLE 1.

	Univariate model		Multivariate model	
BMI class at baseline assessment (% of patients with IP)	Odds ratio	95% confidence intervals	Odds ratio	95% confidence intervals
BMI <25 (32)	Referent		Referent	
BMI 25-29.99 (39)	1.21	0.86 - 1.71	1.45	0.94- 2.23
BMI 30-34.99 (19)	1.72	1.14 - 2.59	1.74	1.04 - 2.91
BMI$\geq$ 35 (10)	3.59	2.09 - 6.15	3.01	1.53 - 5.90

Disclosure statement: All authors have declared no conflicts of interest.

297. DO ELECTRONIC AND PAPER QUESTIONNAIRES PRODUCE EQUIVALENT RESULTS? A SYSTEMATIC REVIEW

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Background: Self-report questionnaires are a crucial part of most epidemiological studies of the burden and/or aetiology of the rheumatic diseases. However paper questionnaire response rates have been decreasing in recent decades which increases the potential of selection bias. It is therefore important to consider other means of response, such as electronic questionnaires, in order to halt the trend of decreasing participation. It is not well known yet whether electronic questionnaires provide data equivalent to that captured in paper questionnaires. Thus, the aim of this study was to review the evidence relating to intra-modality reliability of paper/electronic questionnaires, commonly used in large population-based studies of the rheumatic diseases.

Methods: A literature search was conducted by using five databases, including Embase and Medline, to identify studies published in English or German from 1990 onwards. The bibliographies of selected studies were reviewed for further eligible publications. 19 keywords reflecting the modes of interest, such as ''electronic'', ''web-based'', ''mailed'' and ''paper'' as well as the information collection process, such as ''questionnaire'' or ''health survey'' were used. Eligible studies were those in which (1) participants completed both, a standard paper and electronic questionnaire on pain, general health, mental health or quality of life and (2) in which an estimate of the magnitude of the difference and/or a statistical test of difference was given. Studies using hand-held devices were excluded as these are not (yet) suitable for large-scale population studies.

Results: 18 eligible studies provided data on 8 different questionnaires on general health, mental health and quality of life in 27 comparisons. No eligible studies on pain questionnaires were found. In around half of the comparisons, paper and electronic questionnaires were considered as being equivalent. Statistically significant mean score differences on one or more subscales were detected in 12 comparisons, affecting 37 of 192 subscales (19%). These differences were in 73% related to worse health reports in the paper versions and considered as small (i. e. <10%) and/or not clinically significant in 7 of the 12 questionnaire comparisons. With respect to the mean scores of all questionnaire comparisons, the ratio of worse health reports in paper questionnaires to electronic questionnaires was 3:2.

Conclusions: Generally, paper and electronic questionnaires produce similar results. Although almost half of the questionnaire comparisons identified statistically significant mean score differences, they were mostly considered unimportant. However, investigators should be aware that electronic questionnaires do not necessarily produce data equivalent to the paper originals. More reliability studies, especially those testing pain questionnaires, are needed to underpin the secure application of electronic questionnaires in epidemiological studies of rheumatic diseases.

Disclosure statement: All authors have declared no conflicts of interest.

TABLE 1 Odds Ratio/Relative Risk (95% confidence interval) of RA according to alcohol intake

Study (year)	No alcohol	Low alcohol	Moderate alcohol	High alcohol	Any vs no alcohol	Trend test
Cerhan[a] (2002)	1.00 (r)	0.77 (0.46-1.27)	1.21 (0.80-1.83)	0.83 (0.51-1.36)	0.96 (0.70-1.33)	p = 0.93
Hazes (1990)	1.00 (r)	–	0.62 (0.4-0.98)	0.31 (0.13-0.74)	0.53 (0.33-0.82)	p = 0.10
Heliövaara[a] (2000)	1.00 (r)	1.15 (0.64-2.05)	1.09 (0.59-2.1)	1.04 (0.44- 2.50)	0.90 (0.59-1.36)	p = 0.38
Källberg - EIRA (2009)	1.00 (r)	1.02 (0.78-1.33)	0.59 (0.43-0.80)	0.56 (0.41-0.76)	0.80 (0.62-1.04)	p = <0.01
Källberg - CACORA (2009)	1.00 (r)	0.58 (0.39-0.87)	0.56 (0.36-0.86)	0.35 (0.22-0.55)	0.51 (0.35-0.74)	p = <0.01
Maxwell (2010)	1.00 (r)	0.30 (0.23-0.40)	0.17 (0.12-0.22)	0.15 (0.11-0.21)	0.21 (0.17-0.27)	p = <0.01
Rodriguez (2009)	1.00 (r)	0.94 (0.76-1.17)	1.37 (0.81-2.33)	1.06 (0.46-2.45)	1.00 (0.82-1.22)	p = 0.69
Voigt (1994)	1.00 (r)	1.03 (0.72-1.47)	0.80 (0.51-1.25)	1.21 (0.68-2.16)	1.06 (0.77-1.47)	p = 0.85

[a]Cohort studies; r = reference.

298. A SYSTEMATIC REVIEW AND META-ANALYSIS OF ALCOHOL AS A PROTECTIVE FACTOR AGAINST RHEUMATOID ARTHRITIS

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Background: Recent case-control studies suggest that alcohol may protect against the development of Rheumatoid Arthritis (RA). The evidence is however uncertain, with older studies failing to show this relationship.

We therefore undertook a systematic review and meta-analysis of studies examining alcohol and RA risk. Our primary aim was to establish if alcohol affects the risk of RA. Our secondary aims were to evaluate if this risk varies by alcohol intake and ACPA status.

Methods: *Search Strategy*- We searched Medline/EMBASE (1947-Nov 2011) using the terms ''rheumatoid arthritis.mp'' or ''arthritis, rheumatoid/'' and ''alcohol.mp'' or ''ethanol/'' (limited to ''humans''). Manuscript bibliographies were reviewed.

Inclusion Criteria- observational case-control/cohort studies examining the relationship between alcohol and RA risk and reporting effect size data (odds ratios (OR)/relative risks (RR) with 95% confidence intervals (CI)) in drinkers compared to non-drinkers.

Statistics- Due to the low prevalence of RA, ORs/RRs were used interchangeably. A random effects model was used to estimate pooled ORs/RRs. Dose response relationships between alcohol and RA were evaluated by the Cochran-Armitage trend test.

Results: 611 articles were screened. 8 studies were included (see Table), comprising 6 case-control (3,584 cases/8,477 controls) and 2 cohort studies (247 RA cases from 50,280 individuals).

A non-significant trend towards a reduced risk of RA with alcohol was observed- summary OR for RA in drinkers vs non-drinkers was 0.67 (95%CI 0.43-1.05). A significant risk reduction was seen in ACPA-positive RA- summary OR 0.40 (95%CI 0.17-0.94) - but not ACPA-negative RA- summary OR 0.56 (95% CI 0.24-1.34). There was some evidence of a trend towards a dose-dependent risk reduction (significant in 3 studies).

Conclusions: Our systematic review does not show a definite protective effect of alcohol on the risk of developing RA. Although it shows an inverse relationship between alcohol and ACPA-positive RA caution is needed as only 3 studies evaluated ACPA status, significant heterogeneity was present and unadjusted ORs were used in the summary measures. Additionally causality cannot be proven in case-control studies, with no relationship seen in cohort studies. Further research is required, preferably with prospective cohort studies using ACPA status, to establish if alcohol protects against RA.

Disclosure statement: All authors have declared no conflicts of interest.

299. JOINT HYPERMOBILITY PREDICTS DISABLING AND LIMITING MUSCULOSKELETAL PAIN: RESULTS FROM THE MUSICIAN SURVEY

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Background: Clinical observations of patients with fibromyalgia, a disorder characterized by chronic widespread pain (CWP), have suggested that they may have increased rates of hypermobility (excessive joint laxity) when compared to healthy controls. The aim of this study was to test whether an association between CWP and joint hypermobility was present in a large unselected population sample.

Methods: In a cross-sectional study 45,949 individuals in Aberdeen and Cheshire were mailed a questionnaire which assessed the presence, distribution and duration of pain. The questionnaire include the Chronic Pain Grade (CPG) questionnaire which classifies chronic pain global severity as I (low intensity, low disability), II (high intensity, low disability) to III/IV (high disability, moderately or severely limiting). The Joint Hypermobility Questionnaire (score range 0-5, score $\geq$2 indicates joint hypermobility) was also included. Using their pain reports, subjects were classified as having CWP (ACR 1900 criteria for fibromyalgia), some pain, or no pain. Other questions asked about age, sex, employment status, smoking (regular smoker: yes/no), alcohol use (regular consumption: yes/no), moderate physical activity (none to >3 times/week), and vigorous physical activity (none to >3 times/week). Multinominal logistic regression tested the relationship between joint hypermobility and pain status. Associations were adjusted for age, sex and other putative confounders. Subjects with no pain were the referent category. Results are presented as relative risk ratios (RRR) with 95% confidence intervals (CI).

Results: 13,482 (29.3%) individuals returned a questionnaire and provided complete data. Participants median age was 56 years (range 25-107) and 56.7% (n = 7914) were female. Of those, 2197 (16.3%) had CWP and 6100 (45.3%) some pain (CPG score I 34.7% and 59.9%; II 36.6% and 27.3%; III/IV 28.7% and 12.8% respectively), and 5185 had no pain. A total of 3060 (21.1%) participants were hypermobile. Hypermobile participants were more likely to be female (71.5% vs. 28.5%, $p < 0.001$) and younger (median age 51 years (IRQ 39-64) vs. 57 years (45-68), $p < 0.001$) when compared to participants who were not hypermobile. After adjusting for age and sex, hypermobility was not significantly associated with CWP CPG score I (1.2 (0.97-1.4), p = 0.08) or CWP CPG score II (1.1 (0.91-1.3), p = 0.3), although hypermobile participants were 40% more likely to report CWP CPG scores III/IV (1.4 (1.2-1.7), p = 0.001). Similarly hypermobile participants were 30% more likely to report some pain GCP III/IV. After further adjustments for employment status, smoking, alcohol consumption and physical activity, hypermobility remained significantly associated with CWP CPG score III/IV and some pain CPG score III/IV.

Conclusions: Joint hypermobility was only associated with pain that was both disabling and limiting. The relationship was not specific to CWP.

Disclosure statement: All authors have declared no conflicts of interest.

GENETICS

300. FURTHER REPLICATION OF THE TRAF1/C5 GENETIC ASSOCIATION WITH RADIOLOGICAL DAMAGE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: A rheumatoid arthritis (RA) susceptibility region between the TNF receptor-associated factor-1 and complement component 5 genes (TRAF1/C5) has previously been reported to associate with radiological damage in two studies. We aimed to investigate RA genetic susceptibility markers, including variants at the TRAF1/C5 locus, as determinants of disease severity in an independent inception cohort of UK RA patients and to combine this with a previous study in a UK population.
Methods: Sixty-seven RA susceptibility variants, were genotyped in 474 patients from the Early Rheumatoid Arthritis Study (ERAS) using Sequenom MassArray technology. Correlation between genetic markers and Larsen score was assessed at baseline, year 3 and year 5 follow-up. Data were combined with previously published data from the Norfolk Arthritis Register (NOAR) and analysed using longitudinal statistical models to include repeat measurements in the same individual at different time points. All analyses were adjusted for symptom duration at baseline.
Results: A correlation was observed between rs2900180 at the TRAF1/C5 locus and Larsen score at year 3 (coef. 4.27 95%CI 0.49, 8.04, $p = 0.03$) and in the longitudinal regression analysis (coef. 3.80 95%CI 0.81, 6.79, $p = 0.01$) in ERAS. Combined longitudinal analysis of NOAR and ERAS samples increased the statistical evidence for association at the locus (coef. 2.15 95%CI 0.80, 3.49, $p = 0.002$).
Conclusions: The genetic marker rs2900180 is associated with extent of erosions, as measured by the Larsen score in the ERAS cohort. This represents the third independent study correlating genotype at the TRAF1/C5 locus with radiologic severity in RA.
Disclosure statement: All authors have declared no conflicts of interest.

301. SPINE CURVATURE IS HERITABLE AND ASSOCIATED WITH DISC DEGENERATION

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Background: Degenerative spondylosis (DS) is common in middle age and elderly and, if severe, may lead to respiratory compromise and abdominal content crowding. Lumbar disc degeneration (LDD) is known to be a cause of back pain:- a considerable cause of work absenteeism and a major social problem in industrialized societies. LDD is heritable but its precise relationship with spine curvature is unclear. We performed an MR and plain radiograph study on well characterized twins from the TwinsUK register (www.twinsuk.ac.uk) known to be representative of the general population.
Methods: T2 weighted MR scans and long spine standing radiographs were obtained at the same morning visit on twin pairs. Midline sagittal MR images were coded for LDD on a 4-point scale over 4 subphenotypes: disc signal intensity, disc height loss, anterior osteophytes and disc bulge and summed over the 5 lumbar discs to give a summary LDD score. On the plain films, points were applied to the 4 vertebral body corners using SpineviewTM software which then calculated the angles of curvature of the whole spine. Subjects having vertebral fracture were excluded. A classical twin study was performed to determine the relative contributions of genetic and environmental factors to spine curvature. Multivariate regression analysis was used to determine the association between spine curves, LDD and confounders (age, body mass index).
Results: Complete phenotype data were available on 246 female twins, 110 monozygotic (MZ) and 136 dizygotic (DZ) twins. Mean age was 64.3 years (range 40.1-79.3); age was associated with increasing lumbar lordosis ($p = 0.02$). The AE model (comprising additive genetic and unique environmental factors) was the most suitable model for both lumbar lordosis and thoracic kyphosis (as determined using the Akaike information criterion). Heritability estimates = 59% (42-71%) for lumbar lordosis; and 61% (46-74%) for thoracic kyphosis. After adjusting for age and BMI, lumbar lordosis was significantly associated with a number of features of LDD including disc signal intensity and osteophytes.
Conclusions: Lumbar lordosis and thoracic kyphosis of the spine have considerable heritable component. Furthermore, lumbar lordosis is significantly associated with many of the features of LDD - something which may be clinically apparent but has not, as far as we know, been formally studied in a population sample. Longitudinal work will be required to confirm the direction of effect of this association. That the spine curves themselves are heritable suggests that a search for individual gene variants influencing spine curve would be a reasonable next step. Identifying gene variants for curve would inform the biology underlying the normal degenerative process and might throw light on the pathology of other scoliotic conditions.
Disclosure statement: All authors have declared no conflicts of interest.

302. A SYNONYMOUS VARIANT IN TREX1 IS ASSOCIATED WITH AN INCREASED RISK OF SYSTEMIC SCLEROSIS

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Background: Variants in TREX1, the major 3 DNA exonuclease in mammalian cells, can cause a number of conditions including the neurodevelopmental disorder, Aicardi-Goutières syndrome, familial chilblain lupus and systemic lupus erythematosis. Patients with these conditions can be affected by chilblain-like vasculitic lesions. Many patients with systemic sclerosis (SSc), and especially those with the limited cutaneous subtype (lcSSc), have severe digital ischaemia with Raynaud's phenomenon progressing to digital ulceration, scarring, and sometimes to gangrene necessitating amputation. Our objective was to examine a cohort of patients with SSc to look for associations with TREX1, in particular in those with lcSSc and in those with severe digital ischaemia.
Methods: DNA sequencing of TREX1 was undertaken in 80 patients with lcSSc. Subsequently, genotyping of a synonymous TREX1 variant, 51Ser (rs11797) was undertaken in an additional cohort of 172 white British individuals with SSc and 115 healthy controls. The clinical characteristics of the entire cohort were: lcSSc = 193 (77%); diffuse cutaneous (dcSSc) = 59 (23%). 98 patients (39%) had a history of severe digital ischaemia as defined by a history of admission for intravenous prostanoids, digital debridement or digital amputation. 22 patients (9%) had had amputations. 89 of 251 patients (35%) were anticentromere antibody positive (anticentromere antibody is associated with severity of digital ischaemia in patients with SSc)
Results: The synonymous TREX1 variant 51Ser was present more commonly in patients with SSc than in healthy controls ($OR = 1.4$; $p = 0.03$). This association was confined to lcSSc ($OR = 1.4$; $p = 0.02$). The minor allele was most strongly associated in SSc patients who had a history of amputations ($OR = 2.1$; 95% CI: 1.08 - 4.27; $p = 0.02$). There was no association with anticentromere antibody.
Conclusions: The TREX1 51Ser variant is associated with an increased risk of SSc. This association was strongest in the patients with lcSSc and particularly in those with a predisposition to the most severe digital vascular disease.
Disclosure statement: All authors have declared no conflicts of interest.

303. CORRELATION OF CRP HAPLOTYPES WITH RESPONSE TO ANTI-TNF THERAPY IN UK PATIENTS: RESULTS FROM THE BRAGGSS COHORT

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Background: Anti-TNF medication is the most effective treatment method in patients with RA and reduces inflammation by blocking the TNF pathway. However, this treatment is expensive, costing ~£10,000 per patient, per year. Hence in the UK, restrictions exist around the prescription of anti-TNF medication and both eligibility for, and response to therapy is assessed using the 28 joint disease activity score (DAS28). The DAS28 incorporates one of two markers of inflammation, ESR or CRP; indeed, it has been suggested that DAS28-CRP provides a more reliable measure of disease activity.

C - reactive protein (CRP), an acute phase inflammatory marker that rises rapidly in response to acute inflammation, is elevated in patients with RA and can be used to calculate the DAS28-CRP. However, functional variants exist within the CRP gene that affect basal CRP production, and thus basal levels in a population can vary.

We hypothesize that genetic variation at the CRP locus may influence the baseline DAS28-CRP and the change in DAS28-CRP in patients receiving anti-TNF treatment for RA.
Methods: DNA samples from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) were genotyped for rs1205, rs1800947 & rs3091244 using either TaqMan® or Illumina Infinium genotyping array.

Estimated haplotypes were constructed for each sample using the expectation maximization algorithm implemented in the haplo.stats package within the R statistical programme.

The strength of correlation between haplotypes and baseline CRP, baseline DAS28 and change in DAS28 was estimated using anova in STATA v.10.
Results: Baseline CRP data was available for 371 samples. Follow-up CRP data, 6 months after treatment with an anti-TNF, was available for 276 samples.

Estimated haplotype frequencies corresponded with previous frequencies reported in the literature.

In previous reports, haplotypes H1 and H4 are associated with high CRP production, whilst H2 and H5 are associated with low CRP production. However, this trend was not seen within our cohort of RA patients. Overall, CRP haplotypes did not show a significant change in baseline CRP level, baseline DAS28, or predict a change in DAS28. None of the CRP haplotypes correlated with baseline CRP at the 5% significance threshold ($p = 0.99$). Furthermore, CRP haplotypes were not correlated with baseline DAS28 ($p = 0.99$) or improvement in DAS28 over 6 months after commencing treatment ($p = 0.99$).
Conclusions: Although CRP haplotype may influence baseline CRP levels, in patients with very active disease, no association was found. Therefore, as genetic variation does not influence DAS28-CRP, it may be used as a more reliable measure of eligibility for anti-TNF drugs.

Finally, the lack of correlation could be reflective of a lack of power, particularly for some of the less frequent haplotypes observed. In the future, more powerful studies will be needed to confirm these preliminary results.
Disclosure statement: All authors have declared no conflicts of interest.

HEALTH SERVICES RESEARCH, ECONOMICS AND OUTCOMES RESEARCH

304. DO PATIENTS' TREATMENT PRIORITIES VARY ACCORDING TO ETHNICITY AND CULTURE? A UK COMPARISON OF WHITE BRITISH AND PUNJABI RHEUMATOID ARTHRITIS PATIENTS

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Background: The development of core sets and outcome measures increasingly involve patients as research partners, as recommended in policy guidance [1]. The RA Patient Priorities in Pharmacological Intervention (RAPP-PI) [2] outcomes were generated with a sample consisting of 98.0% White British participants, despite efforts to be inclusive of different ethnicities. This study aimed to explore whether a different ethnic group would identify similar priorities.
Methods: In-depth interviews with female Punjabi-speaking RA patients were conducted by TS in Birmingham, Bristol and Coventry. Purposive sampling was used (English proficiency, disease duration, age, duration in UK). KK interpreted during interviews for participants who only spoke Punjabi or had insufficient English to express themselves in an interview. The data were analysed using Framework, and constant comparison made with the data from the female RAPP-PI interview participants [2]. A Punjabi patient research partner collaborated in the study.
Results: 16 interviews were completed: mean age 49.4 (SD 12.9), disease duration 10.7 years (SD 12.1) and HAQ 1.37 (SD 0.77). 5 spoke no or limited English, and 11 were fluent (5 UK born).

57 of the 63 outcomes identified in the previous interviews were present in the Punjabi data, but excluded outcomes such as 'more predictable disease', 'having a physical relationship', and 'more confidence'. However, there were 18 additional outcomes elicited including: 'doing things more quickly', 'not having to lie down (to rest)', 'feeling less guilty', and 'maintaining dignity'.

Of the RAPP-PI priority outcomes (pain, activities of daily living, avoidance of joint damage, mobility, life enjoyment, independence, fatigue, and valued activities), all were considered important, but sometimes with a different emphasis. Life enjoyment was unanimously connected to family well-being and harmony, rather than personal contentment. Independence was framed as being able to fulfil one's duty as a wife, mother or daughter, in addition to avoiding being a burden to others. More emphasis was placed on reducing medication and side effects than in the White British data. RA was seen as particularly problematic for women diagnosed before marriage (or recently married), since they would be considered less desirable and stigmatized, both for UK and non-UK born patients.
Conclusions: These data collected with Punjabi women with RA illustrate that overall the priority treatment outcomes were similar when compared with a UK mainstream White British patient population. However, there were differences in the outcomes elicited and in the cultural implications of treatment outcomes. Thus, this research indicates that core sets and outcome measures should include participants from different ethnic groups from the outset of their development.
Disclosure statement: All authors have declared no conflicts of interest.

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305. LITIGATION RELATED TO RHEUMATOLOGY: AN ANALYSIS OF CLAIMS AGAINST THE NHS 2000 TO 2010

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Background: Medical negligence claims are on the increase. The NHS Litigation Authority (NHSLA) handles negligence claims against the NHS. Since its inception in 1995, 12,000 claims have been received involving the specialty of medicine at a cost of £1,678,925,000. Rheumatology is generally perceived as a medico-legally low risk specialty. However, the specialty has undergone a remarkable transformation over the last decade and one may hypothesize that the risk of litigation and negligence claims may have risen. This study analyses all clinical claims relating to rheumatology received by the NHSLA over the last decade. It aims to assess the financial impact of claims, to identify any trends in the frequency or type of claim, and to attempt to identify areas of high medico-legal risk.
Methods: Clinical claims are handled by the NHSLA under the Clinical Negligence Scheme for Trusts (CNST). A request was made via the Freedom of Information Act for all claims relating to rheumatology reported to the CNST from April 2000 to April 2010. The data provided included both closed and outstanding claims and for each claim, the incident and notification date, a brief description of the incident, injury, specialty and location were provided. Using the clinical information available each claim was classified according to the IOM classification system for medical error.
Results: One hundred and ninety claims were received in total over the 10 year period. Two claims were excluded (misclassified). For 22 claims rheumatology was not the primary specialty. Eighty-nine percent of claims were closed. Sixty-four percent of all closed claims resulted in financial cost, totalling £7,718,848. There was no trend in the total number, cost or type of claim received per year. The highest pay out for any claim was £1,567,718 (delayed diagnosis of epidural abscess resulting in neurological impairment) and £591,107 for claims involving rheumatology as the primary specialty (delayed diagnosis of bacterial endocarditis resulting in death). The majority of claims (56%) were classified as due to diagnostic error; 90% of which were due to an error or delay in diagnosis, most commonly of infection (21%) or malignancy (21%). More than 1 in 4 of these claims involved the spine. Ten percent of classified claims were due to errors in performing a procedure. Diagnostic errors were most likely to result in fatality (17%), were most likely to incur financial cost (71% of closed

TABLE 1.

Year of audit (n)	Assessment	Within 12 months, n (%)	1-2 years, n (%)	Over 2 years, n (%)	Never performed n (%)
2011 (106)	TTE PFT	54 (50.9) 66 (62.3)	32 (30.2) 27 (25.4)	12 (11.3) 9 (8.5)	8 (7.5) 4 (3.8)
2009 (98)	TTE PFT	34 (34.7) 52 (53.1)	34 (34.7) 29 (29.6)	23 (23.5) 11 (11.2)	7 (7.1) 6 (6.1)

cases) and were associated with the highest mean cost (£67,448 per closed claim).
Conclusions: The frequency and cost of claims related to the specialty of rheumatology is low. There has been no upward trend in either over the last decade despite the evolution of the specialty. The majority of claims are related to diagnostic error and this category of claim incurs the highest financial cost. Incorrect or delayed diagnoses involving conditions of the spine are common and this represents an area of high medico-legal risk.
Disclosure statement: All authors have declared no conflicts of interest.

306. IMPACT OF A RHEUMATOLOGY-BASED ECHOCARDIOGRAPHY AND DEDICATED OUTPATIENT CLINIC SERVICE ON CARDIOPULMONARY SCREENING IN SYSTEMIC SCLEROSIS

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Background: Annual screening for pulmonary artery hypertension (PAH) with trans-thoracic echocardiography (TTE) and pulmonary function tests (PFT) is recommended for asymptomatic patients with systemic sclerosis (SSc). An audit in 2009 highlighted suboptimal adherence with recommended guidelines. Consequently, a novel service facilitating TTE assessment on the day of OPC assessment within a dedicated SSc clinic was set up at our institution during 2010.

We compare the findings of the audit from 2009 with an identical audit undertaken in 2011 to assess the impact of changes to clinical practice on cardiopulmonary screening rates.
Methods: A retrospective case note review of all patients with SSc who had attended outpatient clinic (OPC) over the previous 12 months was undertaken. Notes were scrutinized for clinic subtype and documented TTE and PFT reports. Comparison was made with the findings of the previous audit from 2009.
Results: The case notes of 121 patients were reviewed. Fifteen were excluded as they had confirmed PAH which did not warrant ongoing non-invasive screening assessments. Of the remaining 106 patients, 63 were seen in the Connective Tissue Disease (CTD) service, 37 in the novel SSc clinic and 6 in General Rheumatology clinic.

There was a significant increase in the number of patients in whom TTE had been performed in the previous year compared with 2009 (50.9% vs. 34.7%, $p = 0.02$, see Table 1). The number of patients waiting greater than 2 years, or with no previously documented TTE assessment, fell from to 30.6% to 18.8% ($p = 0.07$). There was a non-significant increase in the number of patients undergoing PFT assessment within the previous 12 months (62.3% vs. 53.1%). Rates of cardiopulmonary screening were similar for patients attending routine CTD and dedicated SSc clinics. Only a small proportion of patients had no previously documented TTE or PFT results, many of whom were recent referrals.
Conclusions: We have demonstrated a significant improvement in adherence with guidance on cardiopulmonary screening in SSc since 2009, as a result of improved recognition amongst clinicians and better access to TTE. Patients have welcomed the introduction of the TTE service which reduces the frequency of hospital appointments and offers an educated and standardized approach to right heart screening. The majority of patients have undergone PFT and TTE assessments within the last 2 years. It is possible that 2-yearly screening continues to be perceived amongst clinicians as sufficient to allow the early identification of indolent PAH in asymptomatic patients. We anticipate screening rates will improve further as more patients are transferred to the SSc service, which aims to provide a comprehensive and holistic approach to the management of SSc.
Disclosure statement: S.B. has received honoraria from, and is on the advisory board of, Actelion. N.M. has received honoraria from, and is on the advisory board of, Actelion. All other authors have declared no conflicts of interest.

307. BIOLOGIC DRUGS ACCOUNT FOR A MAJOR PART OF THE COST BURDEN UP TO 15 YEARS AFTER DISEASE ONSET IN INFLAMMATORY POLYARTHRITIS

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Background: The increasingly widespread use of biologics has changed the economic impact of Inflammatory Polyarthritis (IP) and Rheumatoid Arthritis (RA). In 2002 we reported the health costs incurred by a cohort of patients with early IP up to 5 years into their disease. Here we extend the follow up in this group by up to 15 years, enabling comparison of the long-term costs associated with the diagnosis of IP. Our analysis allows an assessment of the impact of the introduction of biologics.
Methods: The cohort was identified from subjects participating in the Norfolk Arthritis Register (NOAR), a long-term primary-care based prospective cohort of patients with IP. A health economic study was conducted in this group in 2002 in patients with disease-duration up to 5 years. These were traced in 2009 and invited to participate in a longitudinal questionnaire based study that was designed to capture health costs and changes in health status as measured by the EQ5D over a period of 6 months, using previously validated instruments.
Results: A total of 122 patients from the original cohort were traced and were willing to participate. Complete data were obtained from 101 patients (83%). The characteristics of the cohort were as follows: Mean age of 50 years, 63% female, mean disease duration of 13 years with 64 (63%) patients having established RA as defined by 1987 ACR criteria. Biologics were used in 14% of the cohort during this 6 month interval. The average cost per patient with IP over the 6 month period was £1276 and, in those with RA, it was £1715. This compared with direct costs of £496 per patient with IP (accounting for inflation) ten years earlier in their disease. The increased cost was largely associated with biologic use in this group, which accounted for 51% of the total costs incurred. Primary care service use (GP and nurse visits/calls) accounted for 11% of the total direct health care cost in IP, hospital service use (doctor, nurse practitioner and OT/physiotherapy visits and calls) for 19%, use of day care for 12% of the cost and inpatient stay only accounted for 12% of the total cost. In the earlier study of 2002, the highest cost incurred by the health service was for inpatient stays and day unit visits (33% of the total).
Conclusions: This is the first definitive study of long-term health care costs associated with (IP) in the post-biologics era. The analysis shows that the direct health care costs associated with IP in this cohort have risen with increasing disease duration, largely as a result of the use of biologic agents. The RA subgroup incurred the highest costs. Despite improvements in treatments, outpatient attendance and other health service use was similar to the study findings in 2002.
Disclosure statement: All authors have declared no conflicts of interest.

308. WHY DO WE NEED TO PILOT INTERVENTIONS? ESSENTIAL REFINEMENTS IDENTIFIED DURING PILOTS OF A FATIGUE INTERVENTION

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Background: An RCT showed a 6 week group cognitive-behavioural (CB) intervention for RA fatigue self-management was effective, when delivered by a clinical psychologist.[1] Few rheumatology teams have clinical psychologists; therefore the intervention was re-formatted for delivery by the rheumatology team, in preparation for a multi-centre RCT. We piloted the feasibility of the materials, training, and support for clinicians, plus the acceptability of the intervention for patients.
Methods: The clinical psychologist from the original intervention worked with researchers, patient partners and clinicians to re-format a clinician-led version. A clinician's programme manual was developed with timetables, session aims, example scripts and patient handouts. A 2-day training for the rheumatology nurse and occupational therapist was developed, focusing on CB approaches (eg Socratic questioning, goal setting), managing groups, and using the session tools (eg activity diaries). They then co-delivered the intervention to 2 patient cohorts, first supervised by the clinical psychologist, then independently with supervised debriefing. On-going refinements were made, based on a cycle of feedback, review and de-briefing during all stages of the piloting.
Results: Materials for non-CB specialists: Some material has been re-written to be more suitable for non-CB specialists to deliver (eg 'sabotage' re-written as 'self-defeating behaviours'); links between sessions, explaining how they build on each other and relate to CB theory, have been made more explicit.

Training: Clinicians expressed anxiety about using new CB skills, and the need to respond rapidly to differences in session discussions that inevitably occur between different patient groups. Thus training will be increased to 4 days, with more focus on CB theory (eg formulating helpful questions) and more practice delivering sessions (eg explaining metaphors).

Support: An increased emphasis on the use of supervised debrief/reflection emerged; thus a guide to debriefing has been added to the manual, and extra time allocated. Proposed clinical supervision/quality control has been increased by adding supervision of any sessions that clinicians find challenging in their second pilot.

Acceptability: Feedback from the 10 patients was positive. Mean scores on rating scales (0-10, higher scores representing greater acceptability) were: satisfaction 8.8, encouragement from clinicians 9.0, sessions well-run 9.0, helpfulness of handouts 8.4, and recommendation of the intervention to other patients 8.8.
Conclusions: Piloting interventions prior to RCT is recommended but there is little evidence about how it influences development. Iterative feedback during piloting led to essential refinements, particularly in training and support, when re-formatting the CBT intervention for delivery by non-CB specialists. It is now ready for formal testing in an RCT.
Disclosure statement: All authors have declared no conflicts of interest.

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309. RHEUMATOLOGY EMAIL ADVICE AND LIAISON: A NEW SERVICE

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Background: Our Rheumatology email advice liaison service was set up in May 2010 in response to requests from local primary care practitioners. The purpose was to enable easy access to the rheumatology team regarding specific or general rheumatology queries, and to provide a more convenient and rapid response than via letter or telephone message. Eighteen months down the line, we aim to look at how the service is working in practice.

How the Service is Provided:

E-mails are sent from a GP/other primary care practitioner via a generic secure NHS e-mail address to the rheumatology team. These are reviewed daily by one of the rheumatology consultants. The e-mails may be forwarded to another team member if appropriate. The aim is to provide an answer within 24 hours of receipt. At the outset, it was envisaged that the type of queries would fall into one of two categories, either:

1. Specific questions regarding the management of a patient known to the department

or 2. More general rheumatology queries, including appropriateness of referrals.

Methods: The study has been addressed in two ways: 1) an interrogation of the email database regarding type of query, response time and advice given; 2) A survey sent electronically to all users of the service since its inception, using the web-based tool, Survey Monkey.
Results: All email enquiries over the 18 month period were reviewed. There were 322 separate episodes. The average reply time was 14 hours. The most popular days for enquiries were Wednesday and Thursday (27% on each day).

Most commonly, emails requested advice on patient management (58%), especially relating to DMARDs, raised ESR, gout and osteoporosis. 25% of enquiries related to appropriateness of rheumatology referral, especially possible inflammatory arthritis and positive ANA tests. In 75% of cases we advised referral. 12% of enquiries related to specific blood results (mostly positive ANA and low vitamin D) and 5% were requests to see a patient sooner.

Out of 85 service users over the past 18 months (98% GPs, 2% community physiotherapists), we had 40 responses to the survey (47% response rate). 87.5% of responders rated the speed of response of the service as quick (10% as reasonable). 85% rated the advice given as very useful and 15% as quite useful. 87.2% felt that the service was better than trying to obtain advice over the phone and 97.5% found it useful than trying to obtain advice by letter. 97.5% of users would use the service again. Analysis has shown that calls to our secretaries from primary care practitioners has reduced by 21%.
Conclusions: The Rheumatology email advice liaison service is a popular resource among our primary care colleagues and is rated highly. Currently, we are fulfilling the initial aims of the service. The impact on the consultant work load is minimal and there may be significant financial gains in terms of secretarial productivity and generation of new patient referrals (although this requires more detailed analysis).
Disclosure statement: All authors have declared no conflicts of interest.

310. PAN-LONDON STANDARDS OF CARE FOR INFLAMMATORY ARTHRITIS AND INFLAMMATORY BACK PAIN

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Background: The aim was to produce practical and implementable standards to assist Commissioners & Providers in the delivery of services for patients with inflammatory arthritis (IA) & inflammatory back pain (IBP).

Comprehensive standards have been produced in the East of England (EoE) [1]. However, the desire locally was for a more focused approach, considering what was both essential and immediately implementable.
Methods: A project team was established comprising the National Rheumatoid Arthritis Society (NRAS), Ankylosing Spondylitis Society, and London-based clinicians, supported by the British Society for Rheumatology (BSR). The group included Rheumatologists, GPSIs, allied health professionals, patients, and experts in commissioning.

Using the Delphi technique each EoE statement was ranked by individual members as essential and implementable in the short-to-medium term. Group discussion led to a consensus (80% in agreement) set of statements.
Results: The detail is too large to present in the abstract. However, the key components are:

Standard 1: Education

Public Health, General Practice, and Musculoskeletal services should encourage public awareness of IA and IBP.
Standard 1A: Professional and community awareness of early signs, symptoms and impact of IA and IBP.
Standard 1B: Appropriate action by clinicians when patients present with features suggestive of IA and IBP.

Standard 2: Specialty Service Delivery

Access to qualified multi-disciplinary clinical expertise, appropriate diagnostics, therapeutics and follow-up.
Standard 2A: Ensure patients with potential IA or IBP are assessed by a specialist service within 4-6 weeks of referral.
Standard 2B: Service Level Agreements for First to Follow-up ratios should adequately reflect the needs of IA and IBP patients.

TABLE 1 Disease activity and eligibility for biologic therapy

Disease activity, %						Eligible for biologics	
DAS < 2.6 (remission)	DAS 2.6-3.2 (low)	DAS >3.2-5.1 (moderate)	DAS >5.1 (severe)	NICE 2007	BSR 2010		
All patients	6 months (n = 38)	29	16	53	3[a]	0	32
Patients who have completed a	6 months (n = 15)	40	27	33	0	0	20
12-month follow-up period	12 months (n = 18)	61	11	28	0	0[b]	17

[a]Only had 1 DMARD therapy; [b]1 patient qualified for biologics between 6-12 months.

Standard 2C: A specification and resources to meet the Pan-London groups expectations of expertise and facilities.
Standard 2D: Access to NICE approved therapies and technologies, utilizing therapeutic options to achieve optimum control of IA and IBP.

Standard 3: Shared Care

Develop shared care between Community/Primary and Specialist clinicians, with a minimum of an annual specialty review.

Standard 4: Governance

Actively engage in National and local audit of Service Standards, Clinical Outcomes / Safety, and Patient Experience.

Conclusions: These standards are being circulated to Providers and Commissioners with the expectation of their use in 2012/13 commissioning plans. It is also anticipated that they will support the commissioning tool-kit being produced by BSR and the Arthritis Musculoskeletal Alliance. They offer a pragmatic approach to standardizing high quality provision of care for inflammatory arthritic conditions.
Disclosure statement: All authors have declared no conflicts of interest.

Acknowledgements

Dr David O'Reilly, Consultant Rheumatologist, EoE.
The Pan-London Standards steering committee.
BSR Office.

Reference

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311. NORTH WEST REGIONAL AUDIT OF THE DIAGNOSIS AND MANAGEMENT OF RHEUMATOID ARTHRITIS

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Background: There have been significant changes in the management of and attitudes towards rheumatoid arthritis (RA) in recent years. Early diagnosis and target driven therapy with multi-disciplinary team (MDT) input has been shown to improve outcomes. With this in mind, The National Institute for Health and Clinical Excellence (NICE) published guidelines in February 2009, for the diagnosis and management of RA. Key priorities included timely assessment by a specialist with guidance on urgency of referral; initiation of combination disease-modifying drug (DMARD) therapy, ideally within 3 months of symptom onset; monthly monitoring using composite disease indices (e.g DAS-28) with rapid escalation of therapy to control disease and access to a specialist MDT. The North West Rheumatology Regional Audit Group was formed in October 2010. The aims of the group's first project were to compare the diagnosis and management of RA patients in the North West to NICE guidelines and to test the feasibility of conducting a regional audit in rheumatology.
Methods: We conducted a retrospective audit of patients diagnosed with RA after February 2009, who attended outpatient clinic during a designated 2 week period. Each rheumatology department in the region was invited to participate. Data was collected locally by a designated site co-ordinator, then analysed centrally using Microsoft Excel 2007. Information regarding each centre's services was also collected.
Results: Data on 189 patients was collected from 14 centres. Mean age was 56 years and 58% of patients were female. 25% of patients were referred urgently to a rheumatologist, waiting an average of 6.5 weeks (range 0,107) to be seen. 52% of patients started treatment within 12 weeks of symptom onset. 19% received combination DMARD therapy as initial treatment. 52% received methotrexate as first line therapy. 33% of patients were seen monthly and 46% of patients had DAS-28 scores performed. Review with DAS-28 measurement and escalation of therapy every 4 to 6 weeks was carried our in 31% of patients. 85% received written and verbal drug education and 63% were referred to a member of the MDT. Free text comments suggested many patients did not present to their GP until symptoms had been present for some time and that at times referral was not made immediately after presentation. Other comments from a number of centres stated that there was inadequate clinic capacity to accommodate monthly follow up.
Conclusions: Delayed presentation and referral still hinders early treatment and strategies to increase awareness in the community are needed. Combination therapy is only favoured in a minority of cases, the reason for this is unclear. Monitoring guidelines are being met in less than a third of cases often due to lack of service capacity. These issues need to be addressed at both a regional and local level to improve standards of care for RA patients in the North West.
Disclosure statement: All authors have declared no conflicts of interest.

312. HOW MANY EXTRA PATIENTS COULD BE ELIGIBLE FOR BIOLOGICS IF WE ADOPTED BSR GUIDELINES IN AN EARLY ARTHRITIS POPULATION?

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Background: NICE guidelines recommend biologic therapy for patients with severe rheumatoid arthritis (RA) who have DAS28>5.1 having failed standard disease-modifying (DMARD) therapy. Recently BSR have suggested biologic therapy should be available to patients with lower DAS scores in order to suppress disease activity at an earlier stage (DAS28>3.2 with 3 swollen and 3 tender joints). We assessed how many patients with early RA could qualify for biologics according to different guidelines.
Methods: All patients in our early arthritis clinic (EAC) were included (disease duration <2 years, age >18, RA according to ACR/EULAR 2010 criteria). Patients were excluded if they had had DMARDs >3 months prior to attending EAC. Patients were seen every 4-6 weeks and treatment escalated according to local protocol if DAS28≥3.2. Initial treatment was with methotrexate escalating to a combination of 3 DMARDs (details to be presented). If RA was still active patients were then assessed for biologic therapy. We analysed data at 6 and 12 months post initiation of DMARDs to see how many patients would be eligible for biologics according to NICE and BSR guidelines. We also reviewed therapy at 6 months and whether patients progressed to biologics or improved with standard DMARDs.
Results: 41 patients were included. Mean age 58 years (range 35-88), F:M ratio 2.2:1, mean disease duration 11 months (range 3-24). 71% were CCP or RF positive and 17% had erosions at baseline. Mean DAS28 at initial assessment was 4.63 (range 1.7-6.9).

At 6 months 12/38 (32%) patients would have qualified for biologics by BSR guidelines. Of these we had follow-up data for 6 at 9 months and 4 at 1 year. By 9 months 1 patient had qualified for biologics by NICE criteria, however 3/6 (50%) no longer qualified by BSR guidelines. This increased to 3 of 4 (75%) by 1 year. The one patient who would have qualified by BSR guidelines at 1 year met NICE criteria by week 65.

Conclusions: Provisional analysis of our clinic demonstrated that only 1 patient out of 18 treated with step-up combination therapy for 1 year qualified for biologic therapy by NICE criteria within this period. Of the 12 patients who would have qualified for biologic therapy by BSR guidelines at 6 months, 1 met NICE criteria by 9 months and another at 65 weeks. However 3 out of 4 patients (75%) who had been eligible by BSR guidelines at 6 months went into disease remission with standard DMARD therapy by 1 year. Further work is needed to see if these encouraging results are maintained in a larger cohort.
Disclosure statement: All authors have declared no conflicts of interest.

313. STRATEGY TO REDUCE RHEUMATOLOGY AND PAIN CLINIC REFERRALS VIA MONTHLY MULTIDISCIPLINARY TEAM MEETINGS

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Background: Patients often seek more than one specialty for their musculoskeletal symptoms. Therefore a joint monthly multi-disciplinary team (MDT) meeting was established to discuss cases that may have normally resulted in a formal referral to both specialties. Reviewing radiology and investigations is central to the MDT, followed by an action plan for patients, which could include direct listing for pain procedures/appointments in either specialty's clinic. The aim of the meeting was to serve this common cohort of patients more efficiently, whilst reducing costs and significant waiting lists for both specialties. This is a follow up to a 2 year study.
Methods: MDT referral data within the period 2/6/2008 and 4/7/2011 were reviewed retrospectively. Information regarding the referring specialty, presenting problem, working diagnosis, recommendations, action plan recorded for each patient was analysed and costs saved by the primary care trust (PCT) calculated.
Results: 265 patients were discussed in 30 MDT meetings, each lasting 60 minutes, over a 3-year period. The pain team presented 185 cases to rheumatology (69.8%) and 80 cases were presented by rheumatology (30.1%). Of the former, only 29/185 (15.7%) patients required a rheumatology clinic appointment and for the latter 14/80 (17.5%) a pain clinic appointment. 15/80 (18.6%) of patients discussed by rheumatology were directly listed for specialist physical interventions such as epidural injections, obviating the need for a pain clinic outpatient appointment. Physiotherapy referrals were requested in 7/185 (3.8%) patients referred by the pain team. Discussion highlighted serious concerns about undiagnosed disease, resulting in urgent investigations or early referral to the appropriate specialty (orthopaedics, neurosurgery, oncology < 10 patients). New rheumatological conditions considered after discussion included likely ankylosing spondylitis, inflammatory arthritis, SAPHO syndrome, osteoporosis and haemochromotosis. Differences in treatment approaches were discussed and a uniform opinion about management was obtained, especially when discussing distress, illness behaviour, use of opioids and neuroleptics.
Conclusions: Cost to the PCT for a new patient referral to rheumatology is £260 and £156 to the pain team. Therefore savings resulting from this MDT are estimated to be £51,000. 2 year data has shown this to be an important cost saver continuing into the third year, enough to pay for a member of grade 6 or 7 nursing staff. Since new patients in clinic are allocated 30 minutes in rheumatology and 45 minutes in pain clinic, this translates into significant savings in terms of consultant time. This compares to the average time of 7.5 minutes per patient spent on discussion during the meeting. More importantly the MDT allows the patient to benefit from the expertise of a combined rheumatology/pain team opinion in a timely fashion and discussion of investigations in its clinical context.
Disclosure statement: All authors have declared no conflicts of interest.

314. REQUESTING IMMUNOLOGICAL TESTS: THE IMPORTANCE OF RATIONALIZING REQUESTS

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Background: Appropriate use of immunological tests is necessary for optimal patient care. There is evidence in the literature suggesting overuse of common serological tests including antinuclear antibody (ANA), rheumatoid factor (RF), and Anti-neutrophil cytoplasmic antibody (ANCA), leading to unnecessary referrals and further laboratory investigations. Contributing to this, may be a number of factors including inexperience of the requestor, lack of knowledge about the appropriate use of tests, failure to check previous results, or fear of missing a potential diagnosis. Another pitfall is that high value may be applied to test results leading to mis-diagnosis or over treatment.
Methods: We retrospectively investigated 150 sequential requests for immunological investigations within a one month period in a DGH. We compared preliminary diagnosis with final diagnosis and recorded the requesting specialty. We specifically examined requests for RF, ANCA, and ANA.
Results: Over a one month period, 566 requests were made for ANA, ANCA, or RF. Of the 150 sequential requests, requesting specialties were: General practitioner (GP) 81 (56%), gastroenterology 5 (3%), dermatology 3 (2%), rheumatology 14 (9%), renal 4 (2%), neurology 4 (2%), respiratory 4 (2%), accident and emergency/ acute assessment unit 10 (7%), unknown requestor 7 (5%), and other specialties (ophthalmology, endocrine, etc.) 18 (12%).

Final confirmed diagnoses of autoimmune conditions were made in the following cases: rheumatology 7 (50%), gastroenterology 1 (20%), renal 1 (25%), GP 1 (0.01%).
Conclusions: Overall we found that rheumatology immunology requests were associated with a 50% chance of a positive diagnosis. This could be due to the physicians requesting the test ascertaining a high pre-test probability. The numbers analysed were small, however this does give us an overall view that immunological investigations are overly used, particularly by general practitioners.
Disclosure statement: All authors have declared no conflicts of interest.

315. IMPACT OF ANKYLOSING SPONDYLITIS ON WORK AND PRODUCTIVITY

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Background: Ankylosing Spondylitis (AS) has a significant negative effect on quality of life, day to day functioning, on-the-job attendance and performance. Besides imposing a significant burden on the use of health and social care resources, this also costs society due to work disabilities, impairments, withdrawals, and the opportunity costs of time use by care-givers. This study examines various work and productivity related aspects of the AS patients, and estimates the indirect cost of AS to the society.
Methods: Participants in an existing population-based AS cohort were sent questionnaires on work limitation, work productivity and activity impairment. The summary statistics are presented along with bootstrapped confidence intervals and smoothed Kernel distributions. The estimates of the costs of AS due to absenteeism and presenteeism are presented using the human capital approach.
Results: The response rate was 84.8% (419/494) with 222 respondents out of work and 197 in paid-job. Mean ages were 59.9 and 46.9 for the respondents not at work and at work, respectively. The mean score for the detrimental effect of AS on regular daily activities on a 0 (no impact) to 10 (complete prevention from work) scale was 5.18 ($n = 232$; 95% CI: 4.81-5.55). For the 19 work related questions asked using a difficulty scale ($1 =$ most difficult; $5 =$ least difficult), on average 48% (95% CI: 43% - 53%) of the patients indicated that it was 'difficult almost all of the time' to perform the respective activities; and 79% (95% CI: 75% - 84%) of the patients indicated that they find either 'difficult all the times' or 'most of the times'. Responses to another set of questions related to the ability of performing some activities were recorded on an integer scale of 1 to 5 ($1 =$ 'able to perform all of the time', $5 =$ 'able to perform none of the time'). The mean response values for those questions range from 3.26 to 3.58. The percentage of patients in paid work who were ever absent from work during the past 7 days due to AS was 14.76%. On average they missed 11.1 (CI: 0.15 - 22.06) hours of work during the past week attributable to AS. For the working AS patients the self-reported mean productivity loss on a 1 (most productive) to 10 (least productive) scale is 2.07 (CI: 1.76 - 2.37) indicating more than 20% loss of productivity. The productivity impact of doing household works for these working patients is even more, indicating more than 30% loss of productivity. The initial preliminary estimate of the cost for the total group attributable to lost production and inefficient working hours, but not including unpaid work production, is £2012 per person per year (95% bootstrapped CI: 331 - 3694).

Conclusions: Patients with AS experience substantial restrictions while being at work and when performing unpaid tasks, which adds to the personal and societal impact of the disease. Estimates on these costs are essential for informing policy on prescribing expensive biologic drugs for AS patients in UK.
Disclosure statement: All authors have declared no conflicts of interest.

316. EVALUATING HEALTH STATUS OF 620 PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME USING EQ-5D

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Background: EQ-5D is a standardized tool for measurement of health status and is an increasingly popular health-related quality of life instrument but has not been applied to patients with primary Sjögren's syndrome (PSS). EQ-5D provides a simple descriptive profile, a single index value for health status and a visual analogue score (VAS). The key advantages of EQ-5D are that the instrument is preference-based, easy to complete and the value sets can be easily converted to Quality Adjusted Life Years (QALY) to aid cost-utility analysis.
Methods: We evaluated the health status of 620 clinically well characterized PSS patients from the UK PSS registry (UKPSSR) who fulfil the American European Consensus Group classification criteria 2002. All data were collected prospectively using a standardized pro forma as previously described [1]. Data were compared to the UK normative data provided by the EuroQoL. In addition, the relationship between the health status of PSS patients and various clinical and patient reported outcome measures of PSS were examined.
Results: The proportion of PSS patients reporting any problem in mobility, self-care, usual activities, pain/discomfort and anxiety/depression were 42.4, 16.9, 56.7, 81.1 and 49.6 (%) respectively compared to 5.4, 1.6, 7.9, 30.2 and 15.7 (%) in the general UK population. The mean $\pm$ SD VAS score was 59.9 ± 21.2, compared to 81.3 ± 16.8 for the general UK population. Univariate correlation analysis showed that EQ-5D VAS correlated with many clinical features of PSS but most strongly with fatigue, depression and pain with R values >0.5. Among the laboratory measures, only IgG levels, paraproteins and C3 correlated with EQ-5D VAS. Hierarchical cluster analysis showed that depression and fatigue are the most important determinants of variations in health status in this PSS cohort.
Conclusions: This is the first report on the health status of PSS patients using EQ-5D. PSS patients have significantly impaired health status compared to the UK general population. Depression and fatigue are the key determinants of health status in PSS. Our data adds to the growing body of evidence that effective management of fatigue is key to improving the health status of PSS patients.
Disclosure statement: All authors have declared no conflicts of interest.

Other UKPSSR collaborators: Bacabac E, Moots R, Chadravarty K, Lamabadusuriya S, Gendi N, Adeniba R, Hamburger J, Richards A, Rauz S, Brailsford S, Logan J, Mulherin D, McManus A, Booth A, Dimitroulas T, Kadiki L, Kaur D, Kitas GD, Lloyd M, Moore L, Gordon E, Lawson C, Stirton L, Ortiz G, Clunie G, Rose G, Cuckow S, Knight S, Symmons D, Jones B, Carr A, Carrozzo M, Figuereido F, Macleod I, White P, Young-Min S, Pugmire S, Watkins M, Field A, Kaye S, Mewar D, Medcalf P, Tomlinson P, Whiteside D, Pauling J, James J, Olaitan N, Akil M, McDermott J, Godia O Palmer L; Dasgupta B, Katsande V, Long P, Chandra U, MacKay K, Fedele S, Ferenkeh-Koroma A, Marconnell H, Porter S, Allcoat P, Li C, Hall F.

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317. ELICITATION OF HEALTH STATE UTILITIES ASSOCIATED WITH DIFFERENT DURATIONS OF MORNING STIFFNESS IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis, affecting 0.5-1.1% of the global population. A specific symptom of RA is morning stiffness (MS). MS involves pain and functional disability, which can have a significant impact on a patient's health-related quality of life (HRQoL). The objective of this UK-based direct elicitation study was to elicit health state utilities through societal preferences for different durations of MS in RA, to show the impact of MS duration on HRQoL.
Methods: Health states (HS) describe the effect a disease/symptom has on a patient physically, socially and psychologically. Four HS descriptions were developed using relevant scientific literature to describe the effect of 4 different durations of MS in RA. The anchor (base case) HS reflected a patient with approximately 3 hours of MS. The remaining 3 HS showed improvements in MS duration due to treatment: HS1: MS lasts 2-3 hours, HS2: MS lasts 1-2 hours and HS3: MS lasts less than 1 hour.

The HS descriptions were validated by expert clinicians, RA patients with MS and piloted by 10 members of the public. Validated HS were evaluated by 109 members of the UK general public via face-to-face interviews using the Time-Trade-Off (TTO) method. The TTO method asks participants to consider the relative amounts of time (days/months/years) they would be willing to sacrifice to avoid a poorer HS i.e. a certain duration of MS in RA. TTO scores are obtained for each HS and were converted into a utility value. Visual Analogue Scale (VAS) scores, a numerical scale where each HS is valued between 0-100, were used to validate the TTO scores.
Results: The TTO utility score was lowest for the anchor state i.e. longest duration of MS. The TTO utility scores increase with each consecutive HS (Table 1), suggesting that HRQoL improves as the duration of MS decreases. Paired t-tests demonstrate that the difference between each HS utility value is significant.

VAS utility scores were consistent with TTO: utility scores increase as MS duration decreases (Table 1). As expected, the participants' (general population) rated their own health higher than any of the HS.
Conclusions: To date, there have been no direct elicitation studies which specifically compare different durations of MS and the impact

TABLE 1.

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
% Female	77	78	76	74	78	81	64	78	76	78
Mean age (SD)	63 (11.6)	62 (11.6)	62 (11.7)	62 (10.7)	62 (14.8)	63 (11.2)	63 (11.5)	62 (12.5)	64 (12.9)	64 (12.7)
No. OA patients surveyed	122	115	136	105	101	94	116	129	90	120
Total no. surveyed	1294	1304	1418	1590	1535	1572	1702	1910	1877	1310
% OA patients using NSAIDS	39	38	40	25	32	36	25	33	26	34
% RA patients using NSAIDS	59	56	53	47	47	49	51	39	36	31

on HRQoL. This study has shown that utility scores increase as the duration of MS is reduced. This suggests MS has a substantial effect on HRQoL, and that decreasing the duration of MS has a positive cumulative effect on HRQoL. The results of this study are plausible and are consistent with expectations and other utility studies looking at RA.

TABLE 1.

	Mean TTO utility	Standard deviation	Mean VAS utility	Standard deviation
Anchor (MS~3 hours)	0.45	0.29	0.34	0.16
HS1 (MS 2-3 hours)	0.50	0.28	0.41	0.16
HS2 (MS 1-2 hours)	0.61	0.25	0.52	0.16
HS3 (MS<1 hour)	0.78	0.20	0.65	0.16
Participants' health			0.88	0.11

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318. HAS NICE GUIDANCE AFFECTED NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE FOR OSTEOARTHRITIS? 10 YEARS OF CROSS-SECTIONAL DATA FROM A LARGE DISTRICT GENERAL HOSPITAL

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Background: NICE and other institutions have published guidelines on the management of osteoarthritis (OA) and the use of NSAIDs over the last decade. Current advice is that paracetamol or topical anti-inflammatories should be offered as first line pain relief for patients with OA. It is recommended that oral NSAIDs should be used at the lowest effective dose for the shortest possible time.

Since 1988 our department has performed a 4-weekly cross-sectional survey of clinical practice on an annual basis. Data from 2001-2011 were analysed to assess how prescribing habits have changed. We hypothesized that the introduction of NICE guidance would reduce the prescribing of NSAIDs

Methods: Data from surveys performed from 2002-2011 were analysed. All surveyed patients (new patients and patients attending for review) with a primary diagnosis of ''OA'' were assessed for NSAID, steroid (oral; intra-articular; intra-muscular) and DMARD use. Individual patient data was not used. It was not possible to assess the duration of treatment with NSAIDs or whether patients had used different NSAIDs in the past

Results: These data suggest that very little has changed during the last 10 years with regard to use of NSAIDs amongst OA patients attending our secondary care department. The demographics of this group of patients have remained stable from 2002 to 2011 (mean age, 63 ± 12.2 years; mean proportion of females, 76%).

The proportion of OA patients treated with NSAIDs was reasonably low but there was no statistically significant change in that proportion over the last 10 years (mean 31% of OA patients; range 22-39%); this contrasts with a 68% reduction in the use of NSAIDs in surveyed rheumatoid arthritis (RA) patients over the same period

Conclusions: Over the last decade OA patients attending our department (both new patients and patients attending for review) have continued to use NSAIDs with no significant change in the proportion treated with NSAIDs. This is in stark contrast to our RA population where the use of NSAIDs has significantly reduced. More effective treatment options for RA may have allowed a reduction in NSAID use in the RA patients but there has not been a corresponding increase in new therapies for OA. A relative lack of treatment options for OA may be responsible for the continued use of NSAIDs in around a third of OA patients attending our secondary care department over the last 10 years.

Despite NICE and other guidance there has not been a reduction in the proportion of OA patients attending our department using NSAIDs

Disclosure statement: All authors have declared no conflicts of interest.

319. EMPLOYABILITY-ADJUSTED-LIFE-YEARS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH GOLIMUMAB PLUS METHOTREXATE OR METHOTREXATE ALONE

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Background: Work disability is a major economic consequence among patients with rheumatoid arthritis (RA). Treatments that inhibit disease progression may delay the time when patients exit from the labor force due to disability. The purpose of this study was to estimate and compare employability-adjusted-life-years over time for RA patients in the GO-FORWARD clinical trial who were treated with GLM + methotrexate (MTX) vs. MTX alone.

Methods: GO-FORWARD was a double-blind, placebo controlled study of adult patients with active RA ($\geq$4 tender joints and $\geq$4 swollen joints) and inadequate response to MTX. In this analysis, we included patients aged less than 65 years and who received placebo + MTX (MTX Grp) or golimumab (50- or 100 mg) q4 wks + MTX (GLM Grp). Self-reported employment status and physical function measured by Health Assessment Questionnaire (HAQ) were collected from baseline over 3 years. Employability status was defined as 'unemployable' if a patient was unemployed and felt unable to work even if a job was available or 'employable' if patients were employed or felt well enough to work if a job was available. Long-term employability was estimated using a logistic regression model based on age, gender, and HAQ score. HAQ was derived by a progression rate of 0.045 per year for a person being treated with MTX and by 0 (base case) to 0.025 per year (sensitivity analysis) for a patient on biologics (GLM).

Results: At baseline, the mean (SD) HAQ score was 1.36 (0.67); 61.9% of patients under age 65 were employable, and 44.8% of patients were actually employed. At week 24, the average HAQ score was 1.08 in MTX group and 0.92 in GLM group; 33% of patients unemployable at baseline became employable at week 24 in GLM group compared to 15% in the MTX group ($p = 0.04$). GLM group maintained the HAQ improvement from 0.92 at week 24 to 0.88 at week 160. In the logistic regression model, by using the derived HAQ score, age, and gender, in the base case scenarios, over 10-year period for a RA patient cohort with an average of 50 years of age, GLM-treated patients had expected employability-adjusted-life-years of 5.92 for females and 7.15 for males, compared to 4.96 for females and 6.28 for males in MTX-treated patients, an increase of 0.96 years (19.2%) in females and 0.87 years (13.8%) in males. Sensitivity analysis demonstrated an improvement of 0.81 employability-adjusted- life-years in males (16.4%) and 0.74 years (11.8%) in females in GLM-treated patients vs. MTX-treated patients.

Conclusions: Results of analysis on the employability-adjusted-life-years showed that patients treated with GLM + MTX can realize improvement in employability over time.

Disclosure statement: T.G. is an employee of Janssen. C.H. is an employee of Janssen. E.H. is an employee of Centocor. N.T. is an employee of Janssen.

320. PATIENT EXPECTATIONS OF TREATMENT GOALS AND GOAL-SETTING PRACTICES IN RHEUMATOID ARTHRITIS IN THE UNITED KINGDOM

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Background: The treat-to-target (T2T) recommendations are designed to inform all stakeholders, patients included, about strategies to reach optimal outcomes of RA based on evidence and expert opinion. The survey presented here was conducted to evaluate the expectations of patients (pts) regarding their rheumatoid arthritis (RA) treatment and outcomes, particularly their awareness of targeted treatment goals and treatment goal setting.

Methods: RA pts from 6 countries (USA, UK, France, Germany, Italy and Spain) were recruited by an online research panel to complete an Internet survey regarding how RA affects their lives. Eligible pts were aged 25–65 years and had a diagnosis of RA $\geq$6 months. Respondents were queried on perceptions of disease management, treatment expectations, and personal and health care provider (HCP) goal setting (personal/social/treatment) for RA. This study reports the mean

responses to each question computed for the overall population of UK respondents, collated by Opinion Matters.
Results: A total of 306 pts (171 females and 135 males) were recruited in the UK. The majority of participants were aged 55–65 years (46% of females, 59% of males). When asked to describe the severity of their RA, 50%, 29% and 21% of pts responded with 'moderate', 'mild' or 'severe', which was in line with the international survey population.

When asked about goal setting upon starting a new treatment, 71% set personal or social goals, and 82% set treatment goals. Most respondents (79%) agreed that establishing personal treatment targets would positively impact disease management. A total of 61% of respondents agreed that a targeted disease management approach involved setting personal, lifestyle and treatment goals and monitoring progress to achieve them. However, 81% of UK pts reported that their HCP did not manage their RA with strict goals and timeframes and 83% reported that their HCP did not discuss treating RA with an approach that achieved personal or social targets.

Regarding treatment perceptions, 90% of respondents wanted an improvement in signs and symptoms within 3 months of starting new therapy, whilst only 77% expected to feel an improvement within that time. However, 43% of respondents would only wait 4 weeks or less to speak to their HCP if they felt a new treatment was not working. Overall, 52% of respondents shared decisions with their HCP regarding how best to manage RA.
Conclusions: From the perspective of RA pts, a targeted approach to successful disease management means setting personal, social and treatment goals, and monitoring progress to achieve them. People with RA want help from HCPs in determining and setting these goals to assess for themselves whether their treatment is working. As more treatments become available for RA, the expectations of people with RA are likely to increase.
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321. PREVIOUS EXPOSURE TO VARICELLA ZOSTER INFECTION IS THE NORM IN ADULT PATIENTS STARTING BIOLOGIC DRUG THERAPY FOR INFLAMMATORY ARTHRITIS

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Background: In our service, we do not generally test adult patients for previous Varicella zoster infection before treatment with anti-TNF and other biologic agents. Patients are advised to contact the department if exposed to V zoster infection whereupon they are tested for serological immunity, and given passive immunotherapy if negative. This contrasts with the paediatric rheumatology service where children are routinely tested and immunized if negative. We had based our approach on the data from World Health Organization figures (2003) which suggest that 90% of the population are exposed to chicken pox by the age of 16. However, given the increased risk of serious morbidity and mortality of V zoster infection in adults, increased further in those treated with immunosuppressive agents (Sands 2004) and reported unreliability of the patient's history (Shale 2010) we thought we should ascertain the frequency of immunity to V zoster in this patient group.
Methods: We aimed to ascertain serological immunity to V zoster in consecutive patients starting biologic drugs de novo for inflammatory arthritis, from Jan to Sept 2011. Samples were sent for routine laboratory testing when eligibility for biologic drugs was assessed.
Results: 75 patients were tested for V zoster immunity when assessed for eligibility for biologic drugs for a range of rheumatological conditions. Patients were aged between 21 and 80 years. 34 were male and 39 female. 32 patients were not tested, all of whom gave a positive history of prior infection. All but two of those tested were serologically positive. Of these, one had given a positive history of exposure (age 77) and one negative (age 60). Both were male. In particular, younger adult patients did not show lack of exposure to V zoster infection.
Conclusions: Our results confirm that previous V zoster infection is the norm in the north east adult population of patients starting biologic drugs. Only 1/74 tested adults who gave a positive history of infection was actually negative on testing. This accords with the WHO data and suggests that routine serological testing of all adult patients for previous V zoster may not be justified. This does not negate the need for counselling of patients to avoid exposure to V zoster infection where possible, or the need to test patients known to be exposed if their immune status is unknown.
Disclosure statement: L.K. received honoraria from Roche and Pfizer, project management support from Pfizer and administrative support from Abbott. K.N. received administrative support from Abbott. M.R. received administrative support from Abbott.

322. AN ELECTRONIC ALERT SYSTEM TO NOTIFY THE RHEUMATOLOGY TEAM OF HOSPITAL ADMISSION, TRANSFER OR DISCHARGE OF RHEUMATOLOGY PATIENTS TAKING BIOLOGIC DRUGS

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Background: Biologic drugs are highly effective for the management of rheumatological conditions, but carry risks such as increased rates of and altered presentations of infection. Patients with serious infections may present to departments other than rheumatology, and despite presentation of patient-held alert cards, the significance of treatment with biologic drugs in patients' presentations is often under-appreciated by non-rheumatology teams. Prompt advice to admitting teams may prevent complications of urgent and elective surgery and allow early detection and appropriate treatment for example of atypical infections.
Methods: We have an electronic health record, Cerner Millennium. The "Problems" facility was used to generate an automatic RAPA alert. Any attendance of a listed patient to the Emergency Department, admission anywhere in the Trust, transfer (eg to ITU) or discharge, is automatically notified to the Rheumatology Biologics Nurses and to the lead consultant via the home page, viewed electively and at log-in. The message generated includes the patient's identifying information, the biologic, location, consultant in charge and their rheumatologist. A yellow star flags the patient for the admitting teams.
Results: In 2 months we have identified 35 patients with 43 admissions. 26 were elective admissions for procedures, including 11 endoscopies and 9 orthopaedic operations. 8 were not otherwise known to the rheumatology team. There were 9 emergency medical and 3 emergency surgical admissions, for which we contacted the admitting team and discussed the importance of potential immuno-suppression. Examples include: small bowel perforation, where the microbiology team advised a different prophylactic antibiotic regime for the patient once alerted to their medication, newly diagnosed pancreatic cancer proceding to surgery, and the patient with an ankle fracture who developed pneumonia. There were 5 attendances at the emergency department, 3 with exacerbations of musculoskeletal pain. During this period we did not encounter any patients with atypical infections.
Conclusions: This alert system has shown the variety of interactions of these patients with our health care system. This real time notification of admission, transfer or discharge allows the rheumatology team to advise admitting teams about potential diagnostic pitfalls or complications presented by biologic drugs, allowing consideration of appropriate differential diagnoses particularly opportunistic infections. This reinforces the lesson that we cannot expect all clinicians who look after our patients to have knowledge of biologic drugs and their potential clinical impact. We can identify patterns of patient usage of health services which may not be optimal, for example attending the Emergency Department rather than the rheumatology department for exacerbations of articular pain, allowing us to target patient education.
Disclosure statement: L.K. received honoraria from Roche and Pfizer, project management support from Pfizer and administrative support from Abbott. K.N. received administrative support from Abbott. M.R. received administrative support from Abbott. G.W. received administrative support from Abbott.

323. OBSERVATION OF PERSISTENCE RATES AND COSTS SAVINGS ASSOCIATED WITH CERTOLIZUMAB PEGOL TREATMENT FOR RHEUMATOID ARTHRITIS IN ENGLAND, WALES AND NORTHERN IRELAND CLINICAL PRACTICE

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Background: Certolizumab pegol (CZP) was recently introduced for the treatment of rheumatoid arthritis in the UK. Key studies have shown the majority of patients (pts) responded to CZP + methotrexate (MTX) by week 12, and that a pt's response to therapy at 12 wks is

predictive of clinical outcome at 1 year. Continued CZP therapy should be carefully reconsidered in pts who show no evidence of clinically relevant benefit in the first 12 wks of treatment. In the UK, CZP is available via a Patient Access Scheme (PAS), in which pts receive the first 12 weeks of CZP (10 pre-loaded syringes of 200 mg each) and the responders continue. Here we evaluate persistence and report the actual versus potential cost savings.

Methods: This retrospective analysis used anonymized data (March 2010-Aug 2011) from Healthcare at Home. A crude persistence rate was calculated, defined as the percentage of pts continuing to receive deliveries of CZP at 13, 26, 37 or 52 wks after first delivery, with pts censored according to the date of first delivery. Treatment start was the first delivery date and treatment status was determined as current or finished at a specified time point. Pts were defined as naive or switch ($\geq$1 prior anti-TNF, according to Healthcare at Home records). Patients who temporarily discontinued therapy (eg. undergoing surgery) were excluded. A cost analysis was performed by calculating a) the savings from the PAS and b) the potential re-investment which could be made by removing non-responders at 12 wks versus 26 wks.

Results: This analysis included 1,389 pts. The persistence rate was calculated at 4 time points (Table 1). At 52 wks, the persistence rate was 70% in anti-TNF naïve and 51% in switch pts. Analysing first line biological drug costs only, in the first year, the NHS would save £2,363 per pt if CZP is used in place of adalimumab or £2,502 if CZP is used in place of etanercept; this is due to the PAS. Furthermore, stopping CZP treatment for non-responders at wk 12 vs wk 26, could allow the NHS to re-invest £2145 per pt whilst also avoiding unnecessary drug exposure (an equivalent of ~£300,000 for this CZP cohort that could have been used for an alternative treatment).

Conclusions: In this UK population, CZP persistence was in line with observations made by the BSR-BR, in which 71% of RA pts receiving a first biologic remained on treatment at 1 year. Using CZP with a 12 wk treatment decision could result in substantial initial biologic drug-cost savings for the NHS as well as avoiding unnecessary drug exposure and delayed initiation of alternative treatment in non-responders.

Table 1.

	Pesistence, %	
Duration of treatment	Naive pts	Switch pts
13wk	86 (n = 866)	80 (n = 523)
26wk	74 (n = 574)	63 (n = 428)
37wk	72 (n = 328)	51 (n = 319)
52wk	70 (n = 159)	51 (n-170)

Disclosure statement: G.D. is an employee of Healthcare at Home. S.R. received speaker fees and honoraria from UCB. M.R. is an employee of UCB. A.S. is an employee of UCB. J.T. is an employee of UCB.

324. DEVELOPING A PATIENT VISION: GIVING PATIENTS A VOICE

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Background: With potential threats to service it was felt important to establish a patient 'voice' on behalf of the Rheumatology department. A Rheumatology Patient Advisory Group (PAG) was established and met initially in October 2009. Members included both patients and carers from within the Sunderland Rheumatology Department. One aim initially identified by this group was to raise the profile of Rheumatology both at a Trust and Primary Care level. From future meetings in 2010 the idea of a 'patient vision' for Sunderland Rheumatology services was developed and a steering group of patients and carers began work. Standards of Rheumatological care exist in the public domain which any Rheumatology team should be aspiring to deliver. The aim of this piece of work, however, was to look at ways of providing and lobbying for an 'exemplar' service here at Sunderland with patients in the centre of its development.

Methods: An initial meeting was held in December 2010 with 11 members of the group. During this the group was asked how in an ideal world they would like Rheumatology services to be run and key areas for development were established. Patients and carers then reflected at home with family and friends on each section and submitted further thoughts in writing. The initial collated material was distributed prior to a second meeting in June 2011. This second meeting involved a focus group format incorporating two groups, one looking at the clinic journey, the other looked at patient education. Four patients/carers were in each of the groups. Following this meeting an initial draft document was again collated and distributed for further comment. Establishing a patient vision has been an iterative patient centred process.

Results: Ten key areas were highlighted through this process: physical environment, clinic journey and appointments, blood monitoring, communication, staffing, personalized care plans, education, allied services, help services and patient support services/groups. Patients views on each area have been captured into a 'vision' document. This includes direct quotations and suggested action plans. Under communication for example: 'A newsletter is a brilliant way of getting to people. They are more likely to pick one up and read it in the waiting rooms.' -A newsletter has subsequently been established. Under staffing: 'Some days the staff seem overworked due to lack of staff and more patients, and this can be very stressful for them and it can show.' -this example has been used to highlight staffing shortages and support expansion.

Conclusions: This innovation of a PAG group and the development of a Rheumatology Patient Vision, giving patients a 'voice', has provided in-depth patient views over and above normal feedback. Patients have felt engaged in service planning and have been invited to present their 'vision' document to directors of the Trust. They also provide a group with which commissioners may engage.

Disclosure statement: All authors have declared no conflicts of interest.

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

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Background: Inflammatory back pain (IBP) is a characteristic feature of spondyloarthropathies (SpA). 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 Ankylosing Spondylitis (AS) deferring specialist referral until irreversible structural damage has occurred (Feldtkeller E, et. al. 2003). Early assessment and diagnosis is fundamental to provide effective treatment and prevent physical, emotional and socioeconomic consequences (Sieper J, et. al. 2005).

Objectives:

1. Develop an Early Inflammatory Back Pain Service (EIBPS) pathway.
2. Implement an educational campaign focused on early diagnosis of IBP raising awareness to GP's, Allied Healthcare Practitioners (AHP's) 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 SIJ's 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, AHP's and secondary care colleagues.

Results:

92 patients with suspected IBP were screened in the EIBPS over 16M
72/92 patients (78%) were screened within 3 wks of referral.
54/92 patients (59%) were male.
77/92 patients (84%) had symptoms suggestive of IBP and or other SpA features and were therefore investigated further.
36/77 patients (47%) fulfilled Modified New York or ASAS criteria.
41/77 patients (53%) had symptoms suggestive of IBP but did not at this stage fulfil criteria for a specific SpA.
32/36 of the patients who fulfilled the Modified New York or ASAS criteria (89%) commenced NSAIDs at diagnosis.
18/36 of the patients who fulfilled Modified New York or ASAS criteria (50%) were referred appropriately for TNF therapy either through 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.

Disclosure statement: All authors have declared no conflicts of interest.

326. SCREENING FOR LATENT TUBERCULOSIS IN PATIENTS STARTING ANTI-TNF THERAPY

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Background: The British Thoracic Society (BTS) produced guidelines for TB screening in response to concern about latent TB reactivation in patients commencing anti-TNF therapy [1]. For the majority of rheumatology patients treated with immunosuppressants, tuberculin skin testing is unsuitable. The BTS TB screening therefore relies on a TB risk assessment, clinical examination and chest X-ray. The T-spot gamma interferon test is a highly sensitive (96%) and specific (98-99%) test for TB infection and seems unaffected by previous BCG vaccination or immune-compromised states. However, this test is expensive. We audited the sensitivity and specificity of BTS TB screening against T-spot testing for latent TB in rheumatology patients commencing anti-TNF therapy.
Methods: Between 2009-11, all rheumatology patients considered for biologic therapy were assessed for TB risk: 1) using BTS screening guidelines and 2) using the T Spot TB test. All patients had detailed history, clinical examination and chest radiograph but not tuberculin skin testing. A positive BTS TB screen was defined as any of the following: 1) previous TB infection, 2) birth or 3) travel in TB endemic country 4) contact with TB infected person or 5) TB associated abnormality on chest X-ray. The results of the BTS TB screen were compared to the T spot TB test using logistic regression.
Results: Data were obtained on a total of 130 patients (56 males, 74 females), mean age was 53.7 years and all the patients were caucasians. Positive T-spot results were detected in 22 (16.9%) patients, 104 (80%) tested negative and 4 (3.1%) patients had equivocal results. Amongst the 22 patients with positive T-spot test, 12 (54.6%) had no risk factors for TB identified using the BTS TB screen. All patients with equivocal T-spot results had a history of previous contact with TB. Age and gender adjusted logistic regression revealed a strong relationship between a positive BTS TB screen and a positive T-spot (OR 6.8; 95%CI 2.4, 19.1). However, whilst the sensitivity of the BTS TB screen for correctly identifying a negative T- spot result was high 89.4%, the specificity was low 53.9%.
Conclusions: This UK based caucasian rheumatology population are considered low risk for reactivation of TB. However, we detected positive T-spot results in 17% suggesting a much higher prevalence of latent TB than expected. Reliance on BTS TB screening alone would have missed over half of these patients. It is our current practice to conduct T-spot testing on all patients prior to starting anti-TNF therapy. We hoped that demonstrating a high sensitivity and specificity for BTS screening assessments would allow us to reduce our reliance on the more expensive T-spot testing. However, the low specificity of the BTS TB screening has confirmed the need to continue to routinely use T-spot to assess risk of latent TB in our rheumatology population. We recommend the use of T-spot test as a useful adjunctive test to be used before the start of anti-TNF therapy.
Disclosure statement: All authors have declared no conflicts of interest.

327. CAPACITY AND DEMAND IN RHEUMATOLOGY: A SYSTEM DYNAMICS APPROACH

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Background: The length of time a patient waits to be seen by a doctor challenges even the best healthcare organizations. In the UK, waiting time targets have led to a focus on 'new' patient activity within outpatients.

Much work has been undertaken in order to understand 'new' demand. However, there is little focus upon 'follow-up' demand, which often results in large follow-up pools, and delays in reviewing patients.

The follow-up: new ratio (F:N) has been used as a marker of system 'efficiency'. Increasingly F:N ratios are capped by commissioners ensuring value for money from their contracted providers.

Systems thinking suggests it is easier to focus on inflow, rather than outflow, which may partially explain a focus on 'new' demand. This often results in accumulation, leading to a steady increase in the follow-up pool. It would, therefore, be desirable if outflow was at least equal to, or higher than inflow.

One Consultant Rheumatologist wished to understand the follow-up capacity required, and size of follow-up pool that results from his new activity.
Methods: A System Dynamics framework was chosen, as the investigator wished to understand system behaviour. A simulation was produced in iThink in order to answer specific research questions:

1. How many follow-up slots will be required to achieve equilibrium?
2. What factors affect follow-up capacity?
3. Is there a set of basic equations that allows a better understanding of capacity and demand?

A number of scenarios, based were modelled in order to validate the system.
Results: By using one Consultant's data (Table 1) the simulation suggested 57 follow-up slots/week to ensure all patients were seen, resulting in a F:N = 9.4:1. The follow-up pool had 684 patients in it. Reducing follow-up frequency has no effect upon number of follow-up slots at equilibrium, but increased the size of the follow-up pool.

The consultant only has 48 follow-up slots. A N:F of 8:1 suggests a more efficient system, but actually results in delays in reviewing some patients.

A small increase in follow-up discharge has a more dramatic effect on follow-up demand than increasing discharge from new. An increase in discharge rate from 9% to 15% resulted in the consultant only requiring 34 follow-up slots, a F:N of 5.7:1. A basic set of equations describe this behaviour.
Conclusions: The System dynamics simulation reveals the follow-up capacity required to meet new demand. We have challenged the assumptions of N:F ratios as markers of efficiency. Small increases in discharge from follow-up have dramatic benefits upon follow-up requirements. The challenge for clinicians is discharging effectively whilst maintaining a high quality service.

TABLE 1 Consultant activity data

New patients/week	6
Discharge from new	15%
Discharge from follow-up	9%
Follow-up frequency	3 months

Disclosure statement: All authors have declared no conflicts of interest.

328. ATTITUDES TOWARDS PERSONAL HEALTH BUDGETS OF PEOPLE WITH MUSCULOSKELETAL AND RHEUMATOLOGICAL CONDITIONS

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Background: Historically in England, services such as physiotherapy were provided to patients directly by the National Health Service (NHS). Latterly, the introduction of patient choice and private providers has given patients more flexibility and control over the services they receive. In 2011, the Department of Health in England (DH) began piloting personal health budgets (PHBs), giving patients with long term conditions a personalized annual budget to spend on agreed services and equipment (treatments provided directly by doctors such as medications or medical procedures are not included). Pilot sites focused on a range of health areas, but did not include musculoskeletal/rheumatological disorders.
Methods: From August-November 2011, people with musculoskeletal/rheumatological disorders were invited to respond to a survey to characterize their current use of services and views on receiving a PHB. This was developed by Arthritis Research UK with input from DH and several UK health think tanks. The survey was publicized through the newsletters of UK organizations such as Arthritis Research UK, Arthritis Care, NRAS, Age UK and the Patients Association. As well as being available online, paper copies were provided on request.
Results: Initial analysis was conducted of 161 responses. Median age was 60 years, and of the 140 reporting their sex, 24% (33) were male and 72% (101/140) female. The most commonly represented condition was osteoarthritis 41% (66/161), followed by rheumatoid arthritis 32% (51/161) and back pain 24% (33/161). The majority of respondents rated their disease severity as moderate (44%, 71/161) or severe (37%, 60/161). Of the 47% (76/161) of respondents currently receiving services, physiotherapy was most common (40/76) followed by podiatry (25/76), occupational therapy (12/76), and acupuncture (8/76). Whereas 60% (96/161) of respondents agreed NHS services were of high quality, only 35% (56/161) agreed treatments were "available if

you need them", with 47% (76/161) describing waiting times as unacceptable. Overall, 66% (107/161) said they thought PHBs would improve their health. The vast majority (81%, 130/161) said having a PHB would make them feel more in control of their health condition, with only 5% (8/161) disagreeing. While 60% (97/161) of people surveyed thought they were informed enough to make a decision about how to spend a PHB, over one in four (27%, 43/161) disagreed. Overall, 69% (111/161) said they would accept a PHB if offered and just 19% (30/161) said they would not.

Conclusions: Although not necessarily representative, within this diverse sample there was broad enthusiasm for PHBs, with substantial dissatisfaction over services currently received and great appeal of the potential for increased control with a PHB. Nevertheless, any policy change must acknowledge that a substantial minority may prefer the current arrangements, and recognize the information and support needs for those accepting a PHB.

Disclosure statement: All authors have declared no conflicts of interest.

SJÖGREN'S SYNDROME AND OTHER CONNECTIVE TISSUE DISORDERS

329. HOW GOOD ARE THE EULAR SJÖGREN'S SYNDROME DISEASE ACTIVITY INDEX, AND EULAR SJÖGREN'S SYNDROME PATIENTS REPORTED INDEX IN PREDICTING HEALTH STATUS IN PRIMARY SJÖGREN'S SYNDROME?

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Background: Over the past 2 years, the EULAR Sjögren's syndrome study group have developed 2 new instruments, ESSDAI and ESSPRI to measure systemic disease activity and overall symptom burden. The ESSPRI also generates a EULAR sicca score (ESS) which measures the overall symptom of dryness. These instruments are designed to be used as standardized outcome measures for clinical studies and trials. Therefore it is useful to investigate how well these instruments predict the health status of patients with primary Sjögren's syndrome (PSS). EQ-5D is a generic instrument that measures health outcome, the value sets can be converted to Time Trade Off (TTO) values representing the time a patient would be willing to give up to be freed from a reduced health state. In this study, we examined the relationship between ESSDAI and ESSPRI and the TTO values derived from EQ-5D.

Methods: Data including ESSDAI, ESSPRI and EQ-5D were prospectively collected from 633 PSS patients who have participated in the UK PSS registry (UKPSSR) using a standardized pro forma as previously described [1]. TTO values were derived from the UK reference data provided by EuroQoL (the developer of the EQ-5D instrument) which has been transformed so that the values range from -1 to 1, with 1 being the number of years in perfect health state, 0 being dead and negative values representing health states worse than being dead. The relationships between the derived TTO values based on the health state of the patients and ESSDAI, ESSPRI as well as ESS were determined.

Results: The mean $\pm$ SD TTO value of the PSS cohort was 0.624 ± 0.301, with a range of -0.239 to 1. There were statistically significant correlations between TTO and ESSDAI, ESSPRI and ESS; TTO values decreased with increased ESSDAI, ESSPRI and ESS values ($p < 0.001$ for all three). The strength of correlation was strongest with ESSPRI (R = -0.64), followed by ESS (R = -0.29) and ESSDAI (R = -0.15).

Conclusions: The recently developed EULAR PSS outcome assessment tools, in particular the ESSPRI, may be useful predictors of the health status of PSS patients.

Disclosure statement: All authors have declared no conflicts of interest.

Other UKPSSR collaborators: Bacabac E, Moots R, Chadravarty K, Lamabadusuriya S, Gendi N, Adeniba R, Hamburger J, Richards A, Rauz S, Brailsford S, Logan J, Mulherin D, McManus A, Booth A, Dimitroulas T, Kadiki L, Kaur D, Kitas GD, Lloyd M, Moore L, Gordon E, Lawson C, Stirton L, Ortiz G, Clunie G, Rose G, Cuckow S, Knight S, Symmons D, Jones B, Carr A, Carrozzo M, Figuereido F, Macleod I, Tarn JR, White P, Young-Min S, Pugmire S, Watkins M, Field A, Kaye S, Mewar D, Medcalf P, Tomlinson P, Whiteside D, Pauling J, James J, Olaitan N, Akil M, McDermott J, Godia O Palmer L; Dasgupta B, Katsande V, Long P, Chandra U, MacKay K, Fedele S, Ferenkeh-Koroma A, Marconnell H, Porter S, Allcoat P, Li C, Hall F.

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330. MONOCYTE-DERIVED IL-32 EXPRESSION CORRELATES WITH THE LEVEL OF INFLAMMATION IN SALIVARY GLANDS OF SJÖGREN'S SYNDROME

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Background: IL-32, a recently described cytokine promoting pro-inflammatory cytokines such as IL-1β, IL-6, CXCL8 and TNFα, has emerged as a key component in the development of chronic inflammatory diseases such as rheumatoid arthritis. Here we investigated IL-32 expression and identified IL-32 producing cells in the salivary glands (SG) of Sjögren's Syndrome (SS) patients.

Methods: IL-32 mRNA expression level was assessed by Taqman quantitative PCR in SG of SS patients and non-specific chronic sialadenitis (NSCS) as controls. In addition, immunohistochemistry was used to assess IL-32 expression and the formation of B/T cell aggregates. Double immunofluorescence was used to identify the cellular source of IL-32 in the SG.

Results: Expression of IL-32 correlated with the severity of inflammation and was significantly increased in SS patients compared to NSCS controls (mean $\pm$ SEM; 10.3 ± 2.1 vs 4.1 ± 0.5, $p < 0.005$). In addition, IL-32 mRNA correlated with the levels of CXCL13 (Spearman's $r = 0.50$, $p = 0.004$), a lymphoid chemokine strictly associated with the formation of B/T cell aggregates. Immunohistochemistry identified IL-32 + cells in periductal aggregates in SS but not in controls. Conversely, both SS and control SG showed abundant IL-32 staining on salivary ductal epithelial cells. Finally, double immunofluorescence identified monocyte-derived CD68 + cells as the main source of IL-32 within lymphoid aggregates in SS.

Conclusions: Here we show that IL-32 expression is significantly increased in the SG of SS patients where both ductal epithelial cells and monocyte-derived cells abundantly express this cytokine. These data strongly implicate IL-32 in the maintenance of chronic inflammation in the target organ of SS.

Disclosure statement: All authors have declared no conflicts of interest.

SLE AND ANTIPHOSPHOLIPID SYNDROME

331. ULTRASOUND ASSESSMENT OF EROSIVE HAND DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Joint involvement in SLE is common affecting up to 90% of patients at some stage in their disease and has a significant impact on quality of life. Despite this lupus arthritis remains largely understudied in comparison to the abundance of research that exists surrounding rheumatoid arthritis. The traditional idea that lupus patients develop a non-erosive arthropathy with reducible deformities is being challenged by newer imaging techniques which have the potential to provide a framework for a well-defined classification system.
Methods: 31 patients who fulfilled the ACR criteria for the diagnosis of SLE and who complained of painful hands for > 1 year were recruited and included in the study. 12 patients with rheumatoid arthritis were also recruited as a comparator group. Baseline immunological tests were performed; lupus disease activity was measured and clinical examination was carried out. All patients underwent ultrasonography by the same sonographer and the presence of synovitis, erosions, tenosynovitis and Doppler signal were noted and scored according to a recognized scoring system.
Results: See Table 1.
Conclusions: Arthritis with erosion similar to the pattern in rheumatoid arthritis (RA) is thought to be less common in SLE and has been estimated to be < 5% of patients. Our small study has shown that ultrasound may reveal a higher percentage of erosions than previously thought. The role of the anti-CCP antibody in SLE arthritis remains controversial. Some studies have identified a link with erosive disease as in RA however our results are in keeping with other studies to date which have identified no link. While data is accumulating gradually our current understanding of lupus arthritis remains incomplete and a well-defined classification system does not yet exist. It is clear that developments in imaging including MRI and ultrasound are reshaping our understanding of the processes of erosion and joint pathology in the spectrum of rheumatic diseases as a whole. Future continued application of these developments to SLE arthritis will continue to provide answers to several important questions.

TABLE 1 Results

SLE patients (n = 31)		RA patients (n = 12)
Clinical deformity	12 (38)	8 (67)
Wrist synovitis	15 (48)	10 (83)
Erosive disease (2nd or 3rd MCP joint)	9 (29)	10 (83)
Tenosynovitis (extensor carpi ulnaris or 2nd/3rd finger flexor tendon)	9 (29)	5 (41)
Anti-CCP antibody	1 (3.2)	11 (91)
Rheumatoid factor	3 (9.6)	12 (100)
Anti-dsDNA antibody	18 (58)	0 (0)
CRP > 20 mg/l	5 (16)	2 (16)

Data are given as *n* (%).

Disclosure statement: All authors have declared no conflicts of interest.

332. ANTINUCLEAR AUTOANTIBODIES SEROCONVERSION IN 100 PATIENTS WITH LUPUS

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Background: In a recent drug trial using the monoclonal antibody Benlysta it was noted that 29.5% of patients, said to have SLE, were ANA negative. This ostensibly seemed a rather high figure but the literature contains relatively little information about what happens to SLE serological abnormalities over long periods of time.

We have taken the opportunity of auditing results on 97 SLE followed up for ten years who were still alive in order to determine how many were no longer ANA positive. In addition, we sought to determine any variation in the ENA and DNA results and to ascertain whether there was a correlation between the loss of a positive ANA and the amelioration of clinical symptoms.

Methods: We reviewed the notes of 100 randomly selected patients with SLE (all of whom met the revised classification criteria for SLE) and on whom ANA, ENA and anti-dsDNA results were available from the time of diagnoses or shortly after and at follow up ten years later. The ANA results were obtained by immunofluoresence using a Hep2 substrate; the anti-ENA and anti-dsDNA antibodies profile by ELISA (Eurodiagnostica). In three patients insufficient data were available for adequate analysis, so that we report results on 97 patients. At every patient clinic attendance disease activity was assessed by using the classic BILAG system.
Results: There were 83 female (85.5%) and 14 male (14.4%) patients. There were 62 Caucasian, 8 Chinese, 18 Afro-carribean, 8 Asian and one mixed ethnicity (one parent caucasian and one phillipino). We found that there was one patient was persistently ANA negative throughout the 10 year follow up and was also ENA and anti-DNA antibody negative. Thus 96 patients out of 97 (98.9%) were ANA positive at the time of diagnoses. However 17 patients (17.57%) became ANA negative ten years later. Of these ANA negative patients, 15 (88%) are Caucasian. We found that Caucasian patients are more likely to become ANA negative over ten years ($p < 0.0021$).Of the thirty-two (33%) patients initially negative for anti-dsDNA, 18 became positive after ten years. Thus 63 (81%) of the 79 patients were persistently ANA positive. Anti-ENA antibodies also were tested and among 60 ENA negative at the beginning, 20 (33.3%) became ENA positive: 8 Ro+, 15 RNP+, 1 La+ and 9 Sm+ ten years later. Among those historically Ro+, 94.4% remained positive and among those historically Ro-, 83% were still negative. No relationship was found between the ANA negative 'conversion' and treatment with immunosuppressants, antimalarials or disease remission.
Conclusions: We found that ANA positivity disappeared over time in 17.5% of SLE patients and 88% of those who became negative were Caucasians. The effect of the Caucasian race on the ANA seroconversion, after adjusting for confounding variables such as immunosuppressive therapy, the result of anti-DNA and Ro, appears to be independent and statistically significant. In contrast, Anti-ENA antibodies changed relatively little over time.
Disclosure statement: All authors have declared no conflicts of interest.

333. PATTERNS OF IMMUNOGLOBULIN-G GLYCOSYLATION DISTINGUISH DIFFERENT CLINICAL PHENOTYPES OF ANTIPHOSPHOLIPID ANTIBODY POSITIVITY

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Background: Polyclonal IgG and antiphospholipid (aPL) antibodies from patients with different clinical manifestations of the antiphospholipid syndrome (APS) have been shown to exert differential effects on signalling pathways and tissue factor activity in target cells. Interestingly, these biological effects were not distinguished by their degree of aPL binding which did not differ significantly between the different APS subgroups.

Given that glycosylation is known to influence the biological activity of IgG, and that changes in IgG glycosylation patterns have been shown to predict clinical manifestations for various autoimmune diseases, we examined whether differential glycosylation of IgG may be a factor in determining the observed differences in the mechanism of the effects of IgG from APS patients.
Methods: The glycosylation profile of IgG N-glycans, enzymatically released, from protein-G purified IgG from four sets of 8 patients; APS with pregnancy morbidity (PM) alone (aPL+PM), vascular thromboses (VT) alone (aPL + VT), aPL + ve patients without APS (aPL + APS-) and healthy controls (aPL-HC) was examined using MALDI-TOF Mass Spectrometry. IgG glycans were divided into three main groups based on the number of galactose residues: G0, G1 and G2. These biantennary complex glycans may be further modified by the presence / absence of fucose (F) and / bisecting-N-acetylglucosamine (bis).
Results: There were no significant differences in aPL binding between the different APS and aPL + groups. In contrast, the glycosylation profile of IgG was found to be significantly different in the 4 groups examined (Table 1). IgG from the APS patients had significantly higher ratios of total G0:G2 compared with the aPL + APS- patients ($p = 0.038$) and those from aPL- HC ($p = 0.002$). On further, more detailed, analysis, the IgG from patients with VT, which showed the most marked difference in total G0:G2 ratio, could be differentiated

from the PM group based on significant differences in the levels of G1F, G2, G2F and G1Fbis ($p < 0.05$).
Conclusions: Our findings show that IgG from patients with diverse clinical manifestations of APS and aPL positive healthy controls exhibit differential patterns of glycosylation that were not predicted by differences in aPL binding. Therefore, these glycosylation differences, which include the degree of galactosylation as well as fucosylation, could be used as a biomarker to discriminate between patients with VT and PM, and may provide a better insight into the different mechanistic action of IgG in these patients.

TABLE 1 The degree of IgG galactosylation can be used to distinguish different clinical phenotypes of antiphospholipid antibody positivity

Patient groups	Total G0:G2 ratio, mean ± SEM
aPL + PM	1.16 ± 0.25
aPL + VT	1.81 ± 0.25
aPL + APS−	0.89 ± 0.15
aPL- HC	0.42 ± 0.08

Disclosure statement: All authors have declared no conflicts of interest.

334. A CASE CONTROL STUDY OF OSTEOPOROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Osteoporosis is well described in patients with Systemic Lupus Erythematosus (SLE). The aetiology of osteoporosis in SLE is multi-factorial including the underlying autoinflammatory disease, vitamin D deficiency and systemic glucocorticoid therapy.

The aim of this study was to investigate if there was a significant difference in site-specific bone demineralization- hip and lumbar spine, between SLE patients and age and sex matched controls. Risk factors for the development of osteoporosis were also considered.
Methods: Demographic and epidemiological data of SLE patients who underwent dual-energy x-ray absorptiometry (DEXA) scanning at Royal Lancaster Infirmary between 1992 and 2010 were collated. A total of 65 patients were identified. Age and sex controls were obtained from a reference cohort with no indications for DEXA scanning. The statistical difference in bone mineralization was ascertained by using the students t-test.
Results: 65 SLE patients were identified (63 female, 2 male). 65 age and sex matched controls were acquired. The median age of the groups was 50.0 years (IQR of case group 24.8-58.9, control group IQR 24.1-58.9 years). There was no history of fracture in either group. The SLE group had a greater number of indications for DEXA scanning (SLE group mean 3, control group mean 0). 1 patient in the SLE group was currently on corticosteroid therapy at the time of data acquisition, 8 had historical corticosteroid use. 6 patients satisfied WHO criteria of BMD estimation to diagnose osteoporosis (5 vertebral and 1 hip).

A statistically significant difference was observed in the hip t-score between the two groups (SLE group mean −0.704, control group mean −0.28, p-value 0.02). However, despite a numerical lower mean lumbar L1-L4 spine t-score in the SLE group, this did not reach statistical significance (SLE group mean −0.58, control group mean −0.31; p-value 0.26). When patients that were on steroids were excluded for analysis, this did not significantly alter the association.
Conclusions: A lower t-score was observed in both the hip and lumbar spine in SLE patients compared to the age and sex matched controls. However, only the hip region was associated with statistical significance (p-value 0.02). Despite the limitations of this study, these results suggest that SLE patients may have disproportionate loss of bone mineral from their hip compared to the lumbar spine. The development of osteoporosis in SLE is multi-factorial in origin; indeed the SLE group had more indications for DEXA scanning. However, the specific aetiology of accelerated loss of bone mineral at the hip is not known. Future examination of the aetiology of site-specific bone demineralization in SLE is warranted.
Disclosure statement: All authors have declared no conflicts of interest.

335. A COMPARISON OF PULSE AMPLITUDE TONOMETRY AND FLOW-MEDIATED DILATATION OF THE BRACHIAL ARTERY AS MEASURES OF ENDOTHELIAL FUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: SLE is associated with accelerated atherosclerosis and endothelial dysfunction. FMD of the brachial artery (BA) is the standard non-invasive measure of endothelial function, although its use is limited by significant inter-observer variability and variations in both protocol and technique between users. PAT is a fully automated method of assessing endothelial function that eliminates inter-observer variation. PAT analyses changes in the digital pulse wave amplitude (PWA) and appears to correlate with FMD in the general population. PAT has yet to be validated in a SLE cohort. We therefore conducted a comparison study of FMD and PAT in a cohort of SLE patients, as well as a cohort of healthy controls.
Methods: 23 healthy controls (mean (SD) age 41.3 (9.8) years) and 18 SLE (≥4 ACR criteria) patients (mean (SD) age 41.3 (14.2) years) underwent assessment of endothelial function. FMD (%) of the BA was performed by a single operator in a temperature-controlled environment. A 12-MHz ultrasound probe was used to image a longitudinal section of artery proximal to the antecubital fossa, and fixed in position with a stereo-tactic probe holder. A forearm blood pressure (BP) cuff was then inflated (50 mmHg above systolic BP to ≥200 mmHg) for 5 minutes and the BA diameter was continuously assessed using automated edge-tracking software. Endothelial-dependent FMD was assessed at 60 seconds post-cuff deflation. Endothelial-independent FMD was subsequently assessed using sublingual GTN 300mcg. PAT was performed simultaneously using the EndoPAT 2000© device. Pneumatic finger probes on both index fingers analysed the PWA before and after the 5 minute forearm occlusion. Correlation between FMD % and Reactive Hyperaemic Index (RHI) was assessed using Spearman's Correlation Coefficient.
Results: The SLE cohort had a mean (SD) disease duration of 9.5 (6.9) years. 8 patients had Raynaud's phenomenon, and 9 were prescribed anti-hypertensive medication. Mean endothelial-dependent FMD% was reduced in SLE compared to controls (1.55% vs. 5.15%; $p = 0.10$) although endothelial-independent FMD % was similar (12.9% vs. 12.4%; $p = 0.8$). Mean RHI was also lower in SLE (1.97 vs. 2.1; $p = 0.4$). The correlation of FMD and PAT was poor in SLE with a correlation coefficient of −0.07 ($p = 0.9$), which improved when those with Raynaud's were excluded ($r = 0.45$; $p = 0.2$). FMD and PAT did not correlate in the control cohort ($r = 0.17$; $p = 0.4$).
Conclusions: PAT and FMD did not correlate in our cohort of SLE patients. The presence of Raynaud's phenomenon may be a significant contributory factor to this low correlation, suggesting PAT may not be the most sensitive technique in this population. Correlation was also low in the healthy control group. The two measures may not reflect the same physiological processes and should not be used interchangeably in the rheumatic diseases
Disclosure statement: All authors have declared no conflicts of interest.

336. LONG-TERM OUTCOMES IN LUPUS NEPHRITIS: A THREE-CENTRE AUDIT

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Background: Renal involvement in Systemic Lupus Erythematosus (Lupus nephritis, LN) is associated with significant mortality and morbidity, but can be clinically silent. We have audited the outcome of LN at 3 East Midlands centres, to compare this with outcome in clinical trials and assess whether improvements could be made in the screening and detection of LN.
Methods: Retrospective case note review of all biopsy-proven cases of LN types III to V occurring between 1995 and 2010.

Results: Sixty-one cases of LN were identified (56 female), who had a median follow-up 68 months (range 6 to 148 months). Median age of SLE diagnosis was 26 years (range 13 to 80 years). LN was present at the time of SLE diagnosis in 20 cases. Median time from SLE diagnosis to the first episode of LN was 5.3 years (range 3 months to 31 years). All patients were ANA positive and 85% were anti-dsDNA positive, with 57% anti-Ro positive.

35 cases received IV cyclophosphamide and 17 received mycophenolate mofetil as induction therapy. Response to induction was classified according to the American College of Rheumatology (ACR) response criteria. 81.8% of those treated with IV cyclophosphamide and 81.3% treated with mycophenolate had at least ''improved'', and 33.3% and 37.5% respectively had a ''complete'' response.

The majority of cases received subsequent maintenance therapy, with the most frequent agents being mycophenolate mofetil (27) and azathioprine (20).

Despite this, overall 32.8% experienced a flare after a mean time post-induction of 3.5 years, irrespective of the maintenance therapy used ($p = 0.615$). 42.9% of partial responders flared compared with 4.8% of complete responders ($p = 0.019$). End-stage renal failure developed in 8.2%.

Of the patients who developed LN during the follow-up period, analysis of surveillance for LN in the preceding clinic visits revealed that 21.1% did not have a urine dipstick result recorded, which may have resulted in potential delay in treating.

Conclusions: Overall, these outcomes (response, flare rate, end-stage renal failure) are similar to other European clinical studies. Partial responders are more likely to flare compared to complete responders. The results highlight that LN can occur, and also flare, after many years of SLE diagnosis, emphasizing the importance of continued vigilance for LN in all patients, even in apparently clinically silent disease.

Disclosure statement: All authors have declared no conflicts of interest.

337. PERIPHERAL NEUROPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Whilst Neurological disorders are a common manifestation of systemic lupus erythematosus (SLE), peripheral neuropathies have received little attention. The literature consists mostly of small case series with very few studies investigating larger samples. Consequently, various features of SLE-associated peripheral neuropathies such as prevalence, symptoms, severity, chronicity, clinical and serological associations, and electrophysiological and biopsy findings, are poorly described. Small fibre neuropathies are almost entirely un-reported. The aim of this study is to determine the prevalence, clinical features, electrophysiological and biopsy findings of peripheral neuropathies in systemic lupus erythematosus and to identify clinical and laboratory correlations.

Methods: The Hopkins Lupus Cohort is an ongoing study of patients receiving care at the Johns Hopkins Lupus centre. Subjects have clinic visits every 3 months where demographic, clinical and serological data is collected. Patients diagnosed with peripheral neuropathies were selected from this cohort and detailed chart reviews were performed to characterize the neuropathies according to symptoms, distribution, temporality, and electrophysiological and biopsy findings. Neuropathies with other aetiological causes (e.g. Diabetes Mellitus, compression etc) were excluded. Demographic and, SLE-related clinical and laboratory data, of these patients was then compared to cohort patients without peripheral neuropathies using chi-square tests.

Results: Of 2097 patients in the Hopkins cohort, 82 (4.4%) had at least one peripheral neuropathy attributable directly to SLE. Symmetric presentation was most common (67.1%), and occurred most frequently in a stocking distribution (67.1%). Numbness was reported by 65 patients (79.2%), pins and needles by 26 patients (31.7%), pain by 38 patients (46.3%), and weakness by 27 patients (32.9%). Large fiber neuropathy was seen in 68.3% of cases, small fiber neuropathy in 29.3%, and mononeuritis multiplex in 7.3%. Electrophysiological studies indicated axonal loss in 89% of cases, pure sensory deficit in 43.8% and a mixed sensory-motor deficit in 52.1% of patients. Patients with peripheral neuropathy were older at time of onset ($p = 0.026$) and diagnosis of SLE ($p = 0.005$).

Conclusions: In SLE, peripheral neuropathies tend to present symmetrically and affect the lower limbs. Large fiber neuropathy occurs most frequently, but the prevalence of small fiber neuropathy is higher than previously reported in SLE. Though clear and significant differences in clinical features appear to distinguish this subpopulation from SLE patients devoid of peripheral neuropathies, more studies are needed to verify this. Furthermore, more comprehensive criteria for classifying and diagnosing peripheral neuropathies need to be introduced if diagnosis and treatment for these conditions is to improve.

Disclosure statement: All authors have declared no conflicts of interest.

338. MEASUREMENT OF ARTERIAL STIFFNESS IN A CROSS-SECTION OF SLE PATIENTS AND RELATIONSHIP TO TREATMENT WITH INTRAVENOUS METHLYPREDNISOLONE: A PILOT STUDY

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Background: SLE is associated with high cardiovascular (CV) morbidity and mortality. Patients appear to have increased exposure to traditional risk factors and lupus-specific factors, which accelerate plaque formation. Recurrent disease flares may facilitate vascular damage and inflammation, decreasing arterial compliance and increasing arterial impulse that transmits across the artery. Arterial stiffness is a recognized surrogate marker for CV disease and should enable assessment of preclinical disease. In this pilot study, our aim was (a) to determine if SLE patients have significantly different pulse wave velocity (PWV), augmentation index (AI) and augmentation pressure compared to healthy controls in a cross-sectional study and (b) to assess whether these arterial measures are altered by administration of iv methylprednisolone (ivMP) in patients with active disease (new BILAG A or B).

Methods: SLE patients were recruited from established lupus clinics and consented. Healthy volunteers were recruited as controls. Lupus disease activity was measured using the classic BILAG index. PWV, AI and augmentation pressure were measured in both SLE patients and healthy controls. In 5 patients with disease flares, arterial stiffness measurements were repeated at 12 weeks following treatment with intravenous corticosteroids. Differences in arterial stiffness measurements were measured using Student t test.

Results: There were 67 SLE patients of whom 90% were female with a mean (±SD) age of 46 (±12.9) years and mean duration of disease duration of 10 (±7.4) years. In the control group, the mean age was 41 (±11.4) years and 91% were female. The patients had significantly increased PWV at baseline (8.67+/-6.24 m/s vs 6.24 ± 1.23 m/s p 0.009) compared to controls. Augmentation pressure and augmentation index were also higher in SLE patients compared to the control group - $13 \pm 8\%$ vs $9.8 \pm 5\%$ (p0.01) and $30 \pm 10\%$ vs $25 \pm 10\%$ (p0.02), respectively. There was a reduction in PWV in patients with active disease (BILAG $>$ or $= 5$) at 12 weeks post treatment with ivMP compared to baseline (7.6 ± 1.3 m/s vs 10.6 ± 7.5 m/s p0.29).

Conclusions: There was a statistically significant difference in arterial stiffness between SLE patients denoting the presence of early cardiovascular disease compared to the healthy controls. There was a trend to increased arterial stiffness measurements in patients with active disease (BILAG > 5) however this was not statistically significant in this small pilot study. Treating acute flares led to an improvement in augmentation pressure and index and BILAG scores, suggesting that aggressive treatment with immunosuppression may dampen the inflammatory burden, ultimately slowing down progression of CVD. Larger studies will be required to explore this further.

Disclosure statement: All authors have declared no conflicts of interest.

339. BILAG BIOLOGICS PROSPECTIVE COHORT: THE USE OF NOVEL BIOLOGICAL THERAPIES IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS IN THE UNITED KINGDOM

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Background: Off-licence use of new ''biologic'' therapies in SLE is underway and recently belimumab gained a European licence for use in SLE. The long-term risks/benefits of these therapies to patients remain unknown and rare, severe, adverse effects may be missed by randomized controlled trials. The aim of this study is to observe whether using biologics in the routine treatment of SLE is associated with an increased risk of hospitalization for infection. A secondary purpose of the BILAG Biologics Prospective Cohort is to determine the long-term efficacy of biologic therapies in the treatment of SLE.
Methods: This prospective cohort study will recruit approximately 220 SLE patients ($\geq$ 4 ACR 1997 criteria) per biological therapy as well as a comparator group starting standard immunosuppressive therapies, and is open to all UK centres using these agents. Comprehensive data will be collected at baseline, including data on disease activity, risk factors for infection and routine laboratory results. Follow-up data include any changes in medications, adverse events, hospitalizations for infections, disease activity and quality of life along with biological samples for biomarker analysis. All patients will be flagged for lifelong follow-up with the NHS Information Centre for death and cancer outcomes. This study has been adopted onto the NIHR portfolio, ID 8251.
Results: To date 24 centres across the UK are participating and 37 patients have been recruited of whom complete data on 30 are available. Twenty-nine (97%) are female. Eighteen (60%) are white, 5 (17%) are Indo-Asian, 4 (13%) are Black African or Black Caribbean and 3 (10%) are mixed ethnicity. The mean (range) age in the overall cohort is 41.4 (16–75) years and the mean (range) age at diagnosis was 32.4 (12.5 - 60.4) years old. At the time of entry to the cohort, all participants were taking oral steroids, with a mean (range) dose of 15.6 mg/day (5–40). The mean (range) SLEDAI-2K score at therapy start was 6.6 (0–14). 61.5% of the subjects had at least one BILAG A score at enrolment, with the commonest manifestations scoring a BILAG 2004 A or B being renal (69%), musculoskeletal (38%) and mucocutaneous (31%). Twenty-five (83%) have had a biologic, and 5 (17%) are in the control arm. All participants in the biologics cohort received rituximab.
Conclusions: The BILAG Biologics study is open to recruiting patients and has already noted a high proportion of moderate-severe SLE patients from ethnic minorities in the UK. The future aim is to comprehensively capture the use of these drugs in SLE patients across the UK to allow a greater understanding of the risks and benefits of these treatment options. Ultimately this will provide clinicians and patients with the best available evidence when deciding to treat SLE with biologic therapy.

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340. A NESTED CASE CONTROL STUDY OF THE ASSOCIATION BETWEEN SYSTEMIC LUPUS ERYTHEMATOSUS AND CANCER

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Background: There are discrepancies in the literature as to whether patients with systemic lupus erythematosus (SLE) are more or in some cases less, susceptible to cancer.

The factors that probably play a role in the pathogenesis of cancer including medication use, disease activity, disordered immunity, coexistence of other diseases have still not been conclusively clarified.
Methods: We undertook a careful retrospective review of a cohort of over 595 patients with SLE followed up for over a 30 year period at the University College London Hospitals (UCLH) Lupus Clinic. We have sought to determine the risks of malignancy, and to try to identify whether any individual cancers are increased or decreased in this cohort of patients.

We have ascertained if the increased incidence (if any) is associated with any clinical or serological factor or immunosuppressive therapy and if so what cumulative dose or time interval of exposure was associated with this risk. The prognosis and cause of death in the cohort after developing cancer was established.

We identified all the individuals who have been diagnosed with cancer and selected three individuals who had not developed cancer in the cohort carefully matched for age, sex, and ethnicity, onset of SLE and disease duration in order to determine if any obvious differences emerge.

Using multivariate Cox regression analysis to estimate risk for the various factors association with cancer.
Results: 33 patients (30 females and three males) were diagnosed with cancer after SLE.

There was an increase in overall cancer risk standardized incidence ratio (SIR) 1.05 (95% CI 1.02-1.05).There was statistically increased SIRs for lung cancer 1.72 (95% CI 1.36-1.72), cervical 4.00 (95% CI 2.5-4.00), prostate 4.29 (95% CI 2.64-4.29), anal 1.8 (955 CI 1.41-1.82) and pancreatic 1.43 (95% CI 1.21-1.43) cancers.

Using multivariate analysis, haematological manifestations, anti-dsDNA antibodies, low C3, anti-thyroid globulin antibodies, non steroidal anti-inflammatory drug(NSAIDs) use, hypothyroidism and antiphospholipid syndrome were found to be positively associated with cancer risk but mucocutaneous features, lupus anticoagulant and cyclophosphamide use were negatively associated.

No association was found between the dose or duration of cyclophosphamide use and cancer risk.

There appears to be reduction in survival in SLE patients with cancer, with a cancer fatality rate of 84.2%, significantly more people died from cancer than non-cancer causes ($p < 0.0001$)
Conclusions: In this cohort of patients with SLE we found an increased overall cancer risk and reduction in survival.

An association was found between cancer and haematological manifestations, anti-dsDNA antibodies, low C3, anti-thyroid globulin antibodies, NSAID use, hypothyroidism and antiphospholipid syndrome.

Cyclophosphamide use was found to be negatively linked with cancer risk and there was no critical dose or duration effect.
Disclosure statement: I.D. received a training bursary from EULAR. All other authors have declared no conflicts of interest.

341. PROFILING SUB-TYPES OF ANTI-B2 GLYCOPROTEIN I AND ANTI-DOMAIN I ANTIBODIES MAY DISTINGUISH BETWEEN DIFFERENT CLINICAL PHENOTYPES OF THE ANTIPHOSPHOLIPID SYNDROME

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Background: Laboratory classification criteria for the antiphospholipid syndrome (APS) include the quantification of IgG and IgM, but not IgA anticardiolipin (aCL) and anti-β2 glycoprotein I (aβ2GPI) antiphospholipid antibodies (aPL), though recent studies suggest a possible role for IgA. These assays do not reliably differentiate patients with a

history of vascular thrombosis (VT) from those with pregnancy morbidity (PM). Of the five domains of β2GPI, pathogenic IgG aPL are considered to target Domain I (DI). We have developed a direct anti-DI ELISA using bacterially expressed DI. Here we investigate whether IgG, IgM and IgA anti-DI levels correlate with IgG, IgM and IgA anti-β2GPI and which of these tests correlate best with clinical phenotypes.

Methods: We used 9 different ELISAs (IgG/IgM/IgA for each of aCL, aβ2GPI and aDI) to test 168 serum samples - 53 from patients with APS (F:M 46:7, mean age 45.6 ± 12.0); 80 with SLE but not APS (F:M 75:5, mean age 35.0 ± 11.4); and 35 healthy controls (HC) (F:M 23:12, mean age 31.0 ± 7.2). Of 53 APS subjects, 27 suffered VT only, 13 PM only, and 13 both. IgG/IgM/IgA aCL activity was defined as G/M/A-PLU respectively. For all remaining assays, results were expressed in units of activity by reference to an in-house standard. Univariate analysis was performed using one-way ANOVA to determine which assay(s) best differentiate APS from SLE and HC, and whether any were associated with the VT or PM phenotypes within APS.

Results: All 9 assays gave significantly higher antibody titres in APS compared to SLE and HC ($p < 0.0001$ in all cases). For 4 of these 9 assays, titres were raised in SLE compared to HC, thus only 5 assays (IgM aCL, IgG/IgM/IgA aβ2GPI and IgG aDI) selectively recognized APS-derived sera. In the APS group, there was a strong correlation between aβ2GPI and aDI for IgG ($p = 0.0002$, $r = 0.6390$) and IgA ($p = 0.0001$, $r = 0.7771$) but not IgM. In contrast, there were no correlations between aβ2GPI and aDI in the SLE group. Although none of the aβ2GPI assays nor IgG aDI could discriminate between patients with VT compared to PM, IgA aDI was found to be associated with VT ($p \leq 0.01$).

Conclusions: To our knowledge, this is the first study to measure IgG/IgM/IgA aPL against CL, β2GPI and DI simultaneously. aβ2GPI of all isotypes and IgG aDI were found to be most specific for APS. The correlation between aβ2GPI and aDI in APS, but not non-APS subjects supports the idea that pathogenic aβ2GPI bind specifically to DI. The finding that IgA aDI shows a specific association with VT is interesting but needs to be repeated in larger studies.

Disclosure statement: All authors have declared no conflicts of interest.

342. INTERFERON-MEDIATED VASCULAR DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS: FAILURE OF ENDOTHELIAL REPAIR RATHER THAN DIRECT ENDOTHELIAL TOXICITY?

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Background: Patients with Systemic Lupus Erythematosus (SLE) demonstrate increased endothelial dysfunction and a significantly increased risk of premature cardiovascular disease (CVD) compared to healthy control subjects. Type-1 interferons (IFN) are the dominant inflammatory cytokines in SLE. IFNα therapy can induce endothelial dysfunction in patients with viral hepatitis, although the mechanism by which this occurs is unknown. It has been proposed that IFNα contributes to vascular damage by inhibition of endothelial repair mechanisms. IFN has been shown to impair the function of endothelial progenitor cells (EPCs) in vitro, replicating a lupus EPC phenotype. We aimed to determine whether a directly toxic effect of IFN upon mature endothelial cells may also contribute to endothelial dysfunction in SLE.

Methods: Human aortic endothelial cells (HAoECs) were cultured in standard conditions. Circulating Angiogenic Cells (CACs) were obtained by culture of peripheral blood mononuclear cells on human fibronectin in endothelial culture media. The effect of IFNFα2b on HAoECs was measured in terms of: proliferation (cell counting and MTT assay), nitric oxide bioavailability (Griess assay of culture supernatant) and capillary-like network formation (2D in Matrigel and 3D in type-1 rat tail collagen gel). An Affymetrix GeneChip Human Exon 1.0 ST Array was used to determine changes in gene expression at 6 hours following addition of IFNα2b. The effect of IFNFα2b on CAC cell number and morphology was studied.

Results: IFNα2b at concentrations of 0.1-100 ng/ml had no effect on HAoEC proliferation measured by either cell count or MTT assay at up to 72 hours ($n = 3$ for each). The expression of 164 genes was significantly changed (>2-fold change, $q < 0.2$) by the addition of 10 ng/ml IFNα2b at 6 hours. These genes were primarily those previously reported to be regulated by IFNα (e.g. IFIT1, IFI44L, MX1) or those involved in cellular response to virus.

Nitric oxide availability unchanged by the addition of IFNα2b ($n = 3$). The formation of 2-dimensional capillary networks in Matrigel was variable and not consistently impaired by the addition of 10 ng/ml IFN. Furthermore the development of 3-dimensional networks in collagen was not disrupted by the addition of IFNα2b to either the gel or the culture media.

CAC cell number was dramatically reduced by IFNα2b and was specifically associated with loss of spindle-shaped cells.

Conclusions: Interferon α2b did not affect the function of HAoECs in vitro. Gene expression was not influenced beyond those genes important in response to virus. We propose therefore that IFN-mediated vascular damage is secondary to impaired endothelial repair rather than direct IFN toxicity. This has implications for the development of in vitro endothelial models relevant to SLE and the prevention of CVD in lupus.

Disclosure statement: All authors have declared no conflicts of interest.

343. SOLUBLE VASCULAR CELL ADHESION MOLECULE-1 LEVEL IN PATIENTS WITH ANTHIPHOSPOLIPID SYNDROME: ITS ASSOCIATION WITH DISEASE ACTIVITY AND ENDOTHELIUM DYSFUNCTION

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Background: APS is characterized by endothelium perturbation and hyperexpression of cellular adhesion molecule (CAM). In recent studies it was revealed that plasma levels of CAM were significant predictors of coronary artery disease in patients with inflammatory rheumatic diseases, but it has not been established whether increase level of CAM may be a marker of cardiovascular risk in APS. That is why the aim of this observation case was to investigate the link of sVCAM-1 concentration with disease activity and endothelium dysfunction as an early marker of atherosclerosis.

Methods: We studied 67 patients with APS: 21 (31.3%) with primary APS (PAPS), 19 (28.4%) with APS associated with systemic lupus erythematosus (APS-SLE), 27 (40.3%) with SLE without APS and 26 age and sex matched healthy controls (HC). All patients were subjected to complete clinical examination, disease activity and assessment for endothelium-dependent vasodilatation(EDVD) of brachial artery. Also plasma level of sVCAM-1 was evaluated by solid-phase assay in all patients.

Results: In patients with PAPS, APS-SLE and SLE without APS sVCAM-1 levels varied from 398 to 2727 ng/ml. The average level was 1404,9+-61,4 ng/ml, that was in 2,1 times higher than in HC. Increase level of test marker was revealed in 15 (71.4%) patients with PAPS, 13 (68.4%) APS-SLE and 20 (74%) SLE without APS. It was established positive correlation of increase sVCAM level with disease activity: with SLEDAI index ($r = 0{,}556$ $p < 0{,}05$), with C-reactive protein level ($r = 0{,}430$ $p < 0{,}05$) and ESR ($r = 0{,}345$ $p < 0{,}05$) and circulate immune complexes ($r = 0{,}345$, $p < 0{,}05$). No correlations were found with IgG isotype of antiphospholipid antibodies and anti-dsDNA antibodies. Patients with PAPS and APS-SLE with normal EDVD were associated with 1,5-fold increase of sVCAM-1 level, compared with HC and these groups with middle and high deviation of EDVD were associated with 1,8 and 2,4-fold increase of sVCAM-1 level respectively. Increase of sVCAM serum level positively correlated with decrease of EDVD

Conclusions: According to this data it might be hypothesized that increase sVCAM-1 level is a marker of endothelium dysfunction in patients with APS especially in presence of high disease activity.

Disclosure statement: All authors have declared no conflicts of interest.

VASCULITIS

344. PREVENTION OF TREATMENT-RELATED MORBIDITY IN ANCA-ASSOCIATED VASCULITIS: THE PATIENT'S PERSPECTIVE

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TABLE 1 Mean change in fatigue and quality of life measures

	Fatigue severity scale[a]	Multidimensional assessment of fatigue[a]	SF36 Vitality[b]	SF36 Physical function[b]	SF36 Physical role[b]	HADS-Anxiety[a]	HADS-Depression[a]
Week 0	46	34	34	43	25	7	5
Week 7	36	25	50	57	45	7	5
Week 19	37	23	54	60	50	6.2	4
% change between weeks 0 and 19	+21	+32	+59	+40	100	6	17

[a]0 = low symptom level; [b]0 = high symptom level HADS-Hospital Anxiety and Depression Scale.

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Background: Despite advances in therapy, ANCA associated vasculitis (AAV) still has a 5 year mortality of 25% as well as major morbidity. The major causes of death in this time period are no longer active vasculitis (8.1%) but cardiovascular disease (25.7%), malignancy (21.6%) and infection (20.3%), all potentially linked to immunosuppressive therapy. Even with a growing evidence base for treatment of AAV, there are few comprehensive recommendations with regards to prophylaxis and monitoring for patients to reduce potential therapy related complications.
Methods: With the assistance of the patient support group, Vasculitis UK, we designed and distributed a questionnaire to all 700 UK members. This questionnaire assessed patient awareness of potential side- effects associated with vasculitis therapy, as well as uptake of screening
and prophylactic approaches to reduce these complications.
Results: Response rate was 347 (49.6%). Of these 306 responses were analysed from patients with Primary Systemic Vasculitis. 241 (79%) had Granulomatosis with Polyangiitis, 41 (13%) Churg Strauss Syndrome, 15 (5%) Microscopic Polyangiitis and 9 (3%) other "Systemic vasculitis/ANCA Associated Vasculitis". 190 (62%) were female with a mean age of 61.7 (range 15-87 years). Respondents reported treatment received as follows; oral steroids 96%, oral cyclophosphamide 49%, intravenous cyclophosphamide 41%, azathioprine 69%, mycophenolate mofetil 28% and Rituximab 14%. Of potential adverse events, the best recognized were bone problems (20.9%) and weight gain (19.3%) with awareness of increased infection risk only 10.5% and general increased cancer risk 7.5% (skin cancer 6.5% and bladder cancer 3.9%). With regards to prophylaxis/screening received, 63% had undergone DEXA scanning, 59% had received calcium, 25% had received septrin but only 18% and 13% respectively were aware of the need for skin protection and monitoring on certain agents due to increased malignancy risk.
Conclusions: There is a general lack of awareness of potential side effects of therapy amongst vasculitis patients, particularly with regards to infection and cancer risk. There is also variability in reported practice in terms of infection prevention strategies and cancer screening/prevention. In particular skin cancer awareness was very low. More robust and evidence based guidelines may help improve quality and consistency of patient care across the UK in this high risk population.
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345. TAKAYASU'S ARTERITIS IN PREGNANCY: A BRITISH CASE SERIES

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Background: Takayasu arteritis (TA) is a rare, chronic inflammatory disease of the aorta and its branches, typically presenting before the age of 40 years in women of reproductive age. Pregnancy poses a management challenge as physiological rises in blood volume and cardiac output, and vascular steals may exacerbate TA. We report our experience from a tertiary TA centre and make recommendations for management.
Methods: Retrospective review of 92 patients seen between 2000-2011, identified 13 live births in 8 women post-diagnosis of TA. All patients fulfilled ACR diagnostic criteria for TA.
Results: The median age at delivery was 31 years (range 20-39) and time since diagnosis was 3.5 years (range 0.2-10). Three patients had vascular involvement above and below the diaphragm and one patient had isolated lower limb vasculitis. Six patients had pre-pregnancy echocardiography, which excluded pulmonary hypertension and demonstrated aortic regurgitation in two patients. Two patients unknowingly conceived on methotrexate, including one on infliximab, which were stopped during pregnancy. Two conceived on azathioprine, which was continued. Seven patients received antenatal corticosteroids, three were short courses for disease flares (worsening symptoms and rising CRP). Four patients received aspirin, two antihypertensives and one heparin for an antenatal lower limb deep-vein thrombosis. Labour was spontaneous in 50% and two patients suffered pre-term labour. There were three vaginal deliveries and five caesarean sections. Two had caesareans because of undue medical anxiety regarding TA, and had uncomplicated vaginal deliveries in subsequent pregnancies. The median gestation was 38 weeks (range 34-41) and median birthweight 2746g (range 1814-3332 g). One high-risk patient, who previously had an aortoiliac graft and bilateral renal artery revascularization, had three pre-term deliveries and obstetric cholestasis during two pregnancies. All three babies had growth restriction, one an intestinal malformation and another hepatic encephalopathy. Post-partum haemorrhages were observed in two patients. Post-partum disease activity was quiescent in four patients, mild in two and active in one. The latter high-risk patient, who received methotrexate and infliximab pre-pregnancy and prednisolone alone during pregnancy/breast feeding, suffered a severe post-partum systemic disease flare requiring re-introduction of methotrexate and anti-TNF.
Conclusions: Our study shows successful outcome is possible in quiescent TA and pregnancy should not be discouraged. Preconception counselling and echocardiography are recommended, as pregnancy in patients with active disease or pulmonary hypertension should be avoided. Individual strategies for treatment, disease activity and blood pressure monitoring are required. Disease activity assessment is complicated and based on symptoms, CRP, clinical exam, arterial US and MRA if required. Caesarean section is not routinely indicated.
Disclosure statement: All authors have declared no conflicts of interest.

346. MULTI-DISCIPLINARY MANAGEMENT OF FATIGUE IN ANCA-ASSOCIATED VASCULITIS: A PILOT STUDY

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Background: Patients with ANCA Associated Vasculitis(AAV) consider fatigue to be the greatest burden of their disease, even when in remission. Escalation of drug therapy commonly fails to improve fatigue levels and so alternative interventions require investigation. In other auto-immune conditions, exercise and behavioural therapy, delivered by multi-disciplinary(MD) teams, have proven to be effective. Such non-pharmacological interventions have yet to be tested in AAV. This pilot study aimed to assess the feasibility and effectiveness of a MD programme in the relief of fatigue experienced by patients with AAV.
Methods: Clinically stable patients with AAV (Birmingham Vasculitis Activity Score = 0 for > 3months) who reported fatigue for >3 months were invited to attend a 7 week fatigue management programme (FMP). Weekly 2 hr sessions integrated: 1)A graduated aerobic exercise regime based on a circuit training program of 6 activities (step ups, wall squats, timed walk, marching, sit to stand, knee bends) 2)Behavioural therapy, incorporating education on pacing, diet, sleep hygiene, relaxation and coping strategies. The FMP was delivered, in both group and individual settings, by specialists in nursing,

TABLE 1.

Diagnosis	Age, sex	Indication	Clinical response	CRP pre-leflunomide	CRP post-leflunomide	Adverse effects
GCA	64 M	MTX Failure	Came off steroids and MTX	39	3	Nil
GCA	69 F	MTX Failure	Came off steroids and MTX	22	18	Nil
GCA/PMR	69 F	MTX Failure	Came off steroids and MTX	18	9	Nil
GCA	73 M	Relapse on steroid taper	Steroids reduced from 40 to 12.5 mg in 6 months	223	3	Nil
GCA	73 F	Relapse on steroid taper	Steroids reduced from 40 to 7.5/5 mg alternate days	27	9	Nil
GCA	75 F	Relapse on steroid taper	Steroids reduced from 50 mg to 5 mg	24	10	Nil
GCA/PMR	73 F	Relapse on steroid taper	Steroids reduced to 0 on MTX and LEF	19	14	Peritoneal abscess
GCA/PMR	75 M	Relapse on steroid taper	Came off Steroids	14	2	Nil
GCA	81 F	Relapse on steroid taper	Came off steroids	54	9	Nil
PMR	71 F	Relapse on steroid taper	Good Response on MTX and LEF	33	3	Nil
PMR	76 F	Relapse on steroid taper/MTX Failure	Steroids reduced to 2.5 mg	18	2	Diarrhoea, vomitting, pruritis
PMR	75 F	Relapse on steroid taper	Came off steroids	27	7	Nil
PMR	90 F	MTX Failure	Steroid reduced	6	3	Nil
PMR	77 M	Relapse on steroid taper	Steroids reduced to 5 mg	31	4	Nil
PMR	83 F	Relapse on steroid taper	Steroids reduced from 15 to 5 mg	25	9	Nil
PMR	70 M	Unable to reduce steroids below 30 mg	Steroids reduced from 30 to 12.5 mg	90	3	Nil
PMR	63 M	Relapse on steroid taper	Steroids 17.5 to 5 mg	17	3	Nil
PMR	74 F	Relapse on steroid taper/MTX Failure	Steroids from 10 mg to 5/2.5 mg alternate days	18	3	Nil
PMR	74 F	Relapse on steroid taper	Came off steroids	17	3	Nil
PMR	82 F	Relapse on steroid taper	Came off steroids	61	3	Nil
PMR	66 F	Relapse on steroid taper	Came off steroids	19	8	Nil
PMR	59 M	Relapse on steroid taper	Steroid reduced	8	7	Nil
PMR	68 F	Relapse on steroid taper	Developed adverse effects	18	14	Rash, diarrhoea, nausea

physiotherapy, occupational therapy, dietetics and psychology. Participants returned for follow up after 3 months. Quality of life and fatigue measures were collected at weeks 0(baseline), 7(end of FMP) and 19(follow-up). At the same time points, circuit training activity performance was quantified (number of repetitions in a minute). Patients received regular clinical assessments during the period as per standard care.

Results: Participants ($n = 5$) reported clinically meaningful reductions in fatigue, with benefits maintained at week 19(see table). Large improvements in physical health were reported. This was consistent with the observed progress in circuit training performance which increased from 32% (sit to stand) to 159% (wall squats) between weeks 0 and 19. Although no disease relapses occurred, at week 19, 3 of 5 patients were experiencing ill health (2 acute infections, 1 pregnancy). Participants were unanimously positive about the programme, some even regarding it as 'life changing'.

Conclusions: Despite extraneous causes of fluctuating health status, the FMP appeared to be acceptable and effective in improving symptoms of fatigue in patients with AAV. Exercise appears key to this improvement. Further investigation with larger sample sizes is warranted to determine if there is a case to conduct a formal evaluation through a randomized controlled trial.

Disclosure statement: All authors have declared no conflicts of interest.

347. SYSTEMATIC REVIEW OF STEROID TRIALS IN GIANT CELL ARTERITIS

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Background: Giant cell arteritis is the most common systemic vasculitis. Typically affecting adults aged >55yrs and has significant morbidity. 20% of patients suffer visual loss. High dose steroids are the mainstay of treatment but are associated with considerable toxicity. The initial dose, duration of use, and rate of withdrawal are all controversial. The aim of this study was to conduct a systematic review of clinical trials of GCA treatment to determine if evidence supports a particular approach to steroid treatment.

Methods: MEDLINE, CENTRAL and EMBASE searches were used to identify randomized control trials and large observational studies of GCA treatment with steroids. No exclusions were based on study date or language. Searches were carried out independently by two researchers (MY and YL). Trials were included if >20 patients were recruited into each treatment arm and there were clear criteria for GCA classification. Studies were required to be carried out on adults >55yrs of age with a length of follow-up of at least 6 months and reported relapses. Exclusion criteria were a diagnosis of pure PMR, and a failure to report initial dose of steroid; total cumulative dose; or record patient outcomes.

Results: We retrieved 1820 articles. Of these only 36 met the inclusion criteria. 13 reported some information on the steroid regime used and included outcome data. The studies included 1222 individuals (69% female) diagnosed with GCA. The average age at recruitment was 74yrs. Initial starting steroid dose equivalent to prednisolone ranged from 10mg to 1000 mg. 6 studies reported total cumulative steroid dose with a range of 5275 to 9194 mg. These consisted of 482 individuals (75% female). 3 studies compared prednisolone to methotrexate. A total of 224/482 individuals received prednisolone only (46.5%).

Comparing the individuals in the steroid only arms of the trials allowed a comparison of flare rates and type of steroid regime. Some studies reported flares as relapse of symptoms associated with rise in inflammatory markers while others only required the latter. Median duration of steroids ranged from 24 weeks to 191 weeks. 2 studies reported on median duration of steroids to a level <10 mg/day and <7.5 mg/day giving a result of 25 and 28 weeks respectively. Of the 2 studies that reported time of flare, the rate was 10.9% and 33.3% by the end of the 1st year. Studies with longer follow-up reported flare rates as high as 100% (78 weeks). However studies with a total median cumulative dose of >6000 mg of prednisolone seem to be associated with lower relapse rates (100% vs 30%).

Conclusions: There are few high quality studies reporting the use of steroids in GCA and it is impossible from the existing data to determine the optimal initial dose, rate of steroid taper or duration of therapy. The studies report wide variation in the initial steroid dose used and steroid taper. Overall, better clinical outcomes appear to be associated with higher compared with lower cumulative steroid doses.

Disclosure statement: All authors have declared no conflicts of interest.

348. SUCCESFUL USE OF LEFLUNOMIDE IN TREATMENT OF REFRACTORY POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

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Background: Corticosteroid therapy in GCA and PMR is associated with high incidence of flares and adverse events. Therefore more effective steroid-sparing adjuvant therapies are required. Aberrant dendritic cell (DC) activation is considered a pathogenetic mechanism for GCA and PMR. Leflunomide blocks differentiation and function of DCs, inhibits IL-6, is used in inflammatory arthritis and has been shown to be effective in vasculitis.

Methods: This is an open case series of 23 patients with PMR and/or GCA treated with Leflunomide. All patients were treated with an initial dose of 10 mg daily, escalated to 10/20 mg alternate days or 20 mg daily if needed as per clinical response. All were monitored for clinical response, CRP, ability to taper steroids and adverse events.

Results: 22 (8 GCA, 13 PMR) patients had a good response to Leflunomide with 2 or 3 of: >75% improvement in symptoms, normal CRP and significant reduction in steroids. It was well tolerated in all except 2 patients who developed rash and diarrhoea. Steroids were

TABLE 1 Aortic imaging studies of GCA cohorts

First author	Year	Centre	Mean/median time from GCA to imaging studies	Imaging	TAD, *n* (%)	TAA, *n* (%)	AAA, *n* (%)
Schmidt	2002	Berlin-Buch	Newly diagnosed	Ultrasound	–	–	2/33 (6)
Agard	2007	Nantes	8 weeks	Ultrasound	–	–	4/30 (13)[b]
Agard	2008	Nantes	4 weeks	CT angiogram	2/22 (9)	3/22 (14)	–
Garcia-Martinez	2008	Barcelona	5.4 years	CXR +/− CT, USS	7/54 (13)	4/54 (7)	1/54 (2)
Karamagkiolis[a]	2009	Greece	>5 years	Annual CT	–	4/49 (8)	1/49 (2)
Prieto-Gonzalez[a]	2009	Barcelona	Newly diagnosed	CT angiogram	3/24 (13)	0/24 (0)[c]	0/24 (0)[c]
Marie	2009	Rouen	16 months	CT angiogram	3/48 (6)	3/48 (6)	1/48 (2)
Both	2011	Kiel	31 months	MRA thorax	–	14/105 (13)	–
Total (studies pooled)	n/a	n/a	n/a	n/a	15/148 (10)	28/302 (9)	9/238 (4)

[a]Denotes conference abstract only; [b]overlap with another publication; [c]presumed no aneurysm as not stated in abstract.

stopped in 9, reduced in 12. MTX was reduced in 1 and stopped in 2 patients (Table 1).

Conclusions: In this case series, we found that Leflunomide is efficacious, steroid sparing and well tolerated. There is a need for an RCT of Leflunomide in PMR and GCA.

Disclosure statement: All authors have declared no conflicts of interest.

349. DEVELOPMENT OF AN INDEX TO ASSESS DISEASE-RELATED DAMAGE IN TAKAYASU ARTERITIS AND USE IN OUTCOME OF VASCULAR INTERVENTIONS

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Background: Takayasu aorto-arteritis (TA) in India frequently presents with complications, indicating the need for a specific index to capture the accumulation of disease-related scars over time. We devised a clinical damage index for use in these circumstances.

Methods: Disease extent in TA is assessed using the comprehensive tool DEI.Tak. The IRAVAS group set out to modify this established score, using a large data base of cases previously assessed by the group. Items persisting > 6/12, related to accumulating scars, were selected while omitting those used infrequently to produce a shorter form with 42 items focussed on CVS, particularly pulse loss and vascular interventions plus drug-related damage. This new TADS form was compared to VDI and PGO using paper cases. It was then applied to analyse a cohort of 222 cases followed in one clinic over 2 decades.

Results: The increase in damage/scars over time correlated closely with disease duration, continuing to increase over 20 years. TADS scores also related to poor outcomes such as pulse loss. In the cohort of 222 TA patients, the mean age at onset of TA symptoms was 33 years. 122 vascular interventions were performed in 82 of this cohort (31 men, 51 women, mean disease duration 8.9 years). The following procedures were performed: Carotid angioplasty + stenting - 24; vertebral angioplasty + stenting -4; grafts from ascending aorta to Carotids -3; subclavian angioplasty + stenting -14; renal angioplasty + stenting -26; Aortic angioplasty + stenting -14; coronary angioplasty + stenting -24; and CABG Surgeries -11. The mean follow up period was 136 months. Associated clinical features and drug therapy were recorded. Peri-operative complications included infections - 5.3%; Stroke -8%; Myocardial infarction -3.6%; and renal failure - 3.5%. There were no deaths due to the procedures. The patency of stents was higher than in some published series. At 5 years it was 92% and at 10 years was 83%. In the majority (84.7%), drug therapy was also continuing. 18 of the 222 patients died and the scores in fatal disease were higher than in non-fatal cases (7.4 v 4.8).

Conclusions: Damage is a significant factor in TA, as previously noted in small vessel vasculitis. Vessel occlusion is a major feature of TA, often requiring vascular interventions. Recording the new disease-specific damage score TADS helps delineate features associated with pulse loss, long-term stent patency and mortality.

Disclosure statement: All authors have declared no conflicts of interest.

350. ARE THERE SUFFICIENT DATA TO JUSTIFY CHANGING THE BSR GUIDELINES FOR ANEURYSM SCREENING IN GIANT CELL ARTERITIS? A SYSTEMATIC LITERATURE REVIEW

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Background: Subclinical aortitis in giant cell arteritis (GCA) is common. Damage from aortitis may lead to later development of aortic aneurysm, a clinically-silent condition with potentially catastrophic complications. BSR guidelines, based on a systematic literature review to 2007, recommend a chest X-ray (CXR) every 2 years to screen for thoracic aortic aneurysm (TAA). However, CXR is not a sensitive screening test for TAA. We sought to estimate the absolute risk of aortic aneurysm in GCA and to gather information on predictors.

Methods: Systematic review of literature from Embase Classic + Embase (1947–2011) and Ovid Medline (1948–2011). Two reviewers sought and assessed studies of GCA cohorts reporting the frequency of thoracic aortic dilatation (TAD), TAA, or abdominal aortic aneurysm (AAA). Fisher's exact test was used to test for statistical heterogeneity between studies.

Results: The imaging studies are shown in Table 1. There was no significant statistical heterogeneity for TAD, TAA or AAA ($p = 0.678$, $p = 0.338$, $p = 0.108$); pooling these studies gave overall prevalences of 10%, 9% and 4% for TAD, TAA and AAA respectively. The one study using screening CXR +/- CT detected a similar proportion of TAA (4 cases) to the studies where all patients had CT/MRI.

Two studies suggested that males may be at greater risk than females of developing aneurysm in GCA. Inflammatory markers do not appear helpful in assessing aneurysm risk. The way the aneurysm risk changes over time remains uncertain.

Conclusions: Pooled data from 302 GCA patients suggest a consistently high prevalence of TAA, but only 54 of these patients had CXR as the initial screening investigation to select who should have a CT. Now there is consistent evidence that the risk of aortic aneurysm in GCA is significant, studies are needed to directly compare CXR with CT/MRI for TAA screening, and to identify which GCA patients are at greatest risk of aneurysm. On current data, clinicians should be advised to maintain a high index of suspicion for aneurysm in GCA, especially in males and in those patients with aortic regurgitation, and not to be reassured by normalization of inflammatory markers.

Disclosure statement: All authors have declared no conflicts of interest.