1. A LATE PRESENTATION OF LOEYS-DIETZ SYNDROME: BEWARE OF TGFβ RECEPTOR MUTATIONS IN BENIGN JOINT HYPERMOBILITY

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Background: Thoracic aortic aneurysms (TAA) and dissections are not uncommon causes of sudden death in young adults. Loeys-Dietz syndrome (LDS) is a rare, recently described, autosomal dominant, connective tissue disease characterized by aggressive arterial aneurysms, resulting from mutations in the transforming growth factor beta (TGFβ) receptor genes TGFBR1 and TGFBR2. Mean age at death is 26.1 years, most often due to aortic dissection. We report an unusual late presentation of LDS, diagnosed following elective surgery in a female with a long history of joint hypermobility.

Methods: A 51-year-old Caucasian lady complained of chest pain and headache following a dural leak from spinal anaesthesia for an elective ankle arthroscopy. CT scan and echocardiography demonstrated a dilated aortic root and significant aortic regurgitation. MRA demonstrated aortic tortuosity, an infrarenal aortic aneurysm and aneurysms in the left renal and right internal mammary arteries. She underwent aortic root repair and aortic valve replacement. She had a background of long-standing joint pains secondary to hypermobility, easy bruising, unusual fracture susceptibility and mild bronchiectasis. She had one healthy child age 32, after which she suffered a uterine prolapse. Examination revealed mild Marfanoid features. Uvula, skin and ophthalmological examination was normal.

Results: Fibrillin-1 testing for Marfan syndrome (MFS) was negative. Detection of a c.1270G>C (p.Gly424Arg) TGFBR2 mutation confirmed the diagnosis of LDS. Loeasartan was started for vascular protection.

Conclusions: LDS is a severe inherited vasculopathy that usually presents in childhood. It is characterized by aortic root dilatation and ascending aneurysms. There is a higher risk of aortic dissection compared with MFS. Clinical features overlap with MFS and Ehlers Danlos syndrome Type IV, but differentiating dysmorphogenic features include ocular hypertelorism, bifid uvula and cleft palate. Echocardiography and MRA or CT scanning from head to pelvis is recommended to establish the extent of vascular involvement. Management involves early surgical intervention, including early valve-sparing aortic root replacement, genetic counselling and close monitoring in pregnancy. Despite being caused by loss of function mutations in either TGFβ1 receptor, paradoxical activation of TGFβ signalling is seen, suggesting that TGFβ antagonism may confer disease modifying effects similar to those observed in MFS. TGFβ antagonism can be achieved with angiotensin antagonists, such as Losartan, which is able to delay aortic aneurysm development in preclinical models and in patients with MFS. Our case emphasizes the importance of timely recognition of vasculopathy syndromes in patients with hypermobility and the need for early surgical intervention. It also highlights their heterogeneity and the potential for late presentation.

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2. A CASE OF POSTERIOR reversible ENCEPHALOPATHY SYNDROME IN A PATIENT WITH SLE

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Background: Posterior reversible encephalopathy syndrome (PRES) is an increasingly reported condition identified by characteristic clinical manifestations and MRI features. It is characterized by headache, visual disturbances, seizures, altered mental status, hypertension (HT) and radiological findings of oedema in the white matter of the brain. Risk factors include HT, renal disease and immunosuppressive therapies although the pathogenesis remains unclear.

Methods: We present a case of a 16-year-old girl, AR, with SLE, treated with HCQ, mycophenolate and prednisolone since 15 years of age, who went on to develop PRES.

Results: AR was reviewed in clinic in August 2011 with proteinuria, haematuria, hypoalbuminaemia, raising creatinine and low complement. She was normotensive at this point. An urgent renal biopsy confirmed diffuse active LN, stage IVA.

AR was treated with cyclophosphamide (CYC) and commenced on an ACE inhibitor. Despite two cycles of CYC, she became oedematos and gained 10 kg in weight. Her blood pressure (BP) was 155/95. She was started on furosemide and her ACE-inhibitor was increased.

AR was then admitted acutely with recurrent seizures, confusion and visual loss. Blood pressure on admission was 166/100. WCC 14, Cr 182 Ur 15, Alb 23, CRP >5. CT head—low density white matter lesion in left and right occipital lobes. She was sedated and intubated on ICU and required haemofiltration. Infection was excluded and she was commenced on i.v. methylprednisolone (MTP) and IVIG. An MRI showed extensive white matter oedema likely secondary to vasculopathy. She remained hypertensive with reduced level of consciousness, weakness and had further seizures. She was therefore given rituximab. Following neurology review, a diagnosis of PRES was made and MTP was stopped and labetalol and GTN started in an attempt to improve BP. As AR had active SLE, hydrocortisone and RTX were continued on advice of the rheumatology team. She continued to make a slow recovery over 3 months and a repeat MRI showed improvement in oedema. On discharge her vision and mobility had improved and she had no further seizures. Cr 74 on discharge.

Conclusions: PRES occurs in young SLE patients often early in disease. The mean systolic and diastolic BPs on presentation has been reported at 187.6 and 113.5 mmHg respectively. It has been documented that 76.5% of cases of PRES in SLE have hypertension or augmentation of immunosuppressants of a mean duration of 6.9 days prior to development of PRES. The major immunosuppressants identified were i.v. MTP, i.v. CYC and cyclosporine.

Our case reiterates that multiple aetiologies may be responsible for PRES in SLE patients. The diagnosis of PRES needs to be considered when patients present with typical symptoms and MRI findings so possible offending agents can be withheld. However, in patients with active SLE, augmentation of immunosuppression is still strongly warranted to reduce lupus related organ damage.

Disclosures: The authors have declared no conflicts of interest.

3. RITUXIMAB THERAPY IN REFRACTORY MACROPHAGE ACTIVATION SYNDROME SECONDARY TO SLE

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Background: A 45-year-old Jamaican male with SLE (previously meeting the ACR criteria) presented with a one-month history of fever and feeling non-specifically unwell. Medications included a reducing regimen of Prednisolone and Hydroxychloroquine. Examination showed a tachycardia and fever only. Chest X-ray and ECG were unremarkable other than an elevated AST 71 U/l (range 5–40), ALT 139 U/l (range 10–35), CRP of 150 mg/l and ESR 100 mm/h. Despite treatment with broad spectrum antibiotics and hydrocortisone he continued to have fevers and developed a neutropenia (count 0.6) requiring antibiotic cover for potential neutropenic sepsis.

Methods: He acutely deteriorated with the haemoglobin falling to 7.6 g/l, platelet count to 29 x 10^9/l with a rise in creatinine (352 μmol/l), ALT (950 U/l) and AST (293 U/l). Anti-dsDNA was 627 U/ml and complements were low. Serum ferritin was ~2000 mg/dl, with raised triglycerides (300 mg/dl) and a low fibrinogen (100 mg/dl). CT chest/abdomen/pelvis commented on a possible atypical infection in the lungs. Treatment was switched to meropenem, anti-viral and anti-fungal agents to cover possible invasive opportunistic infections and blood products were given. Despite 7 days of treatment the CRP (280 mg/l) and ESR (132 mm/h) remained elevated with continued pyrexia and cytopenias. Multiple blood and urine cultures, viral serology, TB stool, echocardiogram and abdominal ultrasound were unremarkable. Bone Marrow aspiration showed haemophagocytosis.

Disclosures: The authors have declared no potential conflict of interest.

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CSF protein was 1.34 g/l (0.12–0.6) and CSF viral and bacterial cultures were negative.

Results: Macrophage Activation Syndrome (MAS) secondary to acute SLE was diagnosed based on laboratory, clinical and bone marrow findings. Despite Methyprednisolone 1 g/day for 3 days followed by 1 mg/kg/day orally and IVIG 2 g/kg over 5 days, platelet and neutrophil count remained low with significant renal dysfunction. Escalation therapy to Cyclophosphamide or Cyclosporine was considered an infection risk due to ongoing cytopenias and renal impairment. Rituximab (1 g 2 weeks apart) therapy was commenced and within 6 days from the first infusion the platelet and neutrophil counts regained normal. After two infusions a week apart, the patient improved clinically with no further fevers and the cytopenias, inflammatory markers and ferritin levels all normalizing. MMF 2 g/day as maintenance therapy was commenced.

Conclusions: MAS is a life-threatening complication of rheumatic disease. MAS secondary to SLE should be considered in a patient presenting with fevers, pancytopenia, hyperferritinemia, liver failure and bone marrow macrophage haemophagocytosis, with active SLE in the suspacive of alternative diagnosis. When atypical features are present further investigations including imaging and tissue biopsy should be considered to establish diagnosis and commence appropriate treatment.

5. SILASTIC SYNOVITIS: A CASE AND REVIEW OF THE LITERATURE
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Background: A 50-year-old lady presented with a 5-month history of persistent left wrist pain and swelling. She was known to have degenerative cystic changes in the base of the thumb metacarpal and had had a left thumb carpometacarpal joint arthroplasty and resection of the trapezium with insertion of a Swanson Silastic implant 4 years previously in 2008.

Her past medical history included ovarian carcinoma 7 years ago. For her wrist pain, she was taking naproxen and paracetamol which helped provide some pain relief. Her niece has RA. She was a 30-pack year smoker and drank a minimal amount of alcohol. She worked in a warehouse, which involved heavy manual work.

Examination revealed left wrist synovitis with reduced range of movement. She also had some tenderness around the left 3rd and 4thPIPJ. In comparison, examination of her right wrist was normal. Examination of her nails, skin, and other joints was unremarkable. Her cardiorespiratory and abdominal examinations were also unremarkable.

Methods: Initial investigations including rheumatoid factor, anti-CCP, ANA and inflammatory markers and radiographs of the hands and wrists were performed. Further investigations included aMRI of the left wrist and a synovial biopsy.

Results: Blood tests revealed a negative rheumatoid factor and ANA, and her anti-CCP was normal. Her ESR 17, CRP < 5 and normal full blood count, renal and liver function.

A radiograph of the left wrist showed a previous left trapeziectomy with a silastic prosthetic replacement. There was evidence of a considerable erosive process affecting her carpometacarpal, carpals and radiocarpal joints of the left wrist. This suggested that the arthropathy was crossing ligamentous boundaries. Fracture was excluded.

A MRI scan of her left wrist (with gadolinium) was performed and confirmed the presence of an erosive process and a suggestion of fragmentation of the implant. A synovial biopsy was then taken. Histopathology of the left wrist synovium revealed multiple pale grey fragments together measuring 0.7x0.7x0.3 cm. Microscopy showed a florid giant cell reaction to refractile, granular material. The appearances were consistent with previous surgery at this site with a giant cell reaction to foreign material. The acid-fast bacilli culture was negative.

Conclusions: This patient’s wrist pain was due to a giant cell synovitis secondary to particulate silastic from a previous silastic implant.

Silastic synovitis can occur at any joint where there is a prosthetic implant in place. Involvement of the hand and wrist is however most common at the carpals which are more susceptible to stress forces. An inflammatory process occurs in response to foreign particles, which are sloughed off the implant, resulting in erosion of bone and articular cartilage with intraosseous cystic changes. Silastic synovitis has been reported in 5-10% of patients with silastic implants and the diagnosis can be challenging.

Histopathology reveals an inflammatory infiltrate with giant cells around silicone-elastomer particles. A review of the literature will be presented.

Disclosures: The authors have declared no conflicts of interest.
patient at 39 nmol/h/mg protein (normal range 33–134) and genetic testing showed a rare P343L mutation in the GLA enzyme confirming the diagnosis. The patient was treated with enzyme replacement therapy (ERT) and aspirin, which reduced levels of serum Gb3 and normalized her heart function. She subsequently suffered a myocardial infarction which was associated with increased antiphospholipid (ACLA) and J2-GPI antibodies and a cerebrovascular accident. ERT may contribute to endothelial damage which could explain why strokes continue to occur in treated patients. Her lupus disease activity remained relatively inactive clinically although ACLA, anti-J2-GPI and double-stranded DNA antibodies continued to be positive and complement levels low.

Conclusions: The pattern of organ involvement in patients with FD and SLE can be similar (including eye, renal and cardiac involvement) and the coexistence of FD and SLE has been described previously. Furthermore, the presence of ‘lupus associated’ antibodies to dsDNA,ENA and phospholipids can be features of patients with FD. Neonatal screening shows late onset FD has an incidence of 1 in 3100, suggesting the true prevalence is underestimated. Thus the co-existence of FD and SLE may be more common than believed previously.

If untreated, the accumulation of Gb3 leads to progressive organ failure and premature death. Gb3 is immunogenic and creates an autoimmune response which leads to multisystem involvement of sarcoidosis. Aim of this case report is to disseminate knowledge concerning successful treatment of multisystem sarcoidosis. Our case supports the need for randomized controlled clinical trials of anti-TNF therapy in refractory systemic Sarcoidosis.

Disclosures: The authors have declared no conflicts of interest.

8. A FATAL CASE OF ANTI-MDA5 CLINICALLY AMYOPATHIC DERMATOMYOSITIS

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Background: Melanoma differentiation-associated gene 5 (MDA5) has recently been identified as a novel auto-antigen in patients with clinically amyopathic dermatomyositis (CADM) targeted by anti-MDA5-140 antibodies. The typical phenotype includes cutaneous ulceration, palmar papules, oral mucosal pain and a high risk of rapidly progressive ILD (RP-ILD). However, because the ANA and ENA are typically negative, the clinical phenotype may not be identified initially. We are reporting this case to raise awareness of this condition.

Methods: A man in his 7th decade was admitted with a 4 week history of cough, breathlessness, small joint pain and malaise. He had received prior treatment with amoxicillin and clarithromycin with no response. He had no past medical or drug history. He was an ex-smoker.

He had bilateral inspiratory crackles with oxygen saturations of 92% on air, synovitis of the hands and right knee. He had two aphythous tongue ulcers and erythematous lesions on his fingers.

Full blood count, renal and liver function and CK were normal. CRP was 9, ESR 40. Urine dipstick, ANA, ENA, ANCA, RF, dsDNA and anti-GBM were negative. Skin biopsy findings were non-specific, but suggestive of an eczematous process. Chest X-ray was normal. Atypical pneumonia testing was negative. CTPA showed subpleural interstitial opacities consistent with atelectasis or fibrosis. He was treated with further antibiotics for atypical pneumonia and oral prednisolone for presumed reactive arthritis.

Results: Six weeks later he had ongoing dyspnoea with exercise tolerance 10 yards. The synovitis had resolved, but the digital lesions were still present. Prednisolone was increased to 40mg. He was referred for consideration of an open lung biopsy to ascertain the exact diagnosis.

He was re-admitted 6 weeks later with fever, confusion and profound hypoxia requiring ventilation on ITU. CXR showed worsened bilateral interstitial shadowing. Bronchoscopy and BAL were negative. On review by rheumatology he had nail fold infarcts and purpuric papules on the dorsal-ventral junction of his fingers. In view of his finger lesions, oral ulcers and RP-ILD, anti-MDA5 CADM was suspected. He was treated with intravenous methylprednisolone but died within days of multi-organ failure. Subsequently, MDA5 antibodies were identified by immunoprecipitation.

Conclusions: Rheumatologists need to be aware of the expanding clinical phenotype of CADM, in particular the cutaneous features and the antibody subsets which are associated with CADM so that treatment can be targeted appropriately. Typically patients are ANA and ENA negative and therefore are often assumed not to have a CTD. Previous reports have indicated the high prevalence of RP-ILD in this condition and high mortality risk.

Disclosures: The authors have declared no conflicts of interest.

9. RITUXIMAB IN RECURRENT THROMBOEMBOLIC DISEASE IN APS

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Background: We describe the use of Rituximab in a patient with APS with recurrent pulmonary embolism (PE) due to poor compliance with standard anti-coagulation. A 19-year-old female, with no past medical history, presented acutely with exertional breathlessness and pleuritic chest pain. The patient was a non-smoker.

The patient had a history of recurrent PE with deep vein thrombosis (DVT) and was referred for further treatment. Antiphospholipid antibody screen was positive with a lupus anticoagulant present at 2483 μI/g (0–500). CT pulmonary angiography demonstrated large bilateral proximal pulmonary arterial emboli. A standard thrombophilia screen was unremarkable, except for positive anti-β2-glycoprotein-1 (β2GPI) antibodies. Prednisolone for presumed reactive arthritis.

Results: Six weeks later he had ongoing dyspnoea with exercise tolerance 10 yards. The synovitis had resolved, but the digital lesions were still present. Prednisolone was increased to 40mg. He was referred for consideration of an open lung biopsy to ascertain the exact diagnosis.

He was re-admitted 6 weeks later with fever, confusion and profound hypoxia requiring ventilation on ITU. CXR showed worsened bilateral interstitial shadowing. Bronchoscopy and BAL were negative. On review by rheumatology he had nail fold infarcts and purpuric papules on the dorsal-ventral junction of his fingers. In view of his finger lesions, oral ulcers and RP-ILD, anti-MDA5 CADM was suspected. He was treated with intravenous methylprednisolone but died within days of multi-organ failure. Subsequently, MDA5 antibodies were identified by immunoprecipitation.

Conclusions: Rheumatologists need to be aware of the expanding clinical phenotype of CADM, in particular the cutaneous features and the antibody subsets which are associated with CADM so that treatment can be targeted appropriately. Typically patients are ANA and ENA negative and therefore are often assumed not to have a CTD. Previous reports have indicated the high prevalence of RP-ILD in this condition and high mortality risk.

Disclosures: The authors have declared no conflicts of interest.
Idiopathic intracranial hypertension (IIH) is defined by consistent with a diagnosis of Behçet’s disease. The patient reported a rapid and sustained subjective improvement in his symptoms of pain and stiffness that was maintained at 4 months follow up. Repeat ultrasound at that stage demonstrated regression of synovial thickening and less florid Doppler flow confirming the response to treatment. The rope sign remains visible and palpable but is less prominent and is causing less discomfort and restricted movement.

Conclusions: Seropositive RA can present in unusual ways in this case initially with IGD and subclinical synovitis showing an excellent response to IM steroids and MTX monotherapy. Close liaison with the rheumatologist is essential to ensure early diagnosis of RA presenting with unusual skin manifestations to ensure rapid effective treatment and prevention of joint damage and associated morbidity.

Disclosures: The authors have declared no conflicts of interest.

11. SEROPositive NON-EROSIVE RHEUMATOID ARTHRITIS PRESENTING WITH THE CUTANEOUS ROPE SIGN (INTERSTITIAL GRANULOMATOUS DERMATITIS) AND DISCOlINAL SYNOVITIS RESPONSITIVE TO STEROIDS AND METHOTREXATE

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Background: Interstitial granulomatous dermatitis (IGD) is a distinct entity with a typical histological pattern. It tends to present with erythematous papules and plaques on the trunk and proximal limbs with approximately 10% manifesting hard cord-like lesions—the rope sign. There is an established but rare association between IGD and autoinmune disease particularly RA and lupus. We present a case of IGD presenting with the rope sign revealing a diagnosis of RA responsive to steroids and MTX. Written consent was obtained for publication from the patient.

Methods: 36-year-old male smoker who worked as a labourer and was2,3,4,5 American presented to dermatology outpatients with a 10 years’ history of sudden onset dermal lines (the rope sign) extending bilaterally from the iliac crests to the anterior shoulder following an episode of heavy lifting. Skin biopsy demonstrated normal dermis, a mild perivascular and periadnexal lymphocytic infiltrate in the superficial dermis and a fibrotic deep dermis with infiltrating interstitial histocytes. A diagnosis of IGD was made and he was found to be RF and CCP antibody positive.

Rheumatology assessment revealed a 3 year history of low grade fitting arthralgia with a recent exacerbation giving a 6 week history of morning stiffness and intermittent pain in the metacarpophalangeal (MCP) joints, knees and metatarsophalangeal (MTP) joints. There was no overt clinically detectable synovitis but ultrasound demonstrated synovial thickening in all the MCP joints and increased doppler flow throughout consistent with active synovitis. A diagnosis of seropositive non-erosive RA was made. He was administered 120mg of intramuscular (IM) depotmedone and commenced on 15mg of MTX weekly.

Results: The patient reported a rapid and sustained subjective improvement in his symptoms of pain and stiffness that was maintained at 4 months follow up. Repeat ultrasound at that stage demonstrated regression of synovial thickening and less florid Doppler flow confirming the response to treatment. The rope sign remains visible and palpable but is less prominent and is causing less discomfort and restricted movement.

Conclusions: Seropositive RA can present in unusual ways in this case initially with IGD and subclinical synovitis showing an excellent response to IM steroids and MTX monotherapy. Close liaison with the rheumatologist is essential to ensure early diagnosis of RA presenting with unusual skin manifestations to ensure rapid effective treatment and prevention of joint damage and associated morbidity.

Disclosures: The authors have declared no conflicts of interest.

10. BEHÇET’S DISEASE ASSOCIATED WITH IDIOPATHIC INTRACRANIAL HYPERTENSION

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Background: Neurological manifestations occur in up to 20% of patients with Behçet’s disease, with focal parenchymal lesions and complications of vascular thrombosis being the most common abnormalities. Most reports state that intracranial hypertension in patients with Behçet’s disease is usually due to cerebral venous thrombosis. There was no evidence of any of these causes on neuroimaging of our patient, and our patient met all other criteria for diagnosis of IIH. Multiple associations of IIH have been reported, including systemic conditions (such as obesity and sleep apnoea) and medications (such as anticonvulsants and teracenicin).

Methods: Due to poor compliance with treatment and monitoring (INR of <1.5), she went on to suffer two further episodes of pulmonary embolism over the next 6 months. On haematological advice she was switched to dabigatran (a direct thrombin inhibitor) 150 mg b.d. (maximum dose). Four months later she suffered a fourth PE requiring admission and heparin treatment. Echocardiography showed moderate dilatation of the right atrium and proximal pulmonary arteries. Pulmonary arterial systolic pressure was estimated at 82 mmHg.

Results: The patient refused treatment with daily subcutaneous heparin due to needle phobia. A decision to treat with two infusions of rituximab, 1 g 2 weeks apart, was made. Two months post infusion her ACA titre had fallen to 67 U/ml, and anti-B2-GP-I antibodies to 33 U/ml. After 3 infusions of rituximab treatment, she has not had any further PE’s and her ACA and anti-B2-GP-I antibodies remain suppressed.

Conclusions: There are only a handful of case reports published on the use of rituximab in patients with primary, secondary and catastrophic APS. A reduction in aPL antibody titres with rituximab treatment has been reported, as has the prevention of recurrent and/or severe thrombotic events in APS over 10–36 months of follow-up. B cells are required to be central to the generation of aPL-induced clinical manifestations, so could constitute a therapeutic target in APS.

This case appears to show a clinically important response to rituximab treatment in a patient with malignant anti-phospholipid syndrome and suggests that rituximab may have a role in the management of APS when poor compliance or complications of treatment render anti-coagulation ineffective.

Disclosures: The authors have declared no conflicts of interest.

12. A CASE OF ULCERATIVE LUPUS PROFUNDUS RESPONDING TO RITUXIMAB

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Background: Lupus profundus/ganniculitis is a rare cutaneous manifestation of lupus occurring in 2–5% of SLE. It presents with subcutaneous nodules located mainly on the upper part of the body and causing atrophic changes of the skin. Ucleration of these lesions is not uncommon. Antimalarials, corticosteroids and immunosuppressants are the most commonly used forms of treatment.

Methods: We report a case with multiple cutaneous manifestations developing in succession in a patient with SLE, including discoid lupus and lupus profundus with severe disfiguring skin ulcerations. The case...
illustrates the difficulty in management. We reviewed patient’s case notes plus histopathology and performed a literature search for treatment of lupus profundus with Rituximab.

**Results:** A 63-year-old Nigerian lady was diagnosed with SLE in 2005 with clinical presentation of photosensitive facial rash, arthritis and fatigue, with antibody profile of positive ANA (5 units), anti-dsDNA, anti-Ro and La antibodies and lupus anticoagulant. She was initially treated with low dose prednisolone, azathioprine and MTX mainly for arthritis. She was later commenced on HCQ.

In June 2007, she developed skin rash in the form of indurated erythematous plaques on face and right elbow. A biopsy showed hyperkeratosis, deposition of fibrinoid material within collagen and liquefaction of basal layer, all thought to be consistent with lupus which responded to topical and oral steroids.

In May 2010 she developed severe rash with some lesions resembling discoid lupus, scarring alopecia and deeply indurated plaques forming ulcers. They caused disfiguring depressions of the skin on face and shoulders.

The ulcerated lesions remained very resistant to treatment despite prednisolone 60 mg/day, mepacrine, hydroxychloroquine and MTX. She was intolerant to MMF. Antibiotics, topical flamazine and hydrocolloid dressings were required as secondary infection occurred with swabs growing S. Aureus and Pseudomonas on separate occasions.

Biopsies from the indurated lesions showed leucocytoclastic vasculitis, perivascular lymphocytic infiltrate, panniculitis with fat necrosis and hyalinization of collagen consistent with the diagnosis of lupus profundus. Tuberculosis and fungal infections were excluded.

She was then treated with 2 infusions of rituximab 1 g i.v. (2 weeks apart). This halted development of new ulcers and promoted slow healing of the lesions, thus enabling reduction of prednisolone to 10 mg/day.

**Conclusions:** This case illustrates efficacy and safety of rituximab in the treatment of refractory discoid LE and ulcerated lupus profundus developing in an adult patient with multiple corticosteroids and immunosuppressive treatment.

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

13. TOCILIZUMAB FOR THE TREATMENT OF AUTOINFLAMMATORY DISEASE

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**Background:** Autoinflammatory disorders are an uncommon, heterogeneous group of conditions characterized by recurrent, episodic fevers without any associated bacterial or viral infection. Often associated with rash, arthritis, and high inflammatory markers.

A genetic defect has been found for some autoinflammatory diseases including the periodic fevers: Familial Mediterranean Fever (FMF) and TNF receptor-1 associated periodic fever syndrome (TRAPS).

We describe three patients with histories consistent with an autoinflammatory disease, all unresponsive to traditional therapies, who have responded well to Tocilizumab.

**Methods:** A retrospective review of patients’ case notes.

**Results:** We present three patients with a history of: recurrent fevers, anaemia, raised inflammatory markers, rash (panniculitis), arthralgia and reactive bone marrow. Two of these patients also experienced recurrent cardiac events; evidenced by chest pain, increased troponin level and ECG changes.

All three patients had a normochromic, normocytic anaemia; raised CRP and ESR; and reactive bone marrow on bone marrow aspiration. Exhaustive investigation including: immunological testing, infectious screens, imaging and endoscopy were unremarkable.

These patients required frequent, often prolonged, hospital admissions and responded well to high dose steroid administration during exacerbations. Patients were unresponsive to disease modifying anti-rheumatic medications (DMARD’s) and anti-TNF drugs. Two patients had an initial response to Anakinra (anti-IL-1) but this had to be discontinued due to side effects.

Tocilizumab (anti-IL-6) was commenced 4, 16 and 17 months ago respectively. In all three patients fevers have resolved and serological indices have normalized.

**Conclusions:** These patients exhibit features consistent with an autoinflammatory disease that we are not yet able to characterize through genetic testing. Anti-IL-6 treatment appears to have abolished the inflammatory process and may have the potential to benefit other patients with a similar history.

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

14. ATYPICAL MYCOBACTERIAL INFECTION IN THE IMMUNOCOMPROMISED: BEWARE OF THE SKIN LODGERS

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**Background:** Patients on immunosuppressive drugs are at risk of contracting a variety of opportunistic infections which may be difficult to recognize as such. This includes infection with non-tuberculous mycobacteria (NTM). We describe two cases in which Mycobacterium chelonae, a NTM, caused skin infections in immunosuppressed patients leading to management difficulties.

**Methods:** Case no 1: A 78-year-old Caucasian woman with severe deforming erosive Rheumatoid arthritis (RA) with a 40-year history of DMARD therapy including prednisolone was admitted feeling unwell with a 3-month history of multiple ulcerating nodules on her toes and legs. Examination showed what appeared to be vasculitic lesions with multiple ulcerated gregarious toes and papulo-nodular skin lesions in both legs. The histology of skin nodules showed granulomatous abscesses. Acid-fast bacilli were confirmed on culture as M. chelonae. The patient died at home of other causes before therapy for NTM could be instituted.

Case no 2: A 65-year-old Caucasian man with history of myasthenia gravis and membrano-proliferative glomerulonephritis treated with AZA and steroids presented with rapidly spreading ulcerating papulo-nodular rash on the lower legs of several weeks duration. Bioxpy culture and histology confirmed M. chelonae. Clarithromycin and moxifloxacin cleared the lesions without sequelae.

**Results:** Autoimmune and inflammatory diseases present with protean manifestations. The diverse clinical presentations can cause diagnostic difficulties. This is further complicated by the treatment and consequences of immunosuppression. Rheumatoid skin diseases are manifold; granulomatous skin nodules, vasculitis, interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic and granulomatous dermatitis (PNGD) can present as skin nodules which are essentially treated with immunosuppression whilst in cutaneous TB, immunosuppression should be avoided.

**M. chelonae,** an atypical mycobacteria, classified in Runyon group IV, is found in soil, dust and water sources worldwide. It can cause diverse clinical symptoms including lung disease, cutaneous disease, ocular disease and osteomyelitis. Patients who are immunosuppressed often show widespread rapid cutaneous dissemination. Incidence of NTM infection has risen in recent years.

Diagnosis can be made by isolation of the mycobacteria from tissues such as skin, blood, sputum, and bone marrow. Polymerase chain reaction (PCR) analysis is available for certain mycobacteria. Culture and antibiotic sensitivity will guide treatment. Quantiiferon tests (Interferon gamma release assays (IGRA)) and tuberculin skin testing are not useful in atypical mycobacterial infections and immunocompromised patients.

**Conclusions:** The possibility of a mycobacterial infection should be considered when examining an immunosuppressed person with a new cutaneous eruption.

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

15. DRESS SYNDROME CAUSED BY NAPROXEN

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**Background:** Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening condition with the mortality rate estimated at 10–40%. It is characterized by the presence of at least three of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis. There most common medications associated with this condition are anticonvulsants (phenytoin, phenobarbital, carbamazepine), antibiotics (vancomycin, minocycline, nitrofurantoin sulphamides), as well as allopurinol, dapsone, imatinib therapy. DRESS syndrome is a delayed type IV hypersensitivity reaction and generally starts 2–8 weeks after the first exposure to the drug responsible. To the best of knowledge of the authors, this abstract describes the first case of naproxen-induced DRESS syndrome in an adult patient.

**Methods:** A 63-year-old previously fit gentleman was admitted with florid confluent maculopapular rash mainly on his arms, back and lower limbs, which gradually worsened over 4 days, as well as pruritus, paronychia (40%), visual hallucinations, shortness of breath, chest pain, hypoxia, abdominal pain and loose stools. His admission bloods...
shown deranged LFTs (bilirubin-13, ALP-137, ALT-108), raised inflammatory markers (WCC 19.1, neutrophils 17.6, CRP 161, ESR 49) and eosinophilia (initially 0.7 with the peak of 8.8). Vasculitic and myeloma screens were negative. He did not report any past medical history, did not travel abroad recently and was only taking naproxen for the sciatica pain during the previous 2 months. Naproxen was immediately discontinued. He was extensively investigated for an infectious cause of his presentation: measles, influenza viruses, HIV, CMV, HHV virus, respiratory syncytial virus, adenovirus, chlamydia, mycoplasma pneumonia, coxiella burnetii, which all came back negative. His stool culture was negative for clostridium difficile, gram-negative and enteric bacteria and cryptosporidium oocysts. Blood film revealed reactive picture with eosinophils and lymphoeytopenia. Mollusca. Urine HIAA and serum tryptase tests were performed to rule out carcinoid tumour, mastocytosis and anaphylaxis.

Results: The amalgamation of these clinical symptoms and laboratory findings led to a diagnosis. One week after the commencement of 40 mg of prednisolone, an improvement of patient’s liver function, inflammatory markers and resolution of rash were observed. Three months later, he remains well. He was advised to avoid any NSAIDs or COX-2 inhibitors due to severity of his recent reaction and possible cross-hypersensitivity between different NSAIDs.

Conclusions: We encourage clinicians to consider the diagnosis of DBP in patients with rash, multiorgan failure in addition to infections and CTDs. Prompt recognition and steroid initiation appears to be effective steps in managing this condition.

Disclosures: The authors have declared no conflicts of interest.

16. AN UNEXPECTED CAUSE OF SEVERE HYPOKALAEMIA IN A PATIENT WITH SJÖGREN’S SYNDROME: A CASE REPORT
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Background: Hypokalaemia in patients with Sjögren’s syndrome is well described as a consequence of potassium wasting and renal tubular acidosis due to chronic lymphocytic interstitial nephritis. Here we describe a patient with Sjögren’s syndrome and autonomic dysfunction who presents with new onset rhabdomyolysis.

Methods: Our 59-year-old female patient was diagnosed with Sjögren’s syndrome and autonomic neuropathy 3 years previously, when she presented with sicca symptoms and postural hypotension. She was found to have positive Schirmer test, ANA 1:160, Anti-Ro and La antibodies and a polyclonal rise in IgG, and there was autonomic dysfunction on testing with severe postural hypotension with abnormal sympathetic skin response and borderline parasympathetic responses. She was on HCQ 200 mg od, prednisolone 5 mg od and inhibitors due to severity of his recent reaction and possible cross-hypersensitivity between different NSAIDs. ANA remained positive ANA with a coarse speckled pattern on indirect immunofluorescence using Hep-2 cells. DsDNA and ENA antibodies remain negative. This has not previously been reported following treatment with IL1-RA.

Conclusions: The antibody formation in this case remains unclear but will be closely monitored. Further investigation detected an IgM kappa monoclonal (2.2 g/l). Urinary Bence Jones protein was negative. Bone marrow biopsy showed reactive changes and there was no hepatosplenomegaly nor lymphadenopathy on CT scanning.

Results: A 54-year-old female presented to dermatology with a 6 month history of arthralgia and a widespread urticarial rash mainly affecting her trunk and sparing sun exposed areas. Initial wheals measured 1–3 cm, lasted for 24 to 72 h and were painful rather than itchy. Biopsy demonstrated leucocytosis and extravasation of red blood cells but no definite urticarial vasculitis.

Investigations including FBC, ANA, ENA, dsDNA, immunoglobulins, C1q and complement were normal. ESR and CRP were raised. She was initially managed unsuccessfully with antihistamines, dapsone and immunosuppressants including HCQ, AZA and mycophenolate. Prednisolone, at doses above 15 mg od, improved her symptoms minimally.

Disclosures: The authors have declared no conflicts of interest.
The bilirubin peaked at 479 umol/l, ALT at 1609, INR > 15 and the albumin decreased to 19 g/dl. An USS of the abdomen and an MRCP were normal, as was a full liver screen.

Due to concerns of acute liver failure she was transferred to the regional liver unit for continuing observation. A liver biopsy was consistent with drug-induced liver injury (DILI). The patient made a full recovery after the discontinuation of corticosteroids. Currently this patient’s RA is in remission and LFTs have returned to normal. Current treatment is prednisolone 5 mg andydroxychloroquine.

Conclusions: DILI has been described with other anti-TNF agents (adalimumab, infliximab, etanercept). However, this is the first case described with respect to corticosteroids. The diagnosis of DILI, requires a high degree of suspicion, pattern recognition, establishing a temporal relationship and excluding other causes of liver injury. Although the role of liver enzyme monitoring is unclear, an awareness of this adverse effect is important, given the potential for a rapid and complete response to specific treatment. The possible underlying pathological process is thought to be due to hepatic sinusoids involved in the clearance of immune complexes via Fc receptor-mediated interactions that in turn could activate Kupffer cells to release reactive oxygen species or lead to local hepaticocyte damage. It is important to monitor and report adverse events in new drugs, as this can lead to changes in product labelling. Spontaneous reports of cases of severe hepatotoxicity led to the placement in 2004 of a warning on the infliximab product label. The incidence of hepatotoxicity was estimated to be about 1 incident per 16 500 users per year (38 cases among 576 000 treated patients over 8 years).

Methods: We present the case of a 29-year-old Caucasian lady with a 6-week history of fevers, coryzal illness, arthralgia of knees and elbows. She had a normal rheumatoid factor, anti-nuclear antibody and night sweats, together with microscopic haematuria. A renal mass had resolved. The inflammatory markers and c-ANCA had normalized and both renal function tests and urine analysis were unremarkable. The combination of renal granulomatous changes, chest infiltrates and positive c-ANCA clinched the diagnosis of granulomatosis with polyangiitis.

Conclusions: The authors have declared no conflicts of interest.

19. GRANULOMATOSIS WITH POLYANGIITIS PRESENTING WITH A RIGHT-SIDED RENAL MASS

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Background: Renal disease is common in granulomatosis with polyangiitis (GPA). Around 80% of patients develop signs of glomerulonephritis, however it is often not present at the time of diagnosis.

Renal masses have previously been described in patients with GPA and often provide a diagnostic dilemma. Several groups have reported that there is an increased incidence of renal cell carcinoma in patients with GPA. Therefore any renal mass should be taken seriously.

Methods: We present the case of a 29-year-old Caucasian lady with a 6-week history of fevers, cough, arthralgia of knees and elbows and night sweats, together with microscopic haematuria. The patient was cushingoid. Random cortisol was low and response to synacthen was unremarkable. Re-testing after 3 weeks demonstrated adrenal insufficiency. One year later, she requires long-term steroid replacement therapy and insulin. She is pursuing a medicolegal claim against the NHS Trust.

CASE 2: A 58-year-old HIV-infected lady taking entecavir, atazanavir and ritonavir for >2 years was diagnosed with seronegative SpA. At a clinic appointment, complaining of painful shoulders and hips, she was injected with triamcinolone 40 mg into each shoulder and each trochanteric bursa. She presented 7 weeks later with postural dizziness, lethargy, facial swelling and weight gain. Random blood sugar was elevated and she had glycosuria. She was cushingoid with proximal myopathy. Random cortisol was low and challenge with synacthen test demonstrated adrenal insufficiency. One year later, she requires long-term steroid replacement therapy and insulin. She is pursuing a medicolegal claim against the NHS Trust.

CASE 3: A 42-year-old HIV-infected man taking tenofovir, emtricitabine, darunavir and ritonavir for >2 years was diagnosed with adrenal insufficiency. He had 4 sets of negative blood cultures but was found to have a positive Quantiferon TB Gold. Chest radiograph and transsthoracic echocardiogram were normal. CT imaging of chest, abdomen and pelvis revealed bilateral ill-defined low attenuation lesions at both lung bases along with a 3.4 x 5.6 cm ill-defined enhancing mass in the lower pole of the right kidney.

This created several possible explanations:

1. Underlying vasculitic process (most likely GPA)
2. Renal tuberculosis (with false positive c-ANCA)
3. Renal cancer (with false positive c-ANCA)

Methods: Renal core biopsy revealed fibrosis and non-necrotizing, non-caseating granulomatous inflammation. Tuberculous testing was negative. Further biopsy of peri-lesional tissue revealed necrotizing glomerulonephritis with fibrosis.

The combination of renal granulomatous changes, chest infiltrates and positive c-ANCA clinched the diagnosis of granulomatosis with polyangiitis.

She was treated with cyclophosphamide and prednisolone, followed by AZA as maintenance therapy together with isoniazid and pyridoxine to cover for latent tuberculosis.

Results: Imaging with ultrasound at 8 months revealed that the renal mass had resolved. The inflammatory markers and c-ANCA had normalized and both renal function tests and urine analysis were unremarkable. Conclusion: Respect to polyangiitis.

Conclusions: The patient’s RA is in remission and LFTs have returned to normal. Current treatment is prednisolone 5 mg and ursodeoxycholic acid.

20. RHEUMATOLOGISTS BEWARE: SERIOUS ADVERSE REACTION BETWEEN INJECTED TRIAMCINOLONE AND RITONAVIR, COMMONLY USED FOR TREATMENT OF HIV

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Rheumatology, Brighton and Sussex Medical School, Brighton, UK

Background: HIV affects about 90,000 people in the UK. Since the advent of combination anti-retroviral therapies (cART), the prognosis has transformed and life expectancy is normal. It is likely that rheumatologists will increasingly need to treat HIV-infected patients for rheumatic symptoms.

Methods: Ritonavir is a protease inhibitor, widely used as a booster of cART. It inhibits the cytochrome P450 3A4 reducing corticosteroid metabolism. HIV Physicians recommend dose reduction of prednisolone by 50%. A serious interaction has been recognized between inhaled fluticasone and ritonavir so that the combination is now contraindicated. Cases have been reported of acute hypercortisolism induced by triamcinolone in HIV patients, one after 40 mg injected into a shoulder and one after caudal epidural injection of 80 mg. The common factor was ritonavir. We report a series of HIV-infected patients taking ritonavir who received triamcinolone injections.

Results: CASE 1: A 50-year-old HIV-infected woman taking abacavir, lamivudine, darunavir and ritonavir for >2 years was diagnosed with seronegative SpA. At a clinic appointment, complaining of painful shoulders and hips, she was injected with triamcinolone 40 mg into each shoulder and each trochanteric bursa. She presented 7 weeks later with postural dizziness, lethargy, facial swelling and weight gain. Random blood sugar was elevated and she had glycosuria. She was cushingoid with proximal myopathy. Random cortisol was low and challenge with synacthen test demonstrated adrenal insufficiency. One year later, she requires long-term steroid replacement therapy and insulin. She is pursuing a medicolegal claim against the NHS Trust.

CASE 2: A 58-year-old HIV-infected lady taking entecavir, atazanavir and ritonavir for >2 years was diagnosed with adrenal insufficiency. He had 4 sets of negative blood cultures but was found to have a positive Quantiferon TB Gold. Chest radiograph and transsthoracic echocardiogram were normal. CT imaging of chest, abdomen and pelvis revealed bilateral ill-defined low attenuation lesions at both lung bases along with a 3.4 x 5.6 cm ill-defined enhancing mass in the lower pole of the right kidney.

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3. Renal cancer (with false positive c-ANCA)

Methods: Renal core biopsy revealed fibrosis and non-necrotizing, non-caseating granulomatous inflammation. Tuberculous testing was negative. Further biopsy of peri-lesional tissue revealed necrotizing glomerulonephritis with fibrosis.

The combination of renal granulomatous changes, chest infiltrates and positive c-ANCA clinched the diagnosis of granulomatosis with polyangiitis.

She was treated with cyclophosphamide and prednisolone, followed by AZA as maintenance therapy together with isoniazid and pyridoxine to cover for latent tuberculosis.

Results: Imaging with ultrasound at 8 months revealed that the renal mass had resolved. The inflammatory markers and c-ANCA had normalized and both renal function tests and urine analysis were unremarkable. Conclusion: Respect to polyangiitis.

Conclusions: The patient’s RA is in remission and LFTs have returned to normal. Current treatment is prednisolone 5 mg and ursodeoxycholic acid.

21. TAKO-TSUBO CARDIOMYOPATHY ASSOCIATED WITH SYSTEMIC SCLEROSIS: A SIGN OF MYOCARDIAL RAYNAUD’S PHENOMENON?

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The author has declared no conflicts of interest.
Background: A 65-year-old woman with limited SSc (RP, pulmonary fibrosis, anti-centromere antibodies) attended for routine orthopaedic surgery. Comorbidities included hypertension and primary biliary cirrhosis, and she was regularly attended for prostaglandin infusions for her RP. At anaesthetic induction she developed hypotension and non-sustained ventricular tachycardia leading to the procedure being abandoned. She experienced cardiac sounding chest pain and developed pulmonary oedema, with ECG showing ST elevation in I, II, aVL, V5 and V6. She was transferred to the regional cardiology centre for emergency coronary angiography ± angioplasty.

Methods: Coronary angiography showed patent vessels with the exception of a longstanding occlusion of one superficial branch of the right coronary artery. A ventriculogram showed severely impaired left ventricular (LV) systolic function with sparing of basal segments, akinetic mid segments. Although there was a rise in Troponin T levels cardiac MRI showed no evidence of myocardial ischaemia.

She was managed conservatively and 2 days after admission her LV function was graded as moderate, whilst at review 4 weeks post-discharge it had returned to normal.

Results: Takosu -to cardiomyopathy is a rare disorder characterized by transient ballooning of the LV apex leading to acute LV dysfunction, in the absence of acute coronary artery occlusion. The name derives from the Japanese term for octopus pot, due to the resemblance of the ballooning LV to the short-neck round flask shape of the pots traditionally used for catching octopus.

The syndrome, observed predominantly in women >60 years, is provoked by profound physical/psychological stress. It is characterized by transient ECG changes mimicking acute myocardial infarction with a reduction of ejection fraction but minimal release of cardiac enzymes. Most survive, usually with rapid restoration of cardiovascular function and full recovery of ejection fraction.

Though the cause remains unknown, it is suspected that simultaneous vasospasm of multiple coronary arteries contributes to the takosu- to syndrome. Hypersensitivity of the coronary vasculature to the catecholamine surge of the physiological stress response is one proposed mechanism for this co-ordinated spasm throughout the coronary vasculature. It is also well known the myocardial Raynaud’s phenomenon leads to silent coronary vasospasms in patients with systemic sclerosis.

Conclusions: In our patient the hypotension experienced at general anaesthetic (GA) induction is likely to have triggered a Raynaud’s type coronary vasospasm leading to the takosu - to syndrome. Only one previous report of takosu - to cardiomyopathy in association with systemic sclerosis has been published. This case further suggests a link between systemic sclerosis and takosu - to syndrome and acts as a warning when considering a GA in patients with systemic sclerosis.

Disclosures: The authors have declared no conflicts of interest.

22. NECROTIZING BALANITIS DUE TO POLYARTERITIS NODOSA

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Background: Polyarteritis Nodosa (PAN), a rare necrotizing vasculitis affecting small to medium-sized arteries, is extremely difficult to diagnose.

Methods: Here, we present a case of PAN in a middle-aged man who presented to the sexual-health clinic with sterile epididymitis, followed by transient ballooning of the LV apex leading to acute LV dysfunction, from the Japanese term for octopus pot, due to the resemblance of the balloonsing LV to the short-neck round flask shape of the pots traditionally used for catching octopus.

The syndrome, observed predominantly in women >60 years, is provoked by profound physical/psychological stress. It is characterized by transient ECG changes mimicking acute myocardial infarction with a reduction of ejection fraction but minimal release of cardiac enzymes. Most survive, usually with rapid restoration of cardiovascular function and full recovery of ejection fraction.

Though the cause remains unknown, it is suspected that simultaneous vasospasm of multiple coronary arteries contributes to the takosu-tosu syndrome. Hypersensitivity of the coronary vasculature to the catecholamine surge of the physiological stress response is one proposed mechanism for this co-ordinated spasm throughout the coronary vasculature. It is also well known the myocardial Raynaud’s phenomenon leads to silent coronary vasospasms in patients with systemic sclerosis.

Conclusions: In our patient the hypotension experienced at general anaesthetic (GA) induction is likely to have triggered a Raynaud’s type coronary vasospasm leading to the takosu-tosu syndrome. Only one previous report of takosu-tosu cardiomyopathy in association with systemic sclerosis has been published. This case further suggests a link between systemic sclerosis and takosu-tosu syndrome and acts as a warning when considering a GA in patients with systemic sclerosis.

Disclosures: The authors have declared no conflicts of interest.

23. IMPROVEMENT OF COELIAC DISEASE IN A PATIENT WITH SJÖGREN’S SYNDROME TREATED WITH RITUXIMAB

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Background: Sjögren’s/lupus spectrum disorders reflect immune dysregulation which also increases the incidence of other immune-mediated phenomena, such as coeliac disease. B-cell depletion therapy may be effective for these associated conditions. However, economic restrictions require more tangible evidence of efficacy in order for such strategies to be funded.

Methods: A 52-year-old female presented with ascending lymphangitis in the arm and a blistering rash on her legs. She had fatigue, diarrhoea and weight loss of 5 kg. She had a several year history of dry eyes, photosensitivity, tinnitus and pleuritic chest pain. Past medical history included parotitis and cholecystectomy for gallstones 4 years previously. Her father had sicca symptoms and died from a lymphoma.

On examination, she weighed 65.6 kg, had a malar rash, bilateral eyelid oedema, conjunctival injection but general examination was otherwise unremarkable.

Investigations revealed anaemia, normal renal, liver and bone function tests, reduced folate (20 pg/ml), ESR 61 mm/h and CRP 3 mg/l. She had positive ANA, anti-Ro, anti-La, RHF, ACL and anti-TTG. She was negative for anti-dsDNA antibodies, ANCA and cryoglobulins. She had a polyclonal hypergammaglobulinaemia, and a hypocomplementaemia with C4 0.12 g/l.

Minor salivary gland biopsy demonstrated lymphoplasmacytic infiltration with two foci per 4 mm2. Duodenal biopsy showed partial villous atrophy with crypt hyperplasia and chronic inflammatory infiltrate. Biopsy of the vesicular rash revealed a thrombotic capillaritis with neutrophilic exudate but negative immunofluorescence assays.

Discines of primary Sjögren’s syndrome, with lupus spectrum features and coeliac disease were made. The patient commenced on a strict gluten-free diet and was commenced on prednisolone 30 mg od HCQ and MMF.

Results: Conventional immunotherapy for 15 months resulted in resolution of the vasculitic rash and improvement of duodenal histology but constitutional features, including weight loss, continued. After 12 months of rituximab, she exhibited marked improvement of gastrointestinal, constitutional, functional and serological features.

Conclusions: This is the first report of efficacy of B-cell depletion therapy for a composite presentation of coeliac disease with Sjögren’s syndrome.

Table 1. Response to rituximab in addition to conventional therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pre-treatment</th>
<th>Post-diet</th>
<th>HCO and MMF</th>
<th>Post-rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of bowel movement</td>
<td>9/day</td>
<td>7/day</td>
<td>4/day</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65.6</td>
<td>56.3</td>
<td>61.2</td>
<td></td>
</tr>
<tr>
<td>RF (0-30 U/ml), U/ml</td>
<td>128</td>
<td>9.2</td>
<td>5.4</td>
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<tr>
<td>Anti-TTG (0-6 U/ml), U/ml</td>
<td>916</td>
<td>52</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>IgG (9-13 mg/dl)</td>
<td>28.9</td>
<td>4.03</td>
<td>9.9; 2.7</td>
<td>9.9; 2.9</td>
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<tr>
<td>IgA (0.8–3.7 mg/dl), mg/dl</td>
<td>30</td>
<td>10</td>
<td>7.5</td>
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</table>

The authors have declared no conflicts of interest.

24. AN UNUSUAL CASE OF BILATERAL PAROTID AND SUBMANDIBULAR GLAND INVOLVEMENT IN ANCA ASSOCIATED VASCUITIS, REFRACTORY TO CYCLOPHOSPHAMIDE BUT SUCCESSFULLY TREATED WITH RITUXIMAB

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Background: ANCA Associated Vasculitis (AAV) is a disease of unknown aetiology characterized by necrotizing vasculitis of the small and medium vessels. Granulomatosis with Polyangiitis (GPA) typically involves the upper and lower respiratory tract and kidneys. We describe a patient with a rare presentation of aggressive bilateral parotid and submandibular gland involvement with bilateral lower motor neurone facial nerve palsy.

Methods: A 68-year-old female patient presented with a 4-week history of pain and swelling in the right parotid and left submandibular gland region. Initial antibiotic treatment for presumed localized infection was unsuccessful. Due to worsening pain and swelling, a biopsy of the affected area was performed, which demonstrated features in keeping with GPA. The patient reported significant weight loss and malaise but no other clinical features such as skin, eye, respiratory, joint or renal disease were present. Laboratory investigations demonstrated an elevated ESR at 74 mm/h and weakly positive
ANCA (PR3 5.7 IU/ml) and oral prednisolone was therefore commenced. Despite this, the patient developed a right-sided lower motor neuron facial nerve palsy and pulsed intravenous cyclophosphamide was initiated for AAV.

Results: Despite 4 months of 3-weekly pulsed cyclophosphamide, the patient’s disease progressed to a bilateral facial nerve palsy. This was accompanied by further destruction of the parotid and submandibular glands with enlarging sinus tracts to the skin and associated concern regarding secondary infection. Magnetic Resonance Imaging confirmed progressive glandular destruction and air within the cavity, raising the possibility of actinomycosis infection. The ESR remained elevated and ANCA weakly positive and a further submandibular gland biopsy again demonstrated features consistent with granulomatous inflammation. Infection with actinomycosis was not present.

Following exclusion of an alternative diagnosis and in the absence of significant infection, the patient was commenced on rituximab as per the RAVE regime. After 1 month of treatment the sinus tracts had almost healed, the ESR had normalized and the patient had begun to gradually regain weight.

Conclusions: This unusual presentation of AAV involving only the parotid and submandibular glands demonstrates how aggressive localized disease can be. In this case the disease was refractory to cyclophosphamide but effectively controlled with rituximab.

Disclosures: The authors have declared no conflicts of interest.

ULTRASONOGRAPHY: AN OPEN-LABEL STUDY

25. EARLY RESPONSE TO ABATACEPT PLUS MTX IN MTX-IR RA PATIENTS USING POWER DOPPLER

Maria A. D’Agostino1, Richard Wakefield2, Hilde Berner Hammer3, Olivier Vittecoq4, Mauro Galeazzil, Peter Bailin5, Emilio Filippucci6, Ingrid Moller7, Annamaria Iagnocco8, Esperanza Naredo9, Karina Van Holder14, Manuela Le Bars12 and OMERACT US Task Force. 1

Background: EULAR has recommended PDUS global score detection of early signs of improvement in synovitis,全球 PDUS score detected early signs of improvement in synovitis, demonstrating a significant response to abatacept at Day 7, which increased to Month 6. Efficacy and safety data were consistent with a previous abatacept trial in MTX-IR patients.

Results: 104 patients were enrolled; 89 completed the trial. Demographic, clinical and PDUS data are shown (Table 1). Early signs of improvement in global PDUS score were observed at Day 7. Mean change from BL in global PDUS score and its components increased to Day 169. By Day 57, threshold for clinically meaningful improvement of 1.2 was not included in the 95% CI for mean change from BL in DAS28 (CRP). There were no deaths; 6 (5.8%) patients developed a serious adverse event (AE) (atrial fibrillation, bursitis, dementia, endometriosis, pleural effusion and pulmonary fistula, and hypotension), 62 (59.6%) an AE, and 20 (19.2%) an infection.

Conclusions: The study showed that the OMERACT-EULAR-US global PDUS score detected early signs of improvement in synovitis, demonstrating a significant response to abatacept at Day 7, which increased to Month 6. Efficacy and safety data were consistent with a previous abatacept trial in MTX-IR patients.


IMAGING

26. TWINS UK HERITABILITY STUDY OF CANDIDATE LOW BACK PAIN PHENOTYPE SHOWS VERTEBRAL ENDPLATE ABNORMALITIES TO BE HERITABLE.

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Background: Low back pain (LBP) is a very common and disabling problem in adults worldwide. One of the classical risk factors for LBP is MRI-determined lumbar disc degeneration (LDD). One of the features of LDD which has received less attention is vertebral end plate lesions (VEP), which have been linked to LBP. The challenge in LBP research is the lack of a universally accepted phenotype. While heritable factors have been shown to influence other features of the LDD phenotypes, VEP lesions have not been studied to date. The overall objective of this study was to investigate the relative role of genetic and environmental influences on the VEP in the lumbar spine.

Methods: We conducted a classic twin study of VEP changes of 880 – MIRs in 155 monozygotic (MZ) and 265 dizygotic (DZ) twin pairs to determine whether genetic factors affected low back pain. T2
weighted sagittal sequences of the lumbar spine were available from a previously published study conducted 2006–2010, to evaluate VEP changes in the lumbar spine. Each lumbar disc was scored on a scale of 0–3 for severity of endplate change across the disc and a summary VEP score generated by adding the five lumbar discs scores together.

In the classical twin design of twins reared together, three parameters: were modelled: an additive genetic (A), shared (C) and non-shared (E) environmental components. The ACE full model was compared with sub models AE, and CE. The chi-squared test was used to compare the fit of the models while the Akaike’s information criterion was used to determine the relative fit of the model and its parsimony models with lower AIC values, indicate a better balance of fit over parsimony of the data. The majority of the heritability estimates was produced by the Mx-programme.

**Results**: As other features of LDD are similar in men and women, both genders were included in the heritability analysis. Heritability estimates ranged between 41% and 59% for VEP changes. Further more, the model with the best fit was additive and environmental AE, Table 1.

**Conclusions**: Results indicate that there were significant genetic influences over VEP changes visible on MRI in twins. Thus VEP may represent a candidate LBP phenotype for future studies evaluating response to treatment in LBP. Understanding further and identifying the genetic influences on VEP may reveal pathways of pathogenic importance, which is currently poorly understood. With the development of large cohorts having MR information and genome-wide association data, future research should focus on VEP in order to characterize the molecular pathways beyond LBP.

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

### Table 1. Heritability results

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Model for comparison</th>
<th>Univariate estimates</th>
<th>95% CIs</th>
<th>∆OF</th>
<th>AIC</th>
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<th>C</th>
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<td>VEP ACE</td>
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<td>1</td>
<td>22</td>
<td>78</td>
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**VEP**: vertebral end plate.

27. CURRENT PRACTICE IN MUSCULOSKELETAL ULTRASOUND IN THE NORTHERN REGION

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**Background**: The clinical indications and potential of musculoskeletal ultrasound (MSUS) are increasing within rheumatology. Anecdotally, the number of rheumatologists using or seeking to learn the technique is also increasing. However, acquiring, maintaining and demonstrating skills in MSUS remains challenging, and there is uncertainty about the most appropriate and effective means to achieve this. This survey sought to determine the current practice in this area amongst rheumatologists in the Northern Region (north-east England).

**Methods**: A postal survey of all consultant and specialist trainee (STs) rheumatologists in the Northern Deanery. The BSR US experience chart was sent to 58 rheumatologists [46 Consultants, 12 Specialty Trainees (STs)] in the Northern Deanery. It was set to determine the number of rheumatologists using or seeking to learn the technique and the use of MSUS in practice. Short questions identified patients’ current use of MSUS, their access to MSUS equipment and training.

**Results**: Of 250 Newcastle EAC patients scanned, 77 were considered to show evidence of definite inflammatory arthritis on grayscale and/or Doppler views and signs typical of gout or CPPD and 127 scans were considered normal.

**Conclusions**: A pragmatic screening protocol in the context of an EAC is feasible, and provides useful prognostic information. Despite its impressive PPV for persistent inflammatory arthritis, our data suggest that routine MSUS assessments may overlook 20% of inflammatory cases at baseline. The use of NSAIDs and corticosteroids at first clinic attendance was common and has been shown to significantly modify ultrasound appearances.

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

29. 3D CORTICAL THICKNESS MAPPING OF THE HIP AS A NEW IMAGING BIOMARKER OF OSTEOARTHRITIS

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**Background**: Bone goes through three stages as OA develops: early resorption, subsequent sclerosis, and then osteophyte formation. Periarticular cortical bone and subchondral bone pathology is ideally suited to analysis with 3D cortical thickness mapping (CTM), a new technique that uses clinical CT imaging of living patients to visualize and quantify cortical bone thickness and joint space. Comparing 3D cortical thickness maps from individuals with and without disease, we use parametric analysis to identify patches on the femoral surface system. Free text comments indicated a desire for more guidance and assistance with respect to governance and quality, but some expressed difficulties in obtaining this from radiologists.

**Conclusions**: At least 26% of rheumatologists (15/58) in the Northern Region are utilizing MSUS as part of their routine clinical workload. There is a higher proportion of trainees (4/12—33%) than Consultants (11/46—24%), suggesting that this figure is likely to increase further.

Despite debate in recent years, training in MSUS remains variable, and clinicians who wish to develop their skills in this area face challenges with respect to guidance on optimum methods, access to equipment, and mentors with the time and skills to teach them. Similarly, MSUS trainees in the Northern Region are using a number of different methods to demonstrate the validity of their scan results. Further effort in meeting these needs—locally, nationally, and internationally—is necessary to ensure that the benefits of MSUS are available at a high response rate of 60%.

15/35 respondents scanned regularly (11 Consultants, 4 STs). The majority (10/15) performed fewer than 8 scans per week. 14/15 were confident scanning hands and wrists, Consultants, 4 STs). The majority (10/15) performed fewer than 8 scans per week. 14/15 were confident scanning hands and wrists,
where cortical thickness differs, visualizing the magnitude and significance of group differences to discover anatomically relevant regions of interest (ROIs). In this clinical study, CTM was applied to investigate whether areas of hip cortical bone thickening corresponded with expert radiologist assessment of clinically-relevant disease.

**Methods:** We analysed one hip from each participant in a study of 230 women aged 66 ± 17 years who had undergone pelvic CT. The hip was graded by an expert radiologist for OA feature severity using a 3D scoring system. Stradwin (v4.3) software was used to contour each hip semi-automatically and create a 3D surface colour mapped with individual cortical thickness values. Each of the 230 femur maps was registered to an average femur surface. Statistical parametric mapping was then performed to visualize, on a 3D femur model, the statistically significant effects of age and weight on cortical thickness (thickness difference per decade per kilo either as a % or absolute difference in mm). The primary outcome measure was the group difference in cortical thickness per worsening osteophyte score (difference per score either as % or absolute difference in mm), although similar analyses were also conducted for subchondral cysts and joint space width (JSW).

**Results:** There was a statistically significant and highly focal 40% increase in cortical bone thickness for each increase in osteophyte score from score 0 (n27), 1 (n110), 2 (n56) up to score 3 (n37). The regions of cortical thickening were pathologically relevant, encircling the epiphyseal line and extending to the loaded subchondral bone of the superior femoral head. Age was associated with thinning of the cortex, except at sites that are highly stressed during the normal gait cycle. Increasing weight was associated with thicker cortex in these same load bearing regions.

**Conclusions:** Our 3D bone mapping technique identified distinct, focal thickening of marginal articular cortical bone and superior subchondral bone with worsening radiological OA. CTM can also measure the joint space in 3D. Together these results are an important step towards a new automated imaging diagnostic and prognostic biomarker for OA. ROI’s will now be taken to a prospective setting to test the hypothesis that CTM-defined OA features are associated with clinically and symptomatically relevant OA disease.

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

### METABOLIC AND CRYSTAL ARTHROPATHIES

#### 30. HEALTH-RELATED QUALITY OF LIFE IN GOUT: A SYSTEMATIC REVIEW

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**Background:** Gout is the most prevalent inflammatory arthritis affecting 1.4% of European adults. The excruciating pain, chronic arthropathy, comorbidities and frequent use of generic instruments. Gout-specific characteristics and comorbidities contribute to poor health-related quality of life (HRQOL). Our knowledge there are no existing systematic review articles on HRQOL in gout.

**Objectives:** To determine which instruments have been used to measure HRQOL in gout (i) to determine which factors associate with poor HRQOL in gout.

**Methods:** MEDLINE, CINAHL, EMBASE and PsycINFO were searched from inception to November 2012. Search terms pertained to gout, health or functional status, clinimetric properties and HRQOL. Titles and abstracts of all identified articles were independently reviewed by two reviewers. Articles unsuitable for exclusion based on title and abstract screening were included for full-text review by both reviewers. Further exclusions were made based on re-application of the inclusion and exclusion criteria. The references of all full-text papers were examined for relevant studies. Disagreements were arbitrated through consensus meetings. Study data extraction and quality assessment were performed independently by the two reviewers.

**Results:** Of 474 identified studies, 22 met the inclusion criteria (13 cross-sectional, 7 cohort and 2 qualitative). Of the 12 identified instruments, Short Form-36 (SF36) and Health Assessment Questionnaire Disability Index (HAQ-DI) were most frequently used and highest rated with robust construct and concurrent validity, despite high floor and ceiling effects. The Gout Impact Scale (GIS) had greatest content validity with patients at different stages of the disease. However, subscales of the GIS showed poor internal consistency, construct and concurrent validity (weak correlations with physician rated severity as well as other generic instruments). No studies defined or used a cut-off value for poor HRQOL in gout. Those with gout had an overall poorer HRQOL compared with age and sex-matched norms and controls. Gout had a greater impact on physical HRQOL compared with other domains. Both gout-specific features (disease frequency and intensity, impact of gout and treatment involvement) and comorbidities were associated with poor HRQOL.

**Conclusions:** Most studies have used the generic HAQ-DI and SF36. Gout-specific characteristics and comorbidities contribute to poor HRQOL. There is need for a cohort study in primary care (where most patients with gout are treated) to determine which factors predict change in HRQOL over time. This will enable those at risk of deterioration to be identified and better-targeted for treatment.

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

#### 31. THE BURDEN OF GOUT-RELATED ADMISSIONS TO A DISTRICT GENERAL HOSPITAL

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**Background:** In UK adults, the prevalence of gout is 1.4%. Gout is often sub-optimally managed. The impact of this on hospital admission and prolonging hospital stay has been overlooked. Hospital Episode Statistics (HES) data for this District General Hospital (DGH) record 30 admissions per year due to or complicated by gout, with an average length of stay of 7.3 days. The total cost of these admissions is given as £62400. Departmental records of inpatient consultations undertaken for patients with suspected gout suggested 30 admissions to be an underestimate. We explored the role of gout in medical admissions in this DGH, if gout was a pre-existing diagnosis and if it was being treated according to established guidelines pre-admission.

**Methods:** All inpatient records where gout was coded according to ICD-10 as a primary or secondary diagnosis were retrospectively examined over a 3-month period (May 2011 to July 2011). A proforma was used to document the cause of admission, development of gout during admission, prior diagnosis of gout, treatment of gout, serum urate, gout predisposing comorbidities, and discharge plan.

**Results:** In a 3-month period, 79 inpatients had gout coded on their discharge summary. 64 patient records were accessed. 36% (n = 23) of these admissions were either directly related to gout (17%, n = 11) or prolonged by complications of gout (18%, n = 12). This would suggest 92 inpatient admissions for gout a year.

Over the 3 month study period bed days per admission as a result of admission directly to gout was 130 days, with an average length of stay of 12.1 days. Where admissions were complicated due to an attack of gout (n = 12), we examined the hospital records and planned discharge date and found this to be prolonged by an average of 5 days, resulting in an additional 60 inpatient days.

**Conclusions:** The frequency and cost of gout is underestimated in the acute hospital setting. The true cost of acute hospital management is likely to be 3 to 4 fold that estimated by HES data. Our data show an annual cost of £216000 for our hospital catchment population of 320000. Our results also demonstrate that only a minority of patients
were managed with urate lowering treatment and that 97.5% were not treated to target. Appropriate community and hospital management could result in major cost savings to the NHS.

Disclosures: The authors have declared no conflicts of interest.

32. RISK FACTORS FOR HYPERURICAEMIA AMONG A LARGE COHORT OF HIV-INFECTED MEN
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Background: HIV is a global pandemic with approximately 90,000 adults infected in the UK. Combination anti-retroviral therapy (cART) has transformed HIV prognosis but led to increasing numbers of ageing patients with HIV. Increasingly, non-AIDS morbidities have been described including hyperlipidaemia, insulin resistance and diabetes mellitus, and since hyperuricaemia is associated with these other manifestations of the metabolic syndrome, gout may become an increasing problem in longstanding HIV-infected patients. We undertook a survey of the prevalence of hyperuricaemia and explored its association with traditional risk factors and HIV factors.

Methods: A random sample of HIV-infected men was invited to a longitudinal cohort study 2009–10. All participants attended for a detailed baseline visit including a questionnaire which enquired about demographic factors, medication, diet and exercise, and measured anthropometry and blood pressure. Patients gave consent for addition of their data to a longitudinal database for HIV parameters including stage of HIV infection, CD4 count, viral load, duration since diagnosis, current cART. Subjects gave a blood sample for assessment of urate.

Results: 432 participants were recruited, mean age 48 years (range 20-89 years). Most (85%) were Caucasian and most were infected by sexual transmission, predominantly between men. 91% were currently taking cART. 5% reported excess alcohol intake and 24% were current smokers at 10/day.

A median urate was 0.33 mmol/l for this population (range 0.02–0.64). In total, 371/432 had a serum urate >0.42 leaving 61 (14%) with hyperuricaemia according to the local lab reference values. Those with hyperuricaemia tended to be older (50 years vs 48 years) (NSI) and had significantly greater BMI (p=0.0001). Analysed as a continuous variable in tertiles of urate (low <0.31, medium 0.31–0.37, high >0.37), univariate analyses showed that urate was significantly associated with BMI, systolic BP, diastolic BP, hyperlipidaemia and self reported kidney disease. Urate was not associated with current CD4 count, nadir CD4 count or stage of HIV infection. In total, 53 patients had a detectable viral load and increasing viral load was negatively associated with urate. Pro tease inhibitors and Ritonavir use currently were associated with higher serum urate but patients taking Atripla had statistically significantly lower urate levels.

Conclusions: In this large cohort of HIV infected men, 14% had hyperuricaemia. Urate was associated with traditional risk factors including BMI, renal disease and blood pressure. However, patients taking cART had an increased risk of higher urate levels and protease inhibitors appeared to convey that increased risk. It is interesting that protease inhibitors, already implicated as a cause of metabolic syndrome in HIV patients, were significantly associated with urate. Rheumatologists may see more gout in HIV infected adults taking cART.

Disclosures: The authors have declared no conflicts of interest.

33. EFFECT OF PEGLOTICASE ON RENAL FUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE
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Background: Pegloticase is approved in the USA for the treatment of refractory chronic gout (RCG). Chronic kidney disease (CKD) is common in patients with gout; 49% of patients enrolled in replicate phase III clinical trials of pegloticase had stage 3–4 CKD as defined by the National Kidney Foundation. As CKD can impact the use of uric acid-lowering therapies, we retrospectively analysed data pooled from the phase III trials to determine the effects of pegloticase on renal function and the effects of renal dysfunction on pegloticase safety.

Methods: 212 patients were enrolled in the phase III trials and received at least 1 infusion of pegloticase. 103 of the 212 patients had stage 3–4 CKD at baseline and were randomized to pegloticase 8 mg q2Weeks (n = 42), q4weeks (n = 41), or placebo (n = 29) for 6 months.

Renal function was assessed by estimated glomerular filtration rate (eGFR, ml/min/1.73 m²) using the 4-variable Modification of Diet in Renal Disease formula at screening (week 0) and weeks 7, 13, 19, and 25 post-randomization. Linear mixed effects (random intercept) model was used to analyse eGFR. Treatment, time, treatment X time interaction: P = 0.28, independent of age, sex, or race. More than one-third of patients in all groups had either no change or an improvement in renal function during the 25-week randomized treatment phase, and approximately one-half of patients in all groups had no more than a 10% decline in renal function. As was reported for the full pooled trial population, the most common adverse events in the CKD cohort were gout flares and infusion reactions.

Conclusions: Patients with RCG and stage 3–4 CKD had no changes in renal function with up to 6 months of pegloticase therapy. There were no differences in the pegloticase safety profile based on renal function.

34. AUDIT OF ARMA 2012 STANDARDS OF CARE FOR PEOPLE WITH GOUT IN PRIMARY CARE IN EDINBURGH AND THE LOITHANS
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Background: The Arthritis and Musculoskeletal Alliance (ARMA) has recently published Standards of Care for People with Gout, 5 years after publication of EURAr and BSR guidelines. An audit of current care in general practices in Edinburgh and the Lothians has been undertaken using audit criteria based on the 2012 ARMA Standards.

Methods: An online questionnaire was emailed to 712 General Practitioners. A separate postal questionnaire was sent to 282 patients with gout from 79 practices, many of whom had participated in a gout management audit in 2008. Serum urate (SUA) measurements were captured from SCI store eHealth Record.

Results: Questionnaires were completed by 109 (15%) GPs and 145 (51%) patients, 36% of whom had been referred to rheumatology. Confirmation of diagnosis by crystal identification had been undertaken in 21% of patients but was never sought by 28% of GPs. Patients were frequently assessed for some complications and comorbidities (renal function 93%, tophi 73%, hypertension 81%) but less often for others (obesity 69%, hypercholesterolaemia 57%, diabetes mellitus 56%, ischaemic heart disease 48%, OA 44%) and monitoring of any comorbidity with annual checks had only been undertaken in 65%. Obesity (BMI >30) was a comorbidity in 43% of patients but lifestyle modification advice was given in only 50–70%.

Urate lowering therapy (ULT) was prescribed in >80% of patients (allopurinol 94%) but only 56% were offered flare prophylaxis. The SUA was >360 μmol/l in 42% and >300 μmol/l in 72% with a mean dose of allopurinol >300 mg/day in these subjects, but follow up SUA was only measured in 28%. Treatment to a target SUA was the stated aim by 68% of GPs (>300 μmol/l 36%, >360 μmol/l 30%) although only 5 worked in practices with a formal pathway of care. While most GPs had received undergraduate and postgraduate teaching relating to the diagnosis and management of gout, only 39% reported any training in the last 5 years and only 10% and 37% % were aware of the EURAr and BSR guidelines. Patient education was inadequate. While 88% of patients reported receiving explanation of the causes and treatment of gout only 43% were given written information, 40% were unaware that commencement of treatment with ULTs could be associated with gout.
35. HIGH POSITIVE ANTIBODY STATUS IS ASSOCIATED WITH INCREASED MORTALITY IN PATIENTS WITH EARLY INFLAMMATORY ARTHRITIS: RESULTS FROM THE NORFOLK ARTHRITIS REGISTER

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Background: Mortality is increased in RA and this may be partially marked in patients who are rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) positive. We have previously shown that patients with early inflammatory arthritis (EIA) who fulfil the 2010 ACR/EULAR classification criteria for RA have increased mortality compared with those who do not. Within the 2010 criteria, RF and ACPA positive patients are assigned a different weighting depending on whether the titre is low or high, suggesting they may have a differential prognosis. The aims of this study was to examine whether, in a cohort of patients with EIA, patients with low and high positive serology have increased mortality compared with (i) the general population and (ii) patients with EIA who are seronegative.

Methods: Adults with ≥2 swollen joints for ≥4 weeks were recruited to the Norfolk Arthritis Register (NOAR) between 1990 and 2009. Patients included in this analysis had symptom duration <2 years and had not received disease modifying therapy at initial assessment. At baseline visit patients were assessed by a nurse who performed a 51 joint examination and took blood samples for RF and ACPA estimation. All patients registered with NOAR are flagged with the Office for National Statistics (ONS) who provide mortality data. Deaths prior to 31st December 2010 were included. Standardized mortality ratios (SMR, 95% CI) were calculated for all patients with ≥7 years follow up using age and sex matched death rates for the Norfolk population as the comparator. Survival analyses were performed using Cox proportional hazards models univariately, and a multivariate model was developed including all components of the 2010 criteria as well as baseline smoking status, age and gender. Results are shown as hazard ratio (HR, 95% CI).

Results: 1643 patients had complete data for analysis, 1074 (65%) were female, median age at symptom onset 55 years. At baseline, 892 (54%) patients fulfilled the 2010 criteria. 466 deaths were reported by ONS during 2011 person-years follow up. Patients with high positive serology (≥3 times the upper limit of normal), had increased rates of death compared with the general population (SMR 1.77, 95% CI 1.52, 2.30), but not low positive (SMR 1.17, 95% CI 0.70, 2.09) or negative serology (SMR 1.07, 95% CI 0.89, 1.30). In the multivariate Cox proportional models high positive serology predicted early death compared with seronegative patients (HR 1.71, 95% CI 1.32, 2.20); there was no association with low positive serology (HR 0.85, 95% CI 0.55, 1.71).

Conclusions: In patients presenting with EIA, those with high positive RF or ACPA have increased risk of mortality compared with both the general population and to seronegative EIA patients. High seropositivity may be important in predicting long term outcomes in patients with EIA.

Disclosures: The authors have declared no conflicts of interest.

36. THE FALLING PREVALENCE OF EROSIVE DISEASE IN RHEUMATOID ARTHRITIS: A CLINICAL EXPERIENCE

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Background: Rheumatoid arthritis (RA) is a chronic progressive inflammatory arthritides characterized by the development of joint erosions with subsequent joint damage, deformity and potential disability. Historically, the prevalence of erosive disease at diagnosis reported in the literature ranges from 48–83% and data from as recently as 2009 suggest that erosive disease at presentation still remains significant within the UK population. Our clinical impression is slightly different.

Since 2009, at University Hospitals of Bristol (UHB) we have had a standardized pathway to manage newly diagnosed RA patients. All patients must fulfil 1987 ACR classification criteria for RA following which they are stratified into a moderate or severe arm dependent on their baseline level of disease activity. Treatment commences with the ARC regimen or COBRA regimen respectively. Inclusion criteria for the two arms are the same as those in the original studies.

Methods: 115 consecutive patients enrolled onto our RA pathway were included in our analysis. Demographics were obtained by review of patient notes. Baseline X-rays of hands and feet were reviewed by a musculoskeletal radiologist and by a rheumatologist. For the purposes of this study patients were grouped according to the presence or absence of erosions. Results were compared with data from the original ARC and COBRA studies.

Results: Only 11% of our patients (12/115) had erosive disease at presentation compared with 31% in the ARC study (n = 128) (P < 0.05). Disease duration (months) did differ between the two groups (ARC study 15.7 vs 7.8 at UHB) although this is unlikely to fully account for the significant difference in erosions. There was a statistically significant difference in rheumatoid factor (RF) positivity (51% at UHB vs 70% in ARC study) when baseline demographics were compared.

4% of patients (1/24) with severe disease at UHB had erosive disease at baseline compared with 77% of patients in the COBRA study (n = 155). Patients in the COBRA study had a shorter median disease duration compared with our patient population (4.0 months vs 4.8 months). There was no difference in RF positivity between the two groups (P > 0.01).

Patients in our pathway were also significantly older than those in both the ARC and COBRA studies [mean age (6±9) in years 58.4 (±13.6) at UHB vs 49.2 (±10.1) in ARC study].

Conclusions: Our study suggests that the presence of erosive disease in RA at presentation has significantly decreased over the last 15 years and this change cannot be fully accounted for by earlier diagnosis. The average age at diagnosis also appears to have risen and both may suggest a general change in the classic phenotype of RA.

Disclosures: The authors have declared no conflicts of interest.

37. THE IMPACT OF RHEUMATOID ARTHRITIS ON QUALITY OF LIFE ASSESSED USING THE SF-36: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: We have demonstrated in a previous systematic review that RA uniquely impacts on all aspects of quality of life (QoL), with detrimental effects observed in all 8 health domains of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). The recent shift in the paradigm of RA management towards early combination therapies may have altered the impact of RA on QoL. We therefore performed an updated systematic review examining the impact of RA on QoL measured using the SF-36.

Methods: Medline and Embase were searched using the terms RA or RA and quality of life or SF-36. Observational studies were included that reported mean and standard deviation scores for all SF-36 domains in RA patients. Domain scores across studies were combined within a meta-analysis to provide summary scores for each domain.
38. SEROLOGICAL STATUS: A ROLE IN PERSONALIZED MEDICINE FOR RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a heterogenous disease with diverse outcomes. Serological status such as rheumatoid factor (RF) and anti-citrullinated peptide antibody (anti-CCP) positivity are associated with poorer outcomes. Early intensive treatment regimes aiming at achieving remission have shown to reduce disease activity, structural damage and long-term disability. However, it is currently unclear whether all patients should receive the same intensive regimes.

We aimed to investigate the use of serological status as predictors for the need for intensive therapy to induce remission.

Methods: We analysed samples from a published randomized controlled trial (CARDERA study) which compared four treatment regimes in patients with early active RA (disease duration <2 years): MTX monotherapy, double therapy (MTX + ciclosporin or prednisolone), and triple therapy. The triple tone arm received 467 patients; 66% female and their median age was 54 years. Disease activity was assessed using the DAS28. Remission was defined as DAS28 <28 at 12 months. Rheumatoid Factor isotypes (RF IgM and IgA) and ACPA levels were measured using commercial ELISA kits. Statistical analysis used Pearson’s chi-squared test.

Results: 86% was positive for RF IgM, 74% for RF IgA and 74% for ACPA. We further sub-grouped patients into low antibody levels (<3 times upper limit of normal, ULN) and high antibody levels (>3x ULN), 81%, 64% and 68% patient had high levels of RF IgM, RF IgA and ACPA respectively. 355 (76%) of the patients had full datasets at 12 months and analyses were restricted to this group. 75 patients (21%) achieved remission at 24 months. In RF IgM negative patients, the proportions achieving remission at 24 months were similar in all treatment groups (22%-30%). In patients with high RF IgM levels, fewer patients achieved remission with monotherapy (17%) and double (17%) therapy compared with triple therapy (34%) (P = 0.001). There were similar and consistent findings with RF IgA and ACPA serological status. Significantly more patients with high antibody levels achieved remission using triple therapy than monotherapy.

Conclusions: Contemporary treatment of RA emphasize on the use of intensive therapy to achieve remission. However, our study suggests that not all patients require such an aggressive approach to therapy. Given the heterogeneity of this disease, ACPA status should be personalized to the individual. This would minimize costs of treatment as well as potentially toxic side-effects. Our study suggests that only patients who are strongly seropositive should be considered for more intensive therapies.

Disclosures: The authors have declared no conflicts of interest.

39. RHEUMATOID FACTOR IGA AND ANTI-CYClical CITRULLINATED PEPTIDE ANTIBODIES: PREDICTORS OF RADIOGRAPHIC PROGRESSION

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Background: There is a continual need to identify biomarkers to predict poor outcomes in RA. Ongoing radiographic damage is associated with increased disability and high disease activity and therefore it is one of the main measures of poor outcome. The role of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) as predictors of radiographic progression has been studied extensively. However, few studies have investigated the specific isotypes.

Methods: The CARDERA trial (Combination Anti-Rheumatic Drugs in Early RA) was a randomized double blind factorial trial, studying the benefits of various combination therapies. Patients selected had active RA, (88% female, mean age 54 years). 467 baseline serum samples were analysed for RF isotypes and anti-CCP2 using commercial kits, (Euroimmun and Axis Shield respectively). Univariate and multivariate linear regression modelling were used to assess the relationship between RF isotypes and ACPA status and radiographic progression (defined as increase in Larsen Score).

Results: In total, 86% of patients were RF IgM positive, 71% RF IgA positive, 19% RF IgG positive and 71% ACPA positive. In patients who showed no X ray progression at 12 months, 61% RF IgM negative, 54% RF IgA negative, 17% RF IgG negative and 53% ACPA negative. Upon univariate linear regression analyses, RF IgM, RF IgA and ACPA positivity were all significant predictors of radiographic progression at 12 months (β=2.019, β=1.975 and β=1.587, respectively, P-values=0.006 to 0.03). RF IgG positivity was not a significant predictor (Table 1). Upon multivariate regression analysis, with adjustment for potential confounding factors including baseline Larsen score, ESR, Assessor Global Assessment (AGA) score, DAS28 and steroid therapy, RF IgA and ACPA positivity were still significant independent predictors of radiographic progression (β=1.667 95% CI 0.265, 3.070, P=0.02 and β=1.389 95% CI 0.001, 2.778, P=0.05, respectively). However, baseline RF IgM positivity was no longer a significant independent predictor.

Conclusions: Our study found that baseline RF IgA positivity and anti-CCP positivity were significant independent predictors of an increased Larsen score after 12 months. Since baseline RF IgM status was not a significant independent predictor, its use within a disease prediction model may be limited.

Table 1. Increase in Larsen score at 12 months

<table>
<thead>
<tr>
<th>Baseline clinical variables</th>
<th>β Coefficient</th>
<th>95% CI upper</th>
<th>95% CI lower</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF IgM+</td>
<td>2.019</td>
<td>3.848</td>
<td>0.192</td>
<td>0.030</td>
</tr>
<tr>
<td>RF IgA+</td>
<td>1.975</td>
<td>3.371</td>
<td>0.079</td>
<td>0.006</td>
</tr>
<tr>
<td>RF IgG+</td>
<td>0.735</td>
<td>2.355</td>
<td>-0.885</td>
<td>0.373</td>
</tr>
<tr>
<td>ACPA+</td>
<td>1.587</td>
<td>2.996</td>
<td>0.178</td>
<td>0.023</td>
</tr>
<tr>
<td>Larsen score</td>
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<td>0.065</td>
<td>-0.016</td>
<td>0.233</td>
</tr>
<tr>
<td>ESR</td>
<td>0.056</td>
<td>0.077</td>
<td>0.036</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AGA</td>
<td>0.040</td>
<td>0.074</td>
<td>0.017</td>
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</tr>
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<td>DAS28</td>
<td>0.783</td>
<td>1.268</td>
<td>0.300</td>
<td>0.002</td>
</tr>
<tr>
<td>Steroid treatment</td>
<td>-2.041</td>
<td>-0.793</td>
<td>-3.288</td>
<td>0.001</td>
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</tbody>
</table>

Disclosures: The authors have declared no conflicts of interest.

40. SHOULD THERE BE DIFFERENT DISEASE ACTIVITY CRITERIA FOR ASSESSMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS ACCORDING TO ETHNIC BACKGROUND?

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Background: Previous studies on RA features between different ethnic groups have mainly focused on disability and DASs, structural damage, genetic factors and health inequalities. However, data on RA joint involvement according to ethnicity are scarce. We investigated joint involvement distribution and other clinical features in a cohort of ethnically diverse patients with RA.

Methods: We included patients with active RA who previously failed to respond to 2 biologic DMARDs, including MTX and were being considered for TNFi therapy between 2001 and 2012. Data collected included tender joint counts (TJC), swollen joint counts (SJC), inflammatory markers, visual analogue scale (VAS) and DAS28 score. We examined the joint involvement distribution and other clinical manifestations by race, classified as Caucasian, Asian, Afro-Caribbean (AC), and other/mixed race, with the Caucasian group serving as the referent.

Results: The study sample included 401 patients with active RA. Of these, 266 (66%) were Caucasian, 88 (22%) Asian and 28 (7%) Afro-Caribbean, and 19 (5%) were other/mixed race. Compared with Asians, Caucasians were older (62 vs 53 years, respectively; P < 0.001) and heavier (76 vs 67 kg, respectively; P < 0.001). Compared with Caucasians, Asians had a higher ESR (42 and 36, respectively; P = 0.04), which was confirmed after controlling for age, weight, SJC, TJC and smoking (β 11.74; P = 0.003); and a lower CRP (26.8 vs 30; P = 0.6). The overall DAS score was also slightly higher in Asians compared with Caucasian (6.63 vs 6.39; P = 0.09). There were no significant differences with regards to other DAS28 components (i.e. VAS, TJC, SJC). Compared with Caucasians, AC had a higher ESR (47 vs 41, respectively; P = 0.04), which was confirmed after adjusting for age, weight, SJC, TJC and smoking (β 10.9; P = 0.05), and slightly higher CRP (32.4 vs 30; P = 0.5). There were no significant differences with regards to age, VAS, TJC, SJC or DAS28.PIP involvement (presence of swelling or both tenderness and swelling of any PIP joint) was more common in Caucasians than in Asians (84% vs 71%, respectively; P = 0.006), and AC patients (84% vs 64%, respectively; P = 0.01), with right PIP involvement more commonly seen among Caucasians (63% vs 53%; P = 0.006) and 70% vs 54%; P = 0.001). There were no differences with regards to other joint involvement distribution.

Conclusions: Our results show that Caucasian patients with active RA are more likely to have PIP involvement than Asian and AC patients, but with a similar distribution of other joint involvement. In contrast, Asian and AC patients are more likely to have a higher ESR than Caucasians, in line with previous studies. Our data provide further evidence for ethnic variation in ESR, independent of joint involvement. In contrast to previous studies no differences in tender and swollen joint counts and VAS scores were observed.

Disclosures: The authors have declared no conflicts of interest.

41. CAN RADIOGRAPHIC SCORES OF HANDS AND FEET IN THE FIRST THREE YEARS OF RA PREDICT EVENTUAL NEED FOR ORTHOPAEDIC SURGERY OF HAND AND FOOT JOINTS? RESULTS FROM A LONG-TERM INCEPTION COHORT

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Background: The need for hand and foot surgery in Rheumatoid Arthritis (RA) is the result of failed medical treatment and a surrogate marker for joint destruction. Prognostic markers are currently limited but have a potential role in guiding clinicians in early management decisions. This group has previously reported on the value of standard clinical and laboratory measures for predicting joint surgery in RA. This study examines a subset of this cohort with damage scores of hands and feet (Larsen).

Methods: Standard clinical and laboratory measures, and X-rays of hands and feet, were performed at baseline, prior to DMARD therapy, and then yearly in the Early RA Study (ERAS, n = 1465, 1986–1998, median follow up 10years). Treatment of patients included disease modifying, steroid and biologic therapies according to standard UK practices for management of hospital based RA patients. Larsen scoring was performed in a subset (n = 1186) to include wrists, MCP, PIP and MTP joints. Source data of orthopaedic interventions included patient report and medical records, Hospital Episode Statistics (HES) and the National Joint Registry. Larsen follow up was based on the National Death Registry. Joint surgery of hands and feet included synovectomies, arthroplasties and fusion.

Results: Larsen scores of hands and feet at 0, 1, 2, 3 years were available in 1146 patients, as a total score, and 3 subtotal scores of wrists, MCP and PIP, and MTP joints. Joint surgery was performed in a total of 553 patients (38%), of whom 153 had surgery of a wrist, hand or foot joint for RA, at a median of 10, 7 and 8.8 years respectively. Using the first 3 years of Larsen scores, ROC analysis was performed to identify suitable cut-off points of total and subtotal scores to predict surgery of the hands and feet. A Cox regression model with competing risk, and controlling for age at disease onset, sex and baseline disease activity indicated that having a Larsen score >= 10 within the first 3 years increased the risk of hand or foot surgery by more than 2-fold (SHR = 2.58, P = 1.63, 4.08). Results for specific joints were more positive: wrist (SHR 2.67, P = 0.001, 95% CI 1.46, 4.83), MCP/IP (SHR = 2.77, P = 0.003, CI 1.43, 5.38), MTP (SHR = 2.98, P < 0.001, CI 1.58, 5.62). The differences in cumulative hazard between the total, and each domain Larsen score (based on ROC) with eventual need for hand/foot surgery will be displayed graphically.

Conclusions: Orthopaedic surgery is an important and common outcome reflecting structural joint damage in RA, it is not often reported and is difficult to predict. Larsen scores in first 3 years of RA add predictive value for eventual need for hand and foot surgery.

Disclosures: The authors have declared no conflicts of interest.

42. ETHNIC AND SMOKING VARIATIONS IN EARLY RHEUMATOID ARTHRITIS: EXPERIENCE FROM A LARGE SECONDARY CARE CENTRE

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Background: Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by a symmetrical polyarthritis. Early diagnosis and treatment of the disease results in earlier clinical improvement and less progression of joint damage. Racial differences in health-related attitudes of patients have been alluded to in a variety of chronic diseases including RA. Previous studies have also implicated cigarette smoking as an independent risk factor in RA, particularly increasing the risk of anti-cyclic-citrullinated peptide (CCP) antibodies in certain patient groups.

Methods: A retrospective audit of 118 patients on the Early Arthritis database at Northwick Park Hospital between 2009 and 2012. We elicited a variety of parameters including ethnicity, time from symptom onset to secondary care presentation, antibody status, DAS28 score at presentation and 1 year together with smoking history. We assayed anti-CCP antibodies using the anti-mutated citrullinated vimentin (anti-MCV) antibody ELISA assay (OriGene).

Results: In total 118 patients were identified of which 109 belonged to 3 major ethnic groups: Asian (54), white (43) and black (12). There were 14 smokers, 15 ex-smokers and 89 patients who had never smoked. Statistical analysis was by ANOVA (Sofa software).

Mean time from disease onset to presentation to a rheumatologist was 7.04 months for Asians, 7.58 months for whites and 7.75 months for black patients (P = ns). Mean DAS28 at presentation was 6.37 for black patients vs 5.71 for Asians and 5.14 for whites. Mean DAS28 at 12 months was 4.18 for black, 3.17 for Asians and 2.65 for white patients (P = 0.013).

A lower proportion of smokers were positive for anti-CCP antibodies (9/14, 64%) as compared with ex-smokers (10/15, 67%) and non-smokers (66/94, 70%) (P = 0.065 χ²). Smokers also had lower anticyclic and anti-CCP antibodies compared with non-smokers (5.3% vs 0.6% P = 0.17 and again at 12 months (2.24% vs 2.98% vs 3.33% P = 0.20).

Conclusions: Our results suggest that there is a prolonged delay in presentation of early RA amongst all ethnic groups but particularly so in black patients. We also found that black patients had more aggressive disease both at presentation and at the end of year 1 of treatment. This may reflect genetic variations, delayed interaction with primary care or indeed differing attitudes towards disease and early aggressive therapy.

In contrast to previous investigators we found smokers and ex-smokers had less aggressive disease with a lower incidence of anti-CCP antibodies compared with non-smokers. As yet we are unable to explain these results and suggest correlation with earlier arthritis data from other centres.

Further work is required to investigate genetic susceptibility to RA across ethnicities as well as evaluating differences in attitudes to both patients and doctors towards disease symptoms and treatment.

Disclosures: The authors have declared no conflicts of interest.
43. COMORBIDITY AND OBESITY ARE INDEPENDENTLY ASSOCIATED WITH FAILURE TO ACHIEVE REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Clinical remission is increasingly the target for treatment in RA. The majority of studies examining remission in RA are within clinical trials, rather than in patients treated in routine clinical practice. The aim of this study was to examine the prevalence of and clinical factors associated with remission in a cohort of established RA patients on conventional (non biologic) therapy.

Methods: Data were derived from an existing longitudinal RA cohort followed up for 3 years. Patients had an annual research assessment; with their treatment at the rheumatologists discretion. Data collected included; demographics (age, disease duration, gender, BMI), rheumatoid factor (RF), and disease activity (DAS28). Comorbidity was measured using the age adjusted Charlson score (1). Remission was defined as a DAS28 of <2.6. Comparison of clinical and demographic factors according to remission status was carried out using Student’s t or Mann–Whitney U-tests and logistic regression.

Results: 345 RA patients were included in the study with a mean (s.d.) age of 62 (11) years and mean (s.d.) disease duration of 10.3 (9.6) years. 237 (69%) were female). At baseline the mean (s.d.) DAS28 was 4.08 (1.34), with men having a significantly lower DAS28 score than women (3.83 (1.36) vs female 4.19 (1.31), P = 0.019). The prevalence of remission was low: 46/345 (13.3%) at baseline, 47/307 (15.3%) at 1 year, 56/299 (18.7%) at 2 years and 50/249 (20.1%) at 3 years. Patients ever achieving remission had a lower age adjusted Charlson score compared with those never achieving remission, (median age adjusted Charlson score 2, IQR 1–3 vs never-remission median age adjusted Charlson score 3, IQR 2–4, P = 0.0002). Patients achieving sustained remission over the first 2 years had the lowest age adjusted Charlson score (1.5, IQR 0.25–2). No relationship was found between BMI and remission status at baseline, but obese patients (BMI of >30) were less likely to achieve remission within 1 year of baseline than non-obese patients (3.0% vs 13.0%, OR 0.09, 95% CI 0.02, 0.99). Logistic regression analysis revealed that obesity and the presence of comorbidity were independently associated with a failure to achieve remission by any point during the 3-year follow up. Greater age, female sex and RF positivity was also significantly associated with a greater likelihood of failure to achieve remission.

Conclusions: RA patients with obesity or comorbid disease are less likely to achieve remission than non-obese patients or those without comorbidity. Patients with the greatest comorbidity burden are the least likely to achieve remission. These data suggest that RA remission can be significantly influenced by clinical factors other than those usually included in the rheumatoid disease process.

Disclosures: The authors have declared no conflicts of interest.

44. CLINICAL, IMAGING AND HISTOLOGICAL CHARACTERISTICS OF PATIENTS WITH RHEUMATOID ARTHRITIS AT DIFFERENT STAGES OF DISEASE PROGRESSION

Nora Ng1, Frances Humby1, Michele Bombardieri1, Stephen Kelly1, Maria Di Cicco1, Sabrina Dadoun1, Rebecca Hands1, Vidalba Rocher1, Bruce Kidd2, Dev Pyne3 and Costantino Pitzalis4
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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease whose pathogenesis and response to therapy may differ at different disease stages. While an immune-mediated inflammation may drive early disease, at late stages, a stromal reaction may prevail. Consequently tailored therapy within any phase of the disease requires better appreciation of both clinical, imaging and histopathological phenotypes. In this study we investigate these three features in three distinct groups of patients during their course of disease modeled on treatment escalation at different time points during disease evolution.

Methods: Data were collected from 54 RA patients from three stages of disease evolution and treatment, (i) early RA cohort (EAC), n = 20 (onset <1 year and DMARD naive), (ii) DMARD inadequate responders (DMARDir), n = 20 (failed ≥2 DMARDS and fulfilling criteria to start anti-TNF) and (iii) anti-TNF inadequate responders (TNFir), n = 14 (failed ≥1 anti-TNF and switching to different biologic).

Prior to commencing or changing therapy, all patients had a core data set assessment including clinical, biochemical, imaging (including US of 10MCPJ + 2 wrists) and an US guided synovial biopsy of a symptomatic joint.

Results: Mean disease duration of each cohort was 0.5 years (EAC), 6.9 years (DMARDir) and 15.2 years (TNFir). The number of previous DMARD in each of the groups varied significantly—EAC (0), DMARDir (mean 1.6) and TNFir (mean 2.1). About a third of patients in both the DMARDir and TNFir group were receiving concomitant steroid therapy (30%) and 35.6% respectively. DAS28 were similar between groups (P = 0.38) and as expected, there were significant differences between each cohort in terms of disability with TNFir patients having a higher HAQ score (P < 0.001). Rheumatoid factor and anti-CCP positivity were more prevalent in the DMARDir and TNFir cohorts (P < 0.001).

The TNFir and DMARDir cohort showed a significant difference in the presence of radiographic erosions (P < 0.001) compared with EAC. US showed no significant difference in grey scale synovitis (P = 0.78) but marked differences in the power Doppler signal between all groups (P = 0.036).

Histological grading was significantly different between groups (P < 0.04), with 64% of TNFir group having a diffuse histological pattern. Lower levels of T cells (P < 0.04) and B cells (P = 0.02) were also noted in this group. The synovitis score did not differ significantly between groups (P = 0.17).

Conclusions: We have described a number of clinical, imaging and histological differences in RA patients at different stages of disease evolution. This may facilitate better patient stratification and may inform treatment decisions if shown to be prognostic. However, it remains unclear whether these characteristics represent the natural disease progression or are related to therapeutic intervention. Further prospective studies are required to answer this important question.

Disclosures: The authors have declared no conflicts of interest.

45. SHOULD WE CONTINUE TO GROUP ALL SEROPOSITIVE RA PATIENTS TOGETHER? A VERY STRONGLY POSITIVE ANTI-CCP IN THE PRESENCE OF A NEGATIVE/WEAKLY POSITIVE RF: A SEROLOGICAL PERMUTATION WITH AN ATYPICAL CLINICAL PRESENTATION?

Sophie Poore1 and David Hutchinson1
1Rheumatology Department, Royal Cornwall Hospital, Truro, UK

Background: RA has been viewed for many years as a heterogeneous collection of rheumatic diseases. Previously rheumatoid factor (RF) positive and negative patients were regarded as distinct clinical subtypes. Additionally, within seropositive RA those with very strongly positive RF levels were also thought to have a characteristic disease process. The addition of anti-citrullinated protein antibody (anti-CCP) testing has led to a distinction between anti-CCP positive and negative patients. However, no studies have compared the clinical presentation of RA patients with very strongly positive anti-CCP levels associated with a negative or low-positive RF levels with those RA patients with a very strongly positive RF. The objective of this study was to assess the clinical presentation and demographics of RA patients with very strongly-positive anti-CCP levels (>170 IU) in the presence of a negative or low-positive RF (≤30 IU) compared with patients with a very strongly-positive RF (≥300 IU).

Methods: A retrospective study included 64, outpatient-based, RA patients with a disease duration ≤5 years. A negative or low-positive RF associated with very strongly positive anti-CCP levels (arbitrarily >10 fold higher than the upper normal limit (UNL) 0–17, i.e. >170 IU) was present in 22 patients, this group represented the ‘cases’ and will be referred to as the ‘discoidant antibody group’. 42 ‘controls’ were selected from patients with a very strongly-positive RF levels (arbitrarily >30 fold higher than the UNL 0–30, i.e. >300 IU). Data were collected through analysis of clinic letters and a serologically blinded telephone questionnaire. Patients with a personal or family history of psoriasis were excluded.

Results: Demographics: There was a significantly increased prevalence of females in the discordant antibody group (82% vs 45%) P = 0.005
Clinical features: Palindromic rheumatism was significantly more likely to precede the diagnosis of RA in the discordant antibody group [8 of 22 (36.4%) compared with the strongly-positive RF group [1 of 22 (4.5%)]. An asymmetrical onset was significantly more likely in the discordant antibodies group [15 of 22 (68.2%) vs 14 of 42 (33.3%)]. P = 0.008. There was a significantly increased prevalence of large joint involvement in the discordant antibody group [16 of 22 (72.7%) vs 15 of 42 (35.5%)]. P<0.005. Large and small joints were defined according to 2010 ACR-EULAR criteria.

Conclusions: Patients with very strongly-positive anti-CCP levels associated with a negative or low-positive RF levels were significantly more likely to be female and likely to have a palindromic type presentation. Large joint and an asymmetrical presentation were also significantly more prevalent in this group and further studies are required to determine whether this group is a new and distinct subtype of RA.

Disclosures: The authors have declared no conflicts of interest.

RHEUMATOID ARTHRITIS: COMORBIDITIES

46. ASSOCIATION OF ANTI-TNF THERAPY AND THE RISK OF ISCHAEMIC STROKE IN SUBJECTS WITH RHEUMATOID ARTHRITIS: RESULTS FROM THE BSRBR-RA

Audrey Low1, Mark Lunt1, Louise Mercer1, James Galloway2, Rebecca Davies1, Kath Watson1, British Society for Rheumatology Biologics Register Control Centre Consortium1, Will Dixon1, Deborah Symmons1,3 and Kimme Hyrich1 on behalf of the British Society for Rheumatology Biologics Registers

1Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, University of Manchester, Manchester, 2Academic Department of Rheumatology, King’s College London, London and 3NHRI, Manchester Musculoskeletal Biomedical Research Unit, Manchester, UK

Background: Subjects with RA are at increased risk of stroke (CVA). Anti-TNF therapy may influence this risk, potentially by reducing inflammation. The aim of the analysis was to study the association of anti-TNF therapy with ischaemic CVA (isCVA) in routine clinical practice.

Methods: The BSRBR-RA is an ongoing national prospective cohort study. Subjects with RA starting anti-TNF therapy (etanercept, infliximab, adalimumab) and a biologic-naıve comparator cohort treated with non-biologic drugs (nbDMARDs) were recruited from 2001–2008. All were followed by clinician and patient questionnaires 6-monthly for 3 years and annual clinician questionnaires thereafter, and also linked to the national death register. Subjects with prior CVA were excluded from this analysis. Incident CVA’s reported from questionnaires and death certificates were validated against the World Health Organization criteria for CVA and further classified as isCVA using CT brain reports or if isCVA was reported as the underlying cause of death using International Classification of Diseases 10 code I63. Subjects were censored at incident isCVA, death, last of clinician follow-up or 31/10/2010, whichever came first. Risk of isCVA was compared between the nbDMARD cohort and subjects ever exposed to anti-TNF using Cox regression, adjusted using propensity scores stratified by deciles (PD). All-cause mortality at 30 days and 1 year post-isCVA was compared between nbDMARD and anti-TNF cohorts using multivariate logistic regression (MVLR). Confounders in PD and MVLR were age, gender, RA-related factors, comorbidities and drugs (Table 1).

Results: 130 verified incident isCVA occurred: 21 in 3271 nbDMARD subjects, 109 in 11642 anti-TNF subjects (175 vs 178 per 100 000 person-years respectively; Table 1). After adjustment using PD, there was no association between ever exposure to anti-TNF and isCVA risk: hazard ratio (HR) 0.88 (95% CI 0.46, 1.71). Exposure to anti-TNF therapy was not associated with 30-day or 1-year mortality post-isCVA: adjusted odds ratio (OR) 1.41 (95% CI 0.18, 11.05) and OR 1.28 (95% CI 0.22, 7.56) respectively.

Conclusions: No association between ever-exposure to anti-TNF therapy and risk of isCVA or mortality post-isCVA was observed when compared with nbDMARD therapy in routine UK clinical practice.

TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>nbDMARD</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>60 (12)</td>
<td>56 (12)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2420 (74)</td>
<td>2420 (74)</td>
</tr>
<tr>
<td>Disease duration, median (IQR), years</td>
<td>6 (1–15)</td>
<td>11 (6–19)</td>
</tr>
<tr>
<td>DAS28, mean (s.d.)</td>
<td>5.3 (1.1)</td>
<td>6.6 (1.0)</td>
</tr>
<tr>
<td>HAQ, mean (s.d.)</td>
<td>1.5 (0.7)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>Years of follow-up per subject, median (IQR)</td>
<td>4 (2–5)</td>
<td>5 (4–7)</td>
</tr>
<tr>
<td>Risk of isCVA: PD-adjusted* HR (95% CI)</td>
<td>Referent 0.88 (0.46, 1.71)</td>
<td>Referent 0.89 (0.45, 1.76)</td>
</tr>
</tbody>
</table>

*Variables in PD and logistic regression: age, gender, disease duration, DAS28, mean (s.d.), number of previous nbDMARDs, entry year to study, hypertension, ischaemic heart disease, diabetes, smoking, COPD, antiplatelet, NSAIDs/COX2 inhibitors, digoxin/warfarin use.

Disclosures: BSRBR-RA, Abbott Laboratories, Amgen, Merck, Pfizer Limited, Roche, Swedish Orphan Biotech, UCB Pharma Limited—Research Grants. All other authors have declared no conflicts of interest.

47. THE RISK OF LYMPHOMA IN PATIENTS RECEIVING ANTI-TNF THERAPY FOR RHEUMATOID ARTHRITIS: RESULTS FROM THE BSRBR-RA

Louise Mercer1, Mark Lunt1, Audrey Low1, James Galloway2, Kath D. Watson1, William G. Dixon1, BSRBR Control Centre Consortium1, Deborah Symmons1,3 and Kimme L. Hyrich1 on behalf of the British Society for Rheumatology Biologics Registers

1Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, University of Manchester, Manchester, 2Academic Department of Rheumatology, King’s College London, London and 3NHRI, Manchester Musculoskeletal Biomedical Research Unit, Manchester, UK

Background: The risk of lymphoma is increased in people with RA compared with the general population and is greatest in severe RA. Anti-TNF therapy is now widely used to treat severe RA in the UK. The aim of this study was to determine whether anti-TNF influences the risk of lymphoma when used in routine UK clinical practice.

Methods: The analysis was conducted in the BSRBR-RA, a national cohort study. Patients with RA starting treatment with the TNF inhibitors etanercept, infliximab or adalimumab and a biologic-naıve cohort exposed to non-biologic therapy (nbDMARD) were recruited 2001–2009. Subjects with a history of lymphoproliferative cancer prior to registration were excluded. Incident cancers were identified in 3 ways; lifelong flagging with national cancer agencies; 6 monthly patient and physician questionnaires for 3 years and annual physician questionnaires thereafter. Only first lymphoma per subject, confirmed by histology or cancer agency, was analysed. The first 6 months of follow-up (fup) were excluded. Subjects were followed up until 31/01/2011, 3 years fup, first lymphoma or death, whichever came first. The rates of lymphoma and non-Hodgkin lymphoma (NHL) in the nbDMARD cohort and in patients ever exposed to anti-TNF were compared using Cox proportional hazards models adjusted using deciles of propensity score (PD) which included baseline age, sex, DAS, HAQ, disease duration, steroids, no. prior nbDMARD, comorbidity, ethnicity, smoking and registration date. Cumulative time on anti-TNF was calculated in the anti-TNF cohort and categorized <1.5 years, 1.5–3 years and 3–5 years. Hazard ratios (HR) for each category of anti-TNF exposure were calculated.

Results: There were 67 incident lymphomas: 19 in 3368 nbDMARD-treated subjects and 48 in 11 931 anti-TNF (157 vs 90 per 100 000 person-years). After adjusting using PD there was no difference in risk of lymphoma between the cohorts; HR for anti-TNF 1.00 (95% CI 0.49, 2.05). Whilst the HR numerically increased with cumulative exposure to anti-TNF (Table 1), this was not significant (P = 0.410). There were 16 (79%) NHL in the nbDMARD cohort and 42 (83%) in anti-TNF. The most frequent subtype was diffuse large B-cell lymphoma; nbDMARD 7 (37% of NHL) and anti-TNF 16 (38%). There was no difference in risk of NHL between the cohorts; PD adjusted HR 1.15 (95% CI 0.53, 2.48).

Conclusions: There is no evidence that anti-TNF increases the risk of lymphoma over the background risk associated with RA, but further fup is needed to establish if the picture changes with prolonged treatment.

Disclosures: O.T., Abbott Laboratories, Amgen, Merck, Pfizer Ltd, Roche, Swedish Orphan Biotech (SOBI), UCB Pharma Ltd—Research Grant. All other authors have declared no conflicts of interest.

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48. RELATIONSHIP BETWEEN ANTI-TNF THERAPY AND RISK OF MYOCARDIAL INFARCTION IN SUBJECTS WITH RHEUMATOID ARTHRITIS: RESULTS FROM THE BSBRR-RA

Audrey Low1, Mark Lunt1, Louise Mercer1, Ellen Bruce2, British Society for Rheumatology Biologics Registers Centre Consortium1, Will Dixon1, Kimmie Hyrick2 and Deborah Symmons1,2 on behalf of the British Society for Rheumatology Biologics Registers

1Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, University of Manchester, Manchester and 2NHRI, Manchester Musculoskeletal Biomedical Research Unit, Manchester, UK

Background: Subjects with RA are at increased risk of premature cardiovascular disease (CVD) including myocardial infarction (MI), partly through shared inflammatory mechanisms. Anti-TNF therapy may influence this risk through control of inflammation and mediation of other CV risk factors. The aim of the analysis was to study the association of anti-TNF therapy with the risk of MI in routine UK clinical practice.

Methods: The BSBR-RA is an ongoing national prospective observational cohort study. Subjects with RA starting anti-TNF (etanercept, infliximab, adalimumab) and a biologic-naive comparator cohort of subjects exposed to nbDMARD were recruited 2001–2009. All were followed by clinician and patient questionnaires 6-monthly for 3 years, annual clinician questionnaires thereafter and linked to the national death register. All reported MIs from any source were validated against the 2007 AHA/ESC MI criteria. Additional criteria were acute thrombosis/angioplasty for MI or MI as the underlying cause of death on death certificates. Subjects were censored at 20/4/2010, death, incident MI or date of last clinician follow-up, whichever came first. Subjects with prior CVD were excluded from analysis. Risk of MI was compared between nbDMARD and subjects ever exposed to anti-TNF therapy using Cox regression adjusted by propensity score deciles (PD; Table 1). The PD included age, gender, RA-related factors, CV risk factors and drugs. Risk of MI was explored further with different drug exposure models and also modelled over time. 30-day and 1-year all-cause mortality post-MI was compared between nbDMARD and anti-TNF subjects using multivariate logistic regression, adjusted for the same confounders.

Results: 235 verified incident MIs were analysed; nbDMARD: 43 in 10,337 person-years (PY), anti-TNF: 192 in 55,636 PY (4% vs 35 per 10,000 PY; Table 1). There was a trend for a reduced risk of MI in subjects ever exposed to anti-TNF compared with nbDMARD: PD-adjusted hazard ratio 0.65 (0.42, 1.01). Risk estimates were similar when limited to periods receiving anti-TNF drug only and did not vary over time. 30-day and 1-year mortality post-MI was not associated with ever-exposure to anti-TNF: adjusted odds ratios (OR) 0.93 (0.29, 2.95), OR 0.97 (0.33, 2.79) respectively.

Conclusions: Subjects with RA ever exposed to anti-TNF experienced a reduced risk of MI over the medium term, further supporting the role of TNF and inflammation in CVD.

Table 1. Results

<table>
<thead>
<tr>
<th>Follow-up (person-years)</th>
<th>nbDMARD, n = 3368</th>
<th>Anti-TNF, n = 11,931</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>60 (12)</td>
<td>56 (12)</td>
</tr>
<tr>
<td>Drug duration, median (IQR), years</td>
<td>6 (15)</td>
<td>11 (6–19)</td>
</tr>
<tr>
<td>DAS28 score: mean (s.d.)</td>
<td>5.3 (1.1)</td>
<td>Referent</td>
</tr>
<tr>
<td>Lymphoma: age and gender adjusted HR (95% CI)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Risk of MI in subjects ever exposed to anti-TNF therapy</td>
<td>0.65 (0.42, 1.01)</td>
<td></td>
</tr>
<tr>
<td>Risk of MI in subjects on anti-TNF therapy (days lag prior PD), referent (95% CI)</td>
<td>0.67 (0.42, 1.05)</td>
<td></td>
</tr>
</tbody>
</table>

*Baseline variables in PD: age, gender, disease duration, DAS28, HAQ, steroid exposure, number of previous nbDMARDs, entry year to study, hypertension, diabetes, smoking, COPD, antplatelet use, NSAIDs/COX2 inhibitors use.

Disclosures: BSBR-RA, Abbott Laboratories, Amgen, Merck, Pfizer Limited, Roche, Swedish Orphan Biovitrum (SOB), UCB Pharma Limited—Research Grants. All other authors have declared no conflicts of interest.

49. HAS THE CAUSE OF DEATH IN RHEUMATOID ARTHRITIS PATIENTS CHANGED RECENTLY?

Saadia P. Malik1, Clive Kelly2, Jennifer Hamilton2, Carol Heycock2, Vadivelu Saravanani2 and Martin Rynne2

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Background: Most mortality studies in RA have found an increased risk of death due to cardiovascular disease, sepsis, and some malignancies. In addition, patients with RA have been reported as dying up to 8 years earlier than age and gender matched controls without the disease. With the advent of newer and earlier therapeutic interventions, we were interested to see if the causes of death and life expectancy had changed in comparison with an audit undertaken in Gateshead between 2000 and 2004.

Methods: Gateshead rheumatology department serves a population of approximately 250,000. Since 2000, all patients are monitored via an electronic database. All deaths amongst our RA population between January 2005 and December 2010 were identified from the database. Case notes and death certificates were analysed using a standardized pro forma. Where case notes were not available archived clinic letters and computer records were examined. We assessed whether death resulted from direct or indirect effects of RA or its therapy. We also calculated median age and median disease duration at death. Comparison was made with results from the earlier Gateshead study.

Results: The database contained 11,466 patient-years from 2,100 patients monitored during the study period. There were 256 deaths in RA patients, of these, 82% were female. Median age at death was 75.4 years (range 52 to 93 years), with a median duration of RA of 11 years. 60% of patients died in hospital. The predominant cause of death was sepsis (46%), with vascular disease and cancers (most commonly lung cancer) accounting for just 25% each. Sepsis was most commonly related to the respiratory tract (70% of cases), and 21% of these patients were taking long term oral steroids, as compared with 9% of our RA population overall. Only 5 patients (2.4%) died from RA related lung disease and one patient died from bone marrow failure thought to be a contributing factor in only 4 (1.6%) of deaths- 3 patients died from sepsis secondary to bone marrow failure on DMARDs (SSZ 1, MTX 1, and biologics 1) and the fourth from suspected LEF induced lung injury. In comparison with the previous study median age at death has risen from 74.4 to 75.4 years, the commonest cause of death was sepsis vs cardiovascular disease and rate of death per 100 patients has fallen from 2.8 to 2.23.

Conclusions: In comparison with the general population the mean reduction in life expectancy in RA has fallen to <3 years. Deaths directly related to disease or therapy are rare. The proportion of Gateshead RA patients dying from sepsis has increased which is in contrast to the fall in cardiovascular deaths. Patients dying from sepsis were more likely to be on steroids at time of death however further work is needed to identify any other potentially modifiable contributing factors which may lead to further improvements in life expectancy.

Disclosures: The authors have declared no conflicts of interest.

50. SUCCESS OF A SMOKING AND RHEUMATOID ARTHRITIS AWARENESS CAMPAIGN IN FIFE, SCOTLAND

Helen E. Harris1, Fiona Tweedie1, Yiannis Skaparis2, Marie White1, Nicola Scott3 and Kay Samson4

1Fife Rheumatic Diseases Unit, NHS Fife, Kirkcaldy, 2Department of Medicine, University of Dundee, Dundee and 3Smoking Cessation Team, NHS Fife, Kirkcaldy, UK

Background: Tobacco smoking increases the risk of developing RA and is associated with a reduced response to RA drug therapy. The...
study objectives were: 1. Launch a public health awareness campaign about the link between RA and smoking. 2. Assess the knowledge of RA patients about the links between RA and smoking before and after the campaign. 3. Assess the impact of the campaign on RA smokers. 4. Identify factors that motivated smoking cessation in RA ex-smokers.

Methods: 1200 serum positive RA patients in Fife were identified, half were contacted by telephone before the campaign and half afterwards. A group of RA smokers identified before the campaign were followed up afterwards. The campaign materials are available at www.nras.org.uk. The campaign was launched to the media and mailed to all RA patients in Fife on the same day.

Results: In September 2011 the campaign launch resulted in publications in 2 newspapers and interviews on 2 radio stations creating 289,660 media impressions. 306 patients completed questionnaires before the launch and 318 in the 3–12 months afterwards. There was a marked improvement in patients’ knowledge about a link between RA and smoking and that smoking could interfere with the treatment (Table 1). After the campaign 33% remembered receiving an information card and 6% had read a newspaper article. When directly questioned 17–49% of the RA smokers were aware of campaign information and following the telephone interview 42% stated that knowing more about the link between RA and smoking would increase their likelihood of attempting to quit. The reasons that some RA smokers were not planning to quit were cited as pleasure or relaxation in 24% of RA smokers in the pre-campaign group and 15% in the post-campaign group revealed that experiencing a smoking related illness such as a chest infection was the commonest motivator to give up smoking. 63% of RA ex-smokers used pharmacotherapy to quit smoking and 85% quit after 1–3 attempts.

Conclusions: The Fife smoking and RA awareness campaign has successfully increased patients’ knowledge of the link between RA and smoking and the effect of smoking on RA therapy. A modest change in RA smokers’ attitudes to smoking occurred. To increase the number of quit attempts by RA smokers this study suggests that patients may be motivated by learning that RA is a smoking related disease.

Table 1. Pre- and post-campaign knowledge and beliefs about smoking and RA

<table>
<thead>
<tr>
<th>Knowledge of link (all)</th>
<th>Pre (%)</th>
<th>Post (%)</th>
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<tbody>
<tr>
<td>Effect on treatment (all)</td>
<td>4</td>
<td>49</td>
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<tr>
<td>Smokers planning to stop</td>
<td>6.7</td>
<td>9</td>
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<tr>
<td>Smokers thinking about stopping</td>
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<td>51</td>
</tr>
<tr>
<td>Smokers NOT intending to stop</td>
<td>45.8</td>
<td>40</td>
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Disclosures: H.H., Pfizer—Educational grant to fund development of campaign and cost of telephone work and analysis, Pfizer—Consultation Fees and Speaker Fees, Menarini, Napp, MSD—Speaker fees, N.S., Pfizer—Educational grant to fund telephone work, Y.S., Pfizer—Educational grant for telephone work on COBRA regimen, F.T., Pfizer—Educational grant to fund study work, M.W., Pfizer—Educational grant to support telephone work of study. All other authors have declared no conflicts of interest.

51. FRACTURE RISK MANAGEMENT IN PATIENTS WITH NEWLY DIAGNOSED RHEUMATOID ARTHRITIS: RESULTS FROM A CARE PATHWAY

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¹Academic Rheumatology Unit, Bristol, UK

Background: Rheumatoid arthritis (RA) results in generalized bone loss and increased fracture risk. The prevalence of osteoporosis in RA is increased about twofold. High disease activity, immobility and glucocorticoids (GC) substantially increase fracture risk in addition to other factors such as age, BMI and gender. Fracture risk increases rapidly after starting GC treatment. Today we introduce a standardized care pathway for patients with newly diagnosed RA. The protocol included a DXA scan and fracture risk assessment for each patient. We set out to determine the risk for osteoporotic fragility fractures in patients with newly diagnosed RA and the proportion, and demographics, of those subsequently recommended bone protection medication.

Methods: We reviewed data from 100 consecutive patients admitted to the RA ward pathway in 2010 or 2011. Clinical data comprising risks for osteoporotic fragility fractures, medication and DXA scan reports were collected from the case notes. Bone protection was recommended where the lowest T scores (spine, total hip or femoral neck) were ≤ −2.5, or, in a patient with low bone mass, where the calculated fracture risk (major osteoporotic fracture) was ≥ 5%. The Fife smoking and RA awareness campaign has successfully increased patients’ knowledge of the link between RA and smoking and the effect of smoking on RA therapy. A modest change in RA smokers’ attitudes to smoking occurred. To increase the number of quit attempts by RA smokers this study suggests that patients may be motivated by learning that RA is a smoking related disease.

Results: In September 2011 the campaign launch resulted in publications in 2 newspapers and interviews on 2 radio stations creating 289,660 media impressions. 306 patients completed questionnaires before the launch and 318 in the 3–12 months afterwards. There was a marked improvement in patients’ knowledge about a link between RA and smoking and that smoking could interfere with the treatment (Table 1). After the campaign 33% remembered receiving an information card and 6% had read a newspaper article. When directly questioned 17–49% of the RA smokers were aware of campaign information and following the telephone interview 42% stated that knowing more about the link between RA and smoking would increase their likelihood of attempting to quit. The reasons that some RA smokers were not planning to quit were cited as pleasure or relaxation in 24% of RA smokers in the pre-campaign group and 15% in the post-campaign group revealed that experiencing a smoking related illness such as a chest infection was the commonest motivator to give up smoking. 63% of RA ex-smokers used pharmacotherapy to quit smoking and 85% quit after 1–3 attempts.

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52. ARE PATIENTS WITH INFLAMMATORY POLYARTHRITIS EXPERIENCING THE SAME REDUCTIONS IN CARDIOVASCULAR-SPECIFIC MORTALITY AS THE GENERAL POPULATION?

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¹Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, ²Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, Manchester and ³Nordic and Norwich University Hospitals, Norwich and Norwich University Hospitals Trust, Norwich, UK

Background: It is widely acknowledged that cardiovascular (CV) mortality is increased in patients with inflammatory polyarthritis (IP), CV mortality rates have fallen in the UK general population over the last few decades (1), but is the same true for IP patients? This study aimed to examine CV mortality over time in a cohort of recalled IP patients compared with the general population in Norfolk, UK.

Methods: Between 1990–2004, patients ≥16 years with ≥2 swollen joints for ≥4 weeks were registered to the Norfolk Arthritis Register (NOAR), a primary-care based inception cohort. Three cohorts (limited to symptom onset <2 years at baseline assessment) were defined by year of baseline assessment: cohort 1 (1990–1994); cohort 2 (1995–1999) and cohort 3 (2000–2004). At baseline the 1987 ACR and 2010 ACR/EULAR RA criteria were applied. Patients were tracked via the Office for National Statistics (ONS) for notification of death. CV death was defined according to ICD-10 (Chapter I). The ONS also provided CV death rates for the Norfolk general population. CV standardized mortality ratios (SMRs) were calculated for all cohorts over 5 years from baseline and for subgroups fulfilling the 1987 and 2010 RA criteria. Mortality rates per 1000 person-years (PY) for NOAR and Norfolk general population were also calculated.

Results: In NOAR, the median age at onset rose with time, as did the percentage with CV death within 5 years and the crude CV mortality rate (Table 1). Five year CV SMRs were raised in all cohorts but only statistically significant in Cohort 3. Patients fulfilling the 1987 ACR and 2010 ACR/EULAR RA criteria at baseline followed a similar trend, although were not statistically significant. The overall crude CV death rate per 1000 PY in adults >16 years in Norfolk decreased over time: 3.3 (1990–1994); 3.0 (1990–1994) and 2.7 (2000–2004).

Conclusions: Raised SMRs for IP patients in advancing cohort years may be due to the declining CV deaths in the general population over the same time period. CV mortality remains increased in IP patients despite reductions in the general population emphasizing the importance of CV disease management in IP patients.

Disclosures: The authors have declared no conflicts of interest.
53. RA-RELATED INTERSTITIAL LUNG DISEASE: WHICH FACTORS PREDICT ITS DEVELOPMENT?

Esther Chan1, Clive Kelly1, Felix A. Woodhead2, Mohamed Nisar1, S. Arthanari3, Julie Dawson4, Nav Sathi4, Yasmeen Ahmad5, Gouri Koduri6 and Adam Young7

1Rheumatology, Queen Elizabeth Hospital, Gateshead, 2Chest Medicine, University Hospital, Coventry, 3Rheumatology, Queen’s University Hospital, Burton, 4Rheumatology, Knowsley Hospital, St Helens, 5Rheumatology, BCU Hospital, North Wales and 6Rheumatology, ERAS/ERAN City Hospital, St Albans, UK

Background: Rheumatoid arthritis (RA) is associated with clinically relevant interstitial lung disease (ILD) in approximately 5% of patients. The advent of more aggressive treatment regimes in RA over the last decade might have altered the outcome of patients with RA-ILD and a reassessment is appropriate. Hence, we have assessed survival trends in patients with RA-ILD in a large multi-centre UK cohort over a 25 year period.

Methods: We collected data from six centres across the UK on patients with both RA and ILD (proven on high resolution CT) diagnosed between 1987 and 2012 using a standard proforma. We analysed the patients’ age, gender, duration of both RA and ILD, smoking history and serology (rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody) at the time of diagnosis of RA-ILD.

Results: A total of 230 patients were identified from across the UK with proven RA-ILD diagnosed over 25 years. In total 110 patients (48%) were male, giving a male:female ratio of 1.1:0.9 and the median (range) age at diagnosis of RA-ILD was 64 (37–83) years. Articular disease predated ILD in 85%, lung disease predated RA in 10% while the conditions were synchronous in 5%. The median (range) duration of RA at the time of diagnosis of ILD was 9 (0–31) years. A total of 154 patients (67%) were past (121) or present (33) smokers with a median (range) of 26 (5–88) pack years. Smoking was more frequent in males (72%) than females (60%) [P = 0.02], and the median number of pack years was greater in males (35) than females (20) [P = 0.01]. Smoking was less prevalent among RA controls (60%) and median pack year consumption was lower at 21 (5–60) [P = 0.03]. Among patients with RA-ILD, RF was positive in 89% and 94% had anti-CCP antibodies. By comparison, RF and anti-CCP antibodies were present in 58% [P = 0.01] and 55% [P = 0.006] of RA controls respectively. Titres of both antibodies were significantly higher in patients with RA-ILD.

Conclusions: This is the largest study of factors predicting the development of RA-ILD in the UK. It demonstrates that there is an almost equal prevalence of RA-ILD in both genders. In contrast with earlier reports, the condition can occur at a young age and is most often with disease for over a decade of RA. Smoking is strongly associated with the development of RA-ILD and is greater in males, which may contribute to the relatively higher frequency of RA-ILD in men. Seropositivity for rheumatoid factor and CCP antibodies are also strongly associated with the development of RA-ILD, and might suggest that B-cell activation, possibly as a result of smoking, may trigger the development of RA-ILD in some patients.

Disclosures: The authors have declared no conflicts of interest.

54. RA-RELATED INTERSTITIAL LUNG DISEASE: SURVIVAL TRENDS OVER 25 YEARS

Clive Kelly1, Esther Chan1, Yasmeen Ahmad2, Felix A. Woodhead3, Mohamed Nisar1, S. Arthanari3, Julie Dawson4, Nav Sathi4, Gouri Koduri5 and Adam Young6

1Rheumatology, Queen Elizabeth Hospital, Gateshead, 2Rheumatology, BCU Hospital, North Wales, 3Chest Medicine, University Hospital, Coventry, 4Rheumatology, Queen’s University Hospital, Burton, 5Rheumatology, Knowsley Hospital, St Helens and 6Rheumatology, ERAS/ERAN City Hospital, St Albans, UK

Background: Rheumatoid arthritis (RA) is associated with clinically relevant interstitial lung disease (ILD) in approximately 5% of patients. A previous study by the ERAS the prognosis had been poor, with a mean survival of 3 years following diagnosis of RA-ILD. The advent of more aggressive treatment regimes in RA over the last decade might have altered the outcome of patients with RA-ILD and a reassessment is appropriate. Hence, we have assessed survival trends in patients with RA-ILD in a large multi-centre UK cohort over a 25 year period.

Methods: We collected data from six centres across the UK on patients with both RA (EULAR 2010 criteria) and ILD (proven on high resolution CT) using a standard proforma. The period covered patients diagnosed between 1987 and 2012. We analysed the patients’ age, gender, duration of both RA and ILD, outcome and, where appropriate, cause of death. By breaking the data into four clusters based on year of diagnosis, we assessed the change in life expectancy associated with RA-ILD, the percentage of patients dying from ILD and the change in age at death over time.

Results: A total of 230 patients were identified from across the UK with proven RA-ILD diagnosed over a 25 year period. The male:female ratio was 1:1 and the median age at diagnosis of RA-ILD was 64 (37–88) years. A total of 73 deaths were recorded, of which 35 (48%) were related to ILD. Median age at death from ILD increased from 63 years (for onset 1987–93) to 76 years (for onset 2006–12), the percentage of patients dying from ILD fell from 67% to 30% and median survival rose from 33 months to 48 months over the same period. Most patients diagnosed in the last 6 years remain alive, so figures for this period are likely to represent an underestimate of the recent improvement in prognosis. Further details are shown in Table 1.

Conclusions: This is the largest study of RA-ILD in the UK. It is often reported that RA-ILD has a very poor prognosis, but this study demonstrates that the natural history of the condition has improved over the last 25 years, with patients living longer and being less likely to die from their lung disease. The reasons for this remain unexplained at present, but earlier detection and more aggressive management of ILD may be significant contributors. As the commonest cause of death in patients with RA-ILD is ILD, this aspect of their condition should be a priority for therapeutic endeavours.

Disclosures: The authors have declared no conflicts of interest.

55. ANALYSIS OF COMORBIDITIES REPORTED BY PEOPLE LIVING WITH ARTHRITIS CONTACTING A NATIONAL HELPLINE SERVICE

Jo Cumming1, Peter Stannett1 and Richard Hull2

1Information and Helplines, Arthritis Care, London and 2CMAB, Arthritis Care, London

Background: Many in the UK, diagnosed with arthritis report living with comorbidities. It is well recognized that ischaemic heart disease and stroke are associated with acute active arthritis and that the...
Methods: We analysed every contact by telephone, email, letter or online forum received in the helpline which is anonymized and logged onto a secure confidential database complying with the UK Data Protection Act. Self reported comorbidities were analysed.

Results: The helpline received 11,526 contacts in 2011, of which 784 (6.7%) had at least one additional health problem and 76 more than one additional health problem. Whole group analysis (784) showed the most frequently reported health problem was Osteoporosis [23%], Next, 17.8% reported mental health problems, often depression. Heart conditions were third at 2.5% and 10% reported hypertension. Those reporting comorbidities increased with age with exceptions such as Crohn’s disease which varied little over 26 years and a decline (31%) in mental health problems over 64.

Where osteoporosis was reported [n = 186] 42% were aged 26–64 and 58% over 65. 140 people with arthritis reported mental health problems; only 88% under 65 years reported this.

Individual types of arthritis have different comorbidities reported: OA (n = 555) reported osteoporosis [21%], depression [14.9%], heart disease [10%], diabetes [8%] and hypertension [8%]. Of those with mental health issues, the highest percentage (64%) had OA. People reporting comorbidities and RA (n = 70) are likely to also report depression [20%] followed by heart problems [15%]. 23% of those reporting fibromyalgia (n = 43) said they are being treated for mental health problems and 18% with osteoporosis.

Of the 784 with addition health problems, 100% said that they expected to feel pain compared with 82% without comorbidities. 96% of those who have OA experienced pain compared with 56% generally. 28.8% reported feeling low/depressed and experience fatigue. 91% of those with comorbidities were sent information about types of arthritis compared with 61% with none. On every support parameter, the needs of those with comorbidities were higher than those without and 16% of people were referred to other support agencies.

Conclusions: 1. We have demonstrated that 8% of 11,526 contacts had comorbidities which affected their daily life, varying with age and type of arthritis. 2. Higher levels of pain reported may be associated with significant increases in feelings of depression and fatigue and the need for one to one counselling support. 3. Where additional health problems are reported by people with arthritis they have generally higher support and information needs. 

Disclosures: The authors have declared no conflicts of interest.

56. THE EFFECTS OF INDIVIDUALIZED AEROBIC AND STRENGTH TRAINING ON CARDIOVASCULAR OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS

George Metsoi1,2, Antonios Stavropoulos Kalinoglou1, Jef J. Velema1,2,3,4, Jan Zettergren1, Peter Nightingale2, Yannis Koutedakis1 and George D. Kittas2
1Physical Activity and Health, University of Wolverhampton, Walsall and 2Rheumatology, Dudley Group of Hospitals, Birmingham, UK

Background: Rheumatoid arthritis (RA) is characterized by an increased prevalence of cardiovascular disease (CVD) as well as a combination of metabolic risks and sedentary lifestyles (metabolic syndrome). Exercise is also a strong predictor of CVD. Exercise is known to improve VO2max and reduce the risk for CVD in the general population. However, the effects of individualized exercise on CVD risk factors have never been investigated in RA.

Methods: Twenty RA patients received a 6 month individualized aerobic and resistance interval exercise intervention three times per week. Another 20 patients matched for age, gender, BMI, and disease duration formed the control group which only received advice on the benefits of physical activity using relevant leaflets from the British Heart Foundation. VO2max, blood pressure, lipids, insulin resistance and body composition, disease activity (DAS28), health assessment questionnaire (HAQ), and C reactive protein (CRP) were taken at baseline, 3 and 6 months.

Results: The attendance rate to the exercise sessions was 88%, with the adherence to the prescribed exercise intensity 76%. Repeated measures ANOVA revealed significant group by time interaction effects for VO2max (P = 0.001), systolic blood pressure (P = 0.001), high density lipoprotein (P = 0.042), body fat percentage (P = 0.026), as well as CRP (P = 0.042), DAS28 (P = 0.008), and HAQ (P = 0.003). Post hoc analyses showed that these parameters all improved in the exercise group, whereas no change was found in the control group.

Conclusions: The proposed combined aerobic and strength training intervention resulted in a significant improvement in VO2max and disease activity measures in RA patients. This is the first study to show that an exercise programme, specifically tailored to meet individual needs, significantly reduced individual CVD factors. Individualized exercise seems to be a promising intervention that may improve the increased prevalence of CVD risk factors and therefore reduce CVD mortality in RA.

Disclosures: The authors have declared no conflicts of interest.

57. OSTEOPOORATIVE FRACTURE IN RHEUMATOID ARTHRITIS: A STUDY OF INCIDENCE, PREDICTIVE FACTORS AND ECONOMIC BURDEN FROM TWO UK INCISION COHORTS

Elena Nikhiphorou1, Josh Dixey2, Peter Williams3, Patrick Kiley3, David Walsh3,4, Lewis Carpenter1 and Adam Young1
1ERAS, Department of Rheumatology, St Albans City Hospital, St Albans, 2Rheumatology, New Cross Hospital, Wolverhampton, 3Rheumatology, Medway Maritime Hospital, Gillingham, 4Rheumatology, St George’s Healthcare NHS Trust, London, 5Rheumatology, Sherwood Forest Hospitals NHS Trust, Sutton-in-Ashfield, 6Academic Rheumatology, University of Nottingham and 7Centre for Longitudinal Studies, National Centre for Social Research, University of Hertfordshire, Hatfield, UK

Background: There are few data on incidence rates, economic burden of, and predictive markers for osteoporotic fracture in patients with RA studied longitudinally.

Methods: The Early RA Study (ERAS) recruited 1465 DMARD naïve patients from 1986–1998 and the similarly designed early RA Network (ERAN) 1236 from 2002–2012 in 9 and 23 UK centres respectively. Standard clinical, radiological and laboratory measures were performed yearly for a maximum 25 years (median 10 and 3 years).

Conclusions: Results: 176 (6.5%) patients suffered 182 fractures: hip (76, 42%), wrist (32, 17.5%), vertebral (22, 12%), others (52, 28.5%). 13 hip fractures required hip replacements and 57 dynamic hip screw surgery. There were no immediate postoperative deaths but hip and vertebral fractures were recorded as contributory causes of death in 12 and 2 respectively. Fracture incidence rates, types of surgery and direct costs over time will be displayed graphically. For hip fracture, median time from baseline was 5yrs (IQR 5–15) and average length of stay (LoS) was 15 days in 1986–1994, improving to 8 days in 2005–2012, but still considerably greater than national LoS figures for all hip fractures. Fracture prediction included traditional risk factors (age, gender) and for hip fracture, risks also included disease severity measures (DAS28) and cardiovascular risk factors.

Disclosures: The authors have declared no conflicts of interest.
studies question if BR precedes RA and whether BR has a role in the pathogenesis of RA. However, many of these studies are small in numbers (~25 cases), conflicting in results and performed without HRCT evidence of BR.

Methods: Screening outpatient clinics at 3 NHS Trusts we identified 34 patients with symptomatic BR and RA. All had HRCT proven BR without other lung disease, a history of ≥2 respiratory infections/year and met the 2010 ACR/EULAR RA criteria. We interviewed each patient detailing disease natural history and characteristics. We compared these findings between patients whose RA symptoms preceded BR (BRRA) and whose BR symptoms preceded RA (RABR). We also compared the autoantibody profile in terms of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA, 2nd generation assay) of all 34 patients with BR and RA to a control group of 23 patients with RA without lung disease. Mann–Whitney and Fisher’s Exact test were used for analysis.

Results: In total 23/34 patients (68%) BR preceded RA by a mean duration of 25 years. Disease characteristics were similar between the BRRA and RABR groups (Table 1). Duration of BR was significantly shorter in the RABR group averaging 8 years compared with 41 years in the BRRA group (P < 0.0001). Autoantibody positivity in the 34 patients with BR and RA was significantly higher than the control group of 23 RA patients, 37 (97%) were positive for RF compared with 14 (61%) of controls (P = 0.0007) and 32 (94%) were positive for ACPA compared with 11 (48%) of controls (P = 0.0001). There was no significant difference in smoking pack-year history between the groups.

Conclusions: Our data suggest BR typically precedes RA. Disease characteristics are similar irrespective of the primary symptom, although RABR patients have a shorter duration of symptomatic BR. Exceptionally high RA autoantibody positivity is present in patients with BR without RA. Further investigation is required, there is increasing evidence to suggest that BR might initiate RA by the production of autoantibodies in susceptible individuals.

Disclosures: The authors have declared no conflicts of interest.

59. ENDOTHELIAL FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS: THE EFFECTS OF EXERCISE AND ANTI-TNF TREATMENT
Jet J. Veldhuijzen van Zanten1,2, George Metsois1,3, Antonios Stavropoulos-Kalinoglou1,4, Aamer Sando2 and George D. Katsar1
1Sport and Exercise Sciences, University of Birmingham, Birmingham, 2Rheumatology Department, Dudley Group of Hospitals NHS Foundation Trust, Dudley, 3School of Sport, Performing Arts and Health, Wolverhampton University, Wolverhampton, UK and 4Rheumatology Research Group, University of Birmingham, Birmingham.

Background: Patients with RA have an increased risk for cardiovascular disease (CVD). The underlying pathways remain to be determined, but endothelial function has been implicated. Regular physical activity can reduce the risk for CVD in the general population. In RA patients, successful treatment with anti-TNF alpha has also been associated with a reduced risk for CVD. The aim of the current study is to compare the effects of a 3 month exercise intervention with 3 months of anti-TNF treatment on endothelial function in RA.

Methods: Twenty RA patients (14 female, age 55 ± 10 years) underwent a 3 month individualized aerobic and resistance exercise intervention. Twenty-three patients (15 female, age 54 ± 15 years) received anti-TNF treatment for 3 months. Measures of disease activity (DAS28 and CRP), functional ability (HAQ), and endothelial function (flow mediated dilation and GTN-induced dilation) were taken at pre-intervention baseline and after 3 months.

Results: At baseline, patients in the anti-TNF group had higher DAS28 scores and poorer functional ability compared with the patients in the exercise group (see Table 1). Other characteristics were not significantly different between the groups. Group by time ANOVAs revealed that both exercise and anti-TNF treatment resulted in improvements in DAS28, functional ability and CRP. A significant interaction effect indicated a greater improvement in DAS28 and functional ability in response to anti-TNF treatment compared with exercise. There was an overall time effect as well as a group by time interaction effect for macrovascular endothelial function. Post hoc analyses revealed that endothelial function improved in patients in the exercise group, whereas no change was found in response to anti-TNF treatment.

Conclusions: Both exercise and anti-TNF treatment displayed beneficial effects in patients with RA. Anti-TNF alpha treatment was more successful in improving disease activity and functional ability, whereas exercise induced a substantial improvement in endothelial function, which was not evident in patients receiving anti-TNF treatment. This suggests that successful anti-TNF treatment improves cardiovascular risk by reducing disease activity, whereas exercise improves cardiovascular risk by enhancing the function of the vasculature. Therefore, once patients have responded successfully to anti-TNF treatment, increasing levels of physical activity may reduce the risk for CVD even further.

TABLE 1. Characteristics of patients with BRRA and RABR

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<tr>
<th>BRRA</th>
<th>RABR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>69.2 (8.2)</td>
<td>68.6 (6.5)</td>
</tr>
<tr>
<td>Years with BR (median (IQR))</td>
<td>52 (21)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Years with RA, median (IQR)</td>
<td>13 (21)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>DAS28-CRP, median (IQR)</td>
<td>3.8 (1.5)</td>
<td>4.0 (5.0)</td>
</tr>
<tr>
<td>Erosive disease, n (%)</td>
<td>10 (71%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>MRC dyspnoea score, median (IQR)</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Chest infections in past 12 months, median (IQR)</td>
<td>3 (3)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>FEV1% predicted, median (IQR)</td>
<td>66.5 (52.5)</td>
<td>54 (42)</td>
</tr>
</tbody>
</table>

BRRA: n = 20; RABR: n = 10; aBRRA: n = 14; RABR: n = 6; *BRRA: n = 16; RABR: n = 7.

Disclosures: The authors have declared no conflicts of interest.

60. INCIDENCE OF DIABETES AND EFFECT OF ETANERCEPT AND ADALIMUMAB ON HBA1C OVER 1 YEAR: DATA FROM A RANDOMIZED TRIAL IN PATIENTS WITH RHEUMATOID ARTHRITIS
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Background: Inflammation such as that which occurs in RA is associated with insulin resistance and risk of diabetes mellitus (DM). Some DMARDs including TNF inhibitors (TNFi) may improve insulin resistance and DM risk. However, it is unknown whether TNFi improve HbA1c in patients with RA with or without DM. Data on HbA1c were collected in a randomized trial comparing drug continuation rates for etanercept and adalimumab [1]. We estimated the incidence of DM from these data and studied the impact of therapy on HbA1c.

Methods: Participants with active RA, who had previously failed to respond to 2 non-biologic DMARDs including MTX, were randomized to etanercept or adalimumab and followed 3-monthly over 1 year. Data collected included comorbidities, clinical and laboratory parameters, and medications at each visit. The primary endpoint was newly diagnosed DM (HbA1c >48 mmol/mol at any time point. BMI 27.8, mean HbA1c 38 mmol/mol. Of these, 4 (5%) patients had DM (HbA1c >48 mmol/mol) at baseline. 73 participants (73% female) completed 1 year of TNFi therapy; mean age 54 years (s.d. ± 12), mean BMI 27.8, mean HbA1c 38 mmol/mol. Of these, 4 (5%) patients had DM at baseline. A majority of patients were on MTX (67%) and 33% on prednisolone. Baseline characteristics were similar for patients’ allocated to adalimumab (52%) or etanercept (48%), except more patients on etanercept were on prednisolone (49% vs 18%; P = 0.006). More patients on adalimumab were on hydroxychloroquine (24% vs 3%; P = 0.01).

Results: Of the 125 patients with active RA randomized to etanercept or adalimumab, 6 (4.8%) were known diabetics and 88% were RF/ACPA positive. Of the 119 without DM, 7 (5.9%) were diagnosed with DM (HbA1c >48 mmol/mol at baseline. 73 participants (73% female) completed 1 year of TNFi therapy; mean age 54 years (s.d. ± 12), mean BMI 27.8, mean HbA1c 38 mmol/mol. Of these, 4 (5%) patients had DM at baseline. A majority of patients were on MTX (67%) and 33% on prednisolone. Baseline characteristics were similar for patients’ allocated to adalimumab (52%) or etanercept (48%), except more patients on etanercept were on prednisolone (49% vs 18%; P = 0.006). More patients on adalimumab were on hydroxychloroquine (24% vs 3%; P = 0.01).

Disclosures: The authors have declared no conflicts of interest.
After excluding those with known DM at baseline, among those completing 1 year of TNFi (n = 69), 3 (4.4%) patients had an HbA1c >48 mmol/mol at baseline, 1 (1.5%) at 3 months, 1 (1.5%) at 6 months, and 2 (2.9%) at 12 months of follow-up. 2 (2.9%) cases had an HbA1c >48 mmol/mol at 2 follow-up visits. The incidence of DM was 29 new cases per 1000-person years (95% CI 3.51, 105).

Those on adalimumab tended to have higher levels of HbA1c than those on etanercept but the differences between groups at each time point were not significant. However, there was a significant rise in HbA1c levels after 1 year of adalimumab therapy (37.27 mmol/mol and 38.80 mmol/mol; P = 0.01). Etanercept therapy did not influence HbA1c levels over time.

Conclusions: Incidence of diabetes in patients entering a randomized trial of etanercept and adalimumab was considerably higher than other recent data. Treatment with a TNFi did not improve HbA1c levels with either agent in diabetics and non-diabetics. After excluding those with diabetes, those on adalimumab had higher mean HbA1c levels after 1 year of therapy.

Disclosures: The authors have declared no conflicts of interest.

Reference


Pathogenesis and Animal Models

61. INTRA-ARTICULAR INJECTION OF MESENCHYAL STEM CELLS LEADS TO REDUCED INFLAMMATION IN ANTIGEN-INDUCED ARTHRITIS

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Background: Mesenchymal stem cells (MSCs) are a strong candidate cell type for tissue engineering and cell therapy to repair damaged structures in various arthritic conditions. MSCs have been given intravenously or intraarticularly in animal models of RA and lead to different therapeutic effects, varying from significant improvement to no effect so overall the results remains inconclusive. The reason for this may be the route of administration, IA administration of MSCs may be more beneficial than the intravenous/intraperitoneal route, applying this may be the route of administration. IA administration of MSCs may be more beneficial than the intravenous/intraperitoneal route, applying

Methods: Murine mesenchymal stem cells (mMSCs) were isolated from bone marrow of Balb/c mice and expanded in culture. Cells were tested for their ability to form colonies and to differentiate into chondrocytes, osteocytes and adipocytes, in addition to the MSCs immunophenotype. Twenty-one days after the initial immunization murine antigen-induced arthritis was induced in 7-8-week-old male C57Bl/6 mice by IA injection of 10 mg/ml mBSA in the right knee joint. Control animals were injected with only serum-free IMDM. Joint diameters were measured at 7 days post IA mBSA administration (< 0.05). This difference continued for ~7 days post IA mBSA administration (< 0.05). Three days and 7 days after arthritis induction CM-Dil-labelled MSCs were clearly visualized in the subintimal layer of synovium which was in the region of the patella and between femoral and tibial surfaces. At 28 days post induction MSCs could be detected in the synovium. Histologically, the inflammation and cartilage destruction appeared less severe in MSC treated mice compared with control animals although further quantification is needed in this regard.

Conclusions: IA injection of MSCs into the knee joints of mice with antigen-induced arthritis causes reduced inflammation in terms of joint swelling which is a clinical measure of disease severity. The injected MSCs stayed in the knee joint and migrated into the synovium.

Funding: This work was supported by the Engineering and Physical Sciences Research Council [grant number EP/C023/081] and Institute of Orthopaedics Ltd, Oswestry.

Disclosures: The authors have declared no conflicts of interest.

62. MACROPHAGES IN HYPOXIC RHEUMATOID JOINTS PREFERENTIALLY EXPRESS HYPOXIA-INDUCIBLE TRANSCRIPTION FACTOR-2

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Background: Macrophages accumulate in hypoxic disease sites including RA joints where they possess broad pro-inflammatory, destructive and remodeling potential leading to inflammation and joint destruction. Macrophages respond to hypoxia by up regulating the hypoxia inducible transcription factors- HIF-1 and -2 normally degraded in the presence of oxygen. This study will attempt to understand the relative contribution of HIF-2 expressing macrophages in RA and the genes/mechanisms involved in its activation.

Methods: We obtained arthroscopy sections from RA patients for which tissue oxygen levels had been measured. This consisted of a random sample of mild (~40 mmHg), moderate (~15 mmHg) and severe (~3 mmHg) joint hypoxia. We also used samples from a second cohort of patients scored with mild or severe disease (based upon extent of synovitis and vascularity), a sub group of which were also receiving anti-TNF therapy. Sections were immunostained with anti-HIF 1 and 2 and co-localized with the pan-macrophage marker CD68 as well as other macrophage markers (F4/80, CD47, CD206 and Tie2).

Results: In patients with mildly hypoxic joints, macrophages (CD68+) predominately expressed HIF-1 (20%) and CD147 and were found in small clusters localized to the lining layer, whilst macrophages in patients with severely hypoxic joints were in greater numbers (73%), throughout the biopsy. These macrophages predominately expressed HIF-2 (~75%), F4/80, Tie2 and CD206. A similar pattern was observed in patients with severe disease where sections expressed more HIF-2 and Tie2+ macrophages compared with those with mild scores (15 cells per field of view compared with 5 for mild P < 0.01). There was no significant difference in HIF-1 expression. Interestingly, this HIF-2+ macrophage subpopulation was absent in patients who had been successfully treated with anti-TNF.

Conclusions: In patients with both severely hypoxic joints and severe RA macrophage numbers were significantly greater than in patients with mild hypoxia and mild disease. Moreover, macrophages in tissue from these patients predominantly expressed HIF-2, which activates genes associated with both inflammation and angiogenesis. These cells also expressed M2-like macrophage markers including F4/80, Tie2 and CD206, important in tissue remodeling and angiogenesis. We are currently investigating the gene expression profile of these subpopulations using laser capture micro-dissection and gene arrays.

Disclosures: The authors have declared no conflicts of interest.

63. THE EFFECTS OF ANTI-TUMOR NECROSIS FACTOR AGENTS ON THE EXPANSION OF T HELPER-TYPE 17 CELLS DRIVEN BY LIPOPOLYSACCHARIDE-STIMULATED MONOCYTES

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Background: T helper-type 17 (Th17) cells are proinflammatory CD4+ T cells that have been implicated in RA pathogenesis. Lipopolysaccharide (LPS)-stimulated monocytes can promote differentiation of CD4+ cells into Th17 cells driven by LPS-stimulated monocytes.

Methods: Monocytes and CD4+CD45RO+ memory T cells were purified from peripheral blood mononuclear cells isolated from healthy volunteers (positive and negative selection). Co-cultures of purified monocytes and memory T cells (1:1) were incubated for 7 days with CD3/CD28 Human T-Activator Dynabeads in the absence or presence of 1 μg/ml LPS; 4 anti-TNF agents at 10 μg/ml. After 7 days the CD4+ T cells were stained for intracellular Interferon γ (IFNγ) and IL-17A and analysed by flow cytometry. IL-17A and IL-17F secretion into the supernatant was determined by ELISA.
Results: CD4+ T cells positive for IL-17A were increased from 5.7% in the control co-cultures without LPS to 20.5% with LPS (mean of 2 experiments). The frequency of IFNγ-positive CD4+ T cells showed a smaller increase from 4.4% to 10.6% when LPS was added. IL-17A and IFNγ were expressed largely by different cells, suggesting the expansion of both Th17 and Th1 T-helper subsets. The frequency of IL-17A-producing CD4+ T cells in co-cultures of monocytes and memory B cells plus LPS in the presence of the 4 anti-TNF agents were roughly 2.5-fold lower than the LPS-positive control cultures without anti-TNF agents (mean of 4 experiments). Cells exposed to the 4 anti-TNF agents showed a similar level of CD4+ cells producing IL-17A and IFNγ. The level of IL-17A secreted into the supernatant decreased from 580 pg/ml in the LPS positive control to 180 pg/ml in co-cultures generated in the presence of the 4 anti-TNF agents. IL-17F decreased from approximately 8 ng/ml to 2 ng/ml in the LPS control and the anti-TNF exposed cultures (mean of 4 experiments). There were no significant differences in the concentration of IL-17A or IL-17F from co-cultures exposed to the 4 different anti-TNF agents.

Conclusions: The increased frequency of IL-17+ T cells and secretion of IL-17A and IL-17F suggest that LPS-activated monocytes support exposure of IL-17A and IL-17F. The increased frequency of IL-17+ B cells compared with HC irrespective of BAFF levels. %BAFF-R populations in patients with C-R compared with later relapse (Concordant Relapse:C-R) and 10 relapsing (Non-Concordant Relapse:NCR) CD4+ T cells were similar to HC in all sub-populations throughout.


64. RELATIONSHIP OF BAFF-BINDING RECEPTORS WITH SERUM BAFF LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS RELAPSING AFTER RITUXIMAB

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Background: Removal of circulating B cells to <0.1% CD19+ cells using B-cell depletion therapy (BCDT) based on rituximab can significantly reduce symptoms in patients with RA. B-cell, turnover usually after 6–10 months, mirrors ontogeny with naïve B cells regenerating from bone marrow. Clinical relapse can occur either close to (≤3 months) B-cell return or in approximately 1/3 of patients, many months later. The cytokine, B-cell-activating-factor (BAFF) coordinates survival and differentiation of B cells into immunoglobulin secreting cells (ISC) by binding to 3 different receptors; BAFFR, TACI and BCMA. Serum BAFF levels rise after BCDT but the relationship with BAFF-receptor expression has not been investigated.

Methods: We included 10 Healthy Controls (HC) and 20 RA patients at relapse (6 with BCDT) with 3 months after B-cell return (Concordant Relapse:C-R) and 10 relapsing ≥3 months. % B cells in each sub-population expressing BAFFR, TACI and BCMA were defined using combinations of CD19, CD38 and IgD. Serum BAFF levels were measured using commercial ELISA. Statistics for non-parametrically distributed data were applied.

Results: 1) BAFF levels rose post-BCDT. Median levels remained significantly raised (>2.4 ng/ml) or upper limit of normal range-ULNR) at relapse in 1/2 of patients in each group. 2) Comparing B-cell phenotypes, % post-germinal Centre (GC) B cells and plasmablasts were significantly higher in patients with C-R compared with patients with later relapse (P=0.007 and P=0.02 respectively). 3) At relapse, significantly lower %BAFFR+ B cells were found in all sub-populations compared with HC, and negatively associated with BAFF levels above ULNR (P<0.01). 4) When BAFF levels were within normal limits, %BAFFR+ B cells were significantly lower in naïve and post-GC populations in patients with C-R compared with later relapse (P=0.05). 5) %TACI + B cells were significantly reduced in post-GC B cells compared with HC irrespective of BAFF levels. %BCMA+B cells were similar to HC in all sub-populations throughout.

Disclosures: The authors have declared no conflicts of interest.

65. IGG ANTIBODIES TO ENDOGENOUS VIRAL MATRIX SEGMENT OF HERV-K10 AND POTENTIAL IGG1FC VIRAL MIMICS IN RHEUMATOID ARTHRITIS

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1Immuneology Research Group, Research Institute in Healthcare Sciences, University of Wolverhampton, Wolverhampton, 2Academic Unit of Bone Metabolism, Northern General Hospital, Sheffield, UK and 6School of Performing Arts and Leisure, University of Wolverhampton, Wolverhampton, 3Department of Rheumatology, Selly Oak Hospital, Birmingham, 4Sir Joseph Hotung Centre for Musculoskeletal Disorders, St George’s University of London and NHS Trust, London, 5Department of Gastroenterology, The Royal Wolverhampton NHS Trust, Wolverhampton and 7The Renal Unit, The Royal Wolverhampton NHS Trust, Wolverhampton, UK

Background: The human endogenous retrovirus HERV-K10 has been implicated in the aetiology and pathogenesis of RA. In particular the Gag region of this retrovirus, crucial to the development of viral particles, appears to be important with regard to immunological reactivity. Our aim was to identify a key antigenic region within the Gag region of HERV-K10 using bioinformatics, to assess IgG serological reactivity to the immunodominant epitope in RA patients, and to analyse the potential molecular mimicry with a key autoantigen in RA, IgG1Fc.

Methods: To develop an ELISA system, we used bioinformatic algorithms to predict an antigenic peptide segment within the HERV-K10 Gag matrix. The derived biotinylated peptide (MAG1) was coated onto ELISA plate. Serums from RA and controls were tested. HRP anti-human IgG conjugate was employed to detect peptide bound antibodies. All blood samples were collected with full ethical approval and patients consent. We also investigated the possibility of molecular mimicry between HERV-K10 Gag and IgG1Fc. Statistical analysis was performed on serological data where necessary to provide a normal distribution for parametric tests including ANOVA and Student’s t-test. Correlation of patient information was assessed using a two-tailed Pearson’s test.

Results: We determined a peptide sequence on the matrix segment of HERV-K10 (MAG1) and optimized an ELISA system. On screening patients’ serum, we found significant anti-IgG reactivity to MAG1 in RA patients as compared with patients with IBD, patients with OA and healthy individuals. Further bioinformatic analysis of HERV-K10 Gag and the key autoantigen IgG1Fc, highlighted 6 regions with amino acid sequence homology. Molecular modelling revealed that all peptide mimics were solvent accessible and readily exposed to the immune system. Intriguingly, these regions were also identified as key epitopes of rheumatoid factor antibodies.

Conclusions: On screening patients' serum, we found significant anti-IgG reactivity to MAG1 in RA patients compared with disease controls and healthy individuals. The serological activity to MAG1 in disease controls and healthy subjects was perhaps indicative of the ubiquitous presence of this virus in the general population. Consequently our data provide a level of base-line activity that may be useful to future studies. Molecular mimicry between HERV's and autoantigens has been considered a mechanism in the aetiology and pathogenesis of RA. In this respect, we assessed potential homology between HERV-K10 Mag and IgG1Fc proteins using bioinformatic analysis. The serological investigations of potential cross-reactive HERV-K10 antibodies against RA potential autoantigens may provide conclusive evidence of this virus’s role in RA. Further bioinformatic analysis on other RA autoantigens may also shed light on possible epitope spreading.

Disclosures: The authors have declared no conflicts of interest.

66. INVESTIGATION OF THE ROLE OF HISTONE DEACETYLASES IN RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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Background: Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease. In RA, fibroblast-like synoviocytes (FLS) be altering BAFF-binding receptor expression with consequences for survival and selection of autoreactive B cells.

Disclosures: The authors have declared no conflicts of interest.
undergo a transformation leading to an autoaggressive phenotype that augments tissue destruction in the joint. Currently it is not known how the phenotype of the FLS is stably maintained, however epigenetic changes have been implicated. Histone deacetylases (HDACs) are enzymes that contribute to the epigenetic signature by affecting the acetylation of histones. Our aim is to determine the role of HDACs in regulating the autoaggressive phenotype of RA FLS.

Methods: Real-time qPCR was used to measure HDAC1-11 mRNA expression in RA and OA FLS. OA FLS were used as a control as normal FLS were unavailable. HDAC1 mRNA expression was also investigated in RA FLS incubated with TNF (50 ng/ml), LPS (100 ng/ml), hypoxia (0.1%) and dexamethasone (1 x 10^-6 M). To determine the cellular localization of HDACs, joint biopsies from patients (n = 7) group) treated or untreated with anti-TNF were co-stained with anti-fibroblast and anti-HDAC1. In addition, HDAC1 was knocked down in FLS using siRNA transfection and the resulting phenotype investigated using BrdU-labelling (proliferation), flow cytometry (cell viability) and matrigel invasion assays.

Results: All 11 HDACs showed higher mRNA expression in RA than OA. In particular, HDAC1 showed the greatest difference, with mRNA expression 3.9 fold higher in RA compared with OA FLS. Expression of HDAC1 was also not altered by incubation with a range of stimuli. HDAC1 was strongly expressed by FLS in RA but not OA, however the reverse was observed in OA patients receiving anti-TNF therapy. A 70% knockdown of HDAC1 did not affect cell viability or proliferation, however this led to a significant (P < 0.005) reduction in FLS invasion into matrigel compared with FLS transduced with a non-targeting control siRNA.

Conclusions: HDAC1 is expressed more in RA than OA FLS but is unaffected by stimulation with pro/anti-inflammatory mediators. HDAC1 expression significantly increases the invasiveness of FLS but does not affect their proliferation or viability. RA patients on anti-TNF therapy show a significant reduction in HDAC1 compared with untreated patients. Further work will determine the effects of HDAC knockdown in FLS and how this influences gene expression.

Disclosures: The authors have declared no conflicts of interest.

68. SYNOVIAL FIBROBLASTS FROM PATIENTS WITH RHEUMATOID ARTHRITIS DIFFERENTIATE INTO DISTINCT FIBROBLAST SUBSETS IN THE PRESENCE OF CARTILAGE

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Background: Synovial fibroblasts (SF) are key cellular mediators of joint inflammation and destruction in RA. RASF have the potential to migrate to distant cartilage sites where they attack, invade and degrade articular cartilage. Using novel markers of SF subsets to identify lining and sub-lining layer SF we investigated the ability of RASF to undergo self-assembly, transmigration and cartilage degradation in vivo.

Methods: Healthy human cartilage was co-implanted subcutaneously into SCID mice together with RASF. At the contralateral flank, cartilage was implanted without cells. After 60 days, implants and blood were removed and analysed. For the detection of human cells, immunohistochemistry was performed with species-specific antibodies. For in vitro studies SF were isolated from patients established RA and normal healthy controls under defined culture conditions and the expression of phenotypic markers analysed.

Results: RASF at the ipsilateral implant differentiated into distinct fibroblast subsets in the presence of cartilage. Cells proximal to cartilage expressed markers of a lining layer phenotype (GP38, FAP, VCAM-1 and Cadherin-11). These cells attached to, invaded and degraded cartilage. Cells more distal to cartilage expressed sub-lining layer phenotype markers including CD248. These cells were never observed in the lining layer and never invaded cartilage. The development of this stromal architecture was very similar to that observed in vivo in the inflamed synovial membrane. This stromal pattern of distinct lining layer and sub-lining layer differentiation was completely recapitulated in the contralateral implant that contained only cartilage. In addition, we demonstrate that SF in vitro can be directed towards either a lining layer (GP38, FAP, VCAM-1 and Cadherin-11) or sub-lining layer phenotype (CD248 and CD90) following cytokine treatment. The lining layer, but not sub-lining cell phenotype is associated with increased cartilage degradation in vitro.

Conclusions: Our observations demonstrate that although RASF have an activated cell phenotype ex-vivo they also display a degree of plasticity with the capacity to differentiate into distinct fibroblast subsets associated with lining and sub-lining layer cell markers both in vitro and in vivo. Differentiation into distinct subsets of fibroblasts occurs locally at the site of engraftment following vascular transmigration and totally recapitulate the lining and sub-lining anatomy observed at the site of origin. This plastic cell phenotype is dependent on local factors including proximity to damaged cartilage. The formation of such a pathogenic stromal architecture is required for cartilage destruction by RASF. We propose that cellular therapies targeting RASF specific subsets are a potentially important but unexplored therapeutic approach to reduce inflammation and joint damage in patients with RA.

Disclosures: The authors have declared no conflicts of interest.

RHEUMATOID ARTHRITIS: TREATMENT

69. ORAL GLUCOCORTICOIDS AND THE RISK OF INCIDENT TYPE II DIABETES MELLITUS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Glucocorticoid (GC) therapy is used by the majority of patients with RA. GCs are effective but have side effects including diabetes mellitus (DM). The aim of this retrospective cohort study was to quantify the risk of incident type II DM in patients with RA treated with oral GCs, and its relationship with dose.

Methods: Adult patients with RA were identified from a large UK primary care research database (CPRD) using a validated algorithm during the study period 01/92–12/09. Patients with prevalent DM at the
time of their first code for RA were excluded. Oral GC exposure was derived from GP prescriptions. GC exposure from first code for RA was considered using several models including a time-varying binary indicator of current use, current daily dose, average daily dose and cumulative dose. Incident DM was defined as a READ code for DM, at least two anti-diabetic prescriptions or abnormal blood results (blood sugar, Hba1C or glucose tolerance test). Follow-up was censored at onset of DM, transfer out of practice, death or study end date.


discern the safety profile for ADA between patients with moderate and severe disease activity. AE rates were lower among patients with moderate disease, yet the mean percent change in DAS28 and HAQ-DI were comparable or greater among those with severe disease (Table 1). AEs were comparable between patients with moderate and severe disease. AE relating to discontinuation (8.2 vs 8.7 E/100PY), serious infections (3.2 vs 3.0 E/100PY).

Conclusions: Through 5 years of ADA treatment, more patients with moderate disease achieved LDA and remission. Patients with severe disease had greater clinical response rates and a similar degree of improvement, while fewer achieved treatment targets of LDA and remission. Given the impact of achieving these targets on preventing complications, we consider treatment response of moderate and severe disease.

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71. HIGH RETENTION ON METHOTREXATE AT 1 YEAR FOLLOWING TIGHT CONTROL OF RHEUMATOID ARTHRITIS

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Background: Methotrexate (MTX) is the gold standard DMARD in the UK for RA and is the cornerstone of most combination therapies. Good response to MTX and on-going drug retention usually predicts a better prognosis and lower disease activity. However, side effects and intolerance, though mostly not serious, frequently prevent full escalation of MTX dose and both of these, along with clinical inefficacy, often lead to drug withdrawal. Historically retention rates on low dose MTX (typically <12.5 mg per week) at 1 year are better than with other DMARDs, but usually only 70–75%, with the main reason for termination being lack of efficacy.

Methods: We wished to assess MTX retention rates in our new Treat-To-Target monthly review clinic for patients with RA of under 2 years’ duration (started 2010). This was set up as an extra service to pre-existing clinic slots were freed up by moving patients with stable disease to annual review with access to urgent assessment if needed. Patients were managed to a strict treatment protocol based partly upon NICE clinical guideline 79 and agreed by all clinicians with MTX being the principal anchor drug. We have previously reported 56% remission/low disease activity at 1 year. In this study we retrospectively analysed all data on MTX use, including dose escalation, management of adverse events and retention rates at 6 months and 1 year.

Results: 108 patients with newly diagnosed RA, based on the American College of Rheumatology classification criteria 2010, were included. Mean age 60 years, male:female 1:1.3, 70% of patients were seropositive for rheumatoid factor or anti-CCP. At the time of the study all patients had been on treatment for at least 6 months and 81 patients for more than 1 year, 96% patients were started on MTX at diagnosis and of these 94% and 92% remained on it at 6 months and 1 year, respectively. Around 80% were started at a dose of 15 mg per week and the remainder on a lower dose. At 6 months the weekly MTX dose for 95% of these patients was 15 mg or more with 60% receiving
between 20 and 25 mg. A similar trend was also seen at 1 year. Four patients had been switched to subcutaneous MTX by 6 months due to lack of efficacy and another 2 because of intolerance. Morning stiffness improved from a median of 60 min to 30 min by 3 months and from 45 min weekly to 30 min weekly by 6 months for the remaining patients.

Methods: We identified patients with a clinical diagnosis of RA starting TNF therapy. A reason could be lack of awareness regarding the disease and availability of medicines. Some patients with chronic diseases such as RA are seen at 1 year.

Results: 11,188 patients with clinical diagnosis of RA starting TNF inhibitors at first time were studied. Their mean age was 56 years and 76% were female. Season of initiation did not predict DAS, DAS change, adverse events or discontinuation at 6 months. However, we examined the effect of latitude, as a continuous measure. There was a significant linear association between more northern latitude and poorer DAS response (adjusted OR 0.95; 95% CI 0.91, 0.98; P = 0.007). Further, the effect of latitude on DAS response varied with season (interaction P = 0.072). The difference between living in the North (above 53.5°) vs other quartiles was most marked in those initiated in the winter season (71.1% response vs 76.9% response, P = 0.007).

Conclusions: We identified patients with a clinical diagnosis of RA starting TNF inhibitors at first time were studied. Their mean age was 56 years and 76% were female. Season of initiation did not predict DAS, DAS change, adverse events or discontinuation at 6 months. However, we examined the effect of latitude, as a continuous measure. There was a significant linear association between more northern latitude and poorer DAS response (adjusted OR 0.95; 95% CI 0.91, 0.98; P = 0.007).

Disclosures: The authors have declared no conflicts of interest.

72. LATITUDE BUT NOT SEASON OF INITIATION PREDICTS CLINICAL RESPONSE TO TNF THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS: THE BSR BIOLOGICS REGISTER-RA

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Background: While the management of RA has been revolutionized by the advent of TNF inhibitors, less than a quarter achieve an excellent response as defined by the ACR 70 in clinical trials. There is a growing body of evidence that vitamin D deficiency directly influences the inflammatory responses in addition to deleterious effects on muscle and bone health in patients with RA. We explored whether vitamin D status was associated with the clinical response to TNF inhibition using season of therapy initiation as a surrogate marker of vitamin D status using the BSR Biologics register.

Methods: We identified patients with a clinical diagnosis of RA starting TNF therapy. We randomized into two groups; group A, n = 64 received dedicated 10 min education and counseling using audio-visual aids regarding RA at the first consultation which was followed by annual reinforcement session at the first follow up visit at 4 weeks; group B, n = 58 was given only standard information regarding RA during the first consultation. Both groups received printed articles in Malayalam (local language) and English regarding autoimmune diseases including RA. Non compliance to follow ups and drugs were recorded.

Results: There was no significant difference in the age, proportion of female patients, disease duration, baseline disability and disease activity between the two groups. Majority of patients in both groups had secondary education or more. The compliance both with follow ups (cumulative 88% vs 72%, P = 0.038) and medications (at 12 and 24 weeks 100% vs 90%, P = 0.026 and 98% vs 82%, P = 0.011, respectively) was significantly higher in the group A. Disease activity was lower in group A.

Conclusions: This study highlights the importance of dedicated education and counseling on adherence to follow ups and medication. A larger study can confirm the benefits of such approach on the clinical outcomes in RA.

Disclosures: The author has declared no conflicts of interest.

74. PREDICTORS OF SIGNIFICANT DISEASE ACTIVITY SCORE-28 (USING C-REACTIVE PROTEIN) REMISSION ACHIEVED WITH INTRAVENOUS GOLIMUMAB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS DESPITE METHOTREXATE THERAPY: RESULTS OF THE PHASE III, MULTICENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Background: Intravenous (i.v.) golimumab (GLM) is efficacious in treating patients with active RA despite MTX. We evaluated rates of DAS28-CRP remission and ACR/EULAR remission in these patients.

Methods: 592 patients with active RA (≥6/68 swollen joints, ≥6/68 tender joints, CRP≥1.0 mg/dl, RF and/or anti-CCP antibody-positive) despite ≥3months of MTX (15–25 mg/week) participated in this multicentre, randomized, double-blind, placebo (PBO)-controlled phase III study. Patients were randomized (2:1) to i.v. GLM 2 mg/kg or PBO at weeks0,4 and 8w; all patients continued stable MTX doses. The primary end point was defined as DAS28-CRP <2.6 and recently developed ACR/EULAR remission using SDAI<3.3. DAS28-CRP analyses used last-observation-carried-forward.

Results: Statistically significantly higher DAS28-CRP remission rates were observed with GLM + MTX vs PBO + MTX at week14 (15.4% vs 4.6%, respectively; P < 0.001) and week 24 (17.7% vs 5.1%, respectively; P < 0.001). Similar trends were seen with remission defined by SDAI score <3.3 (Week14: 4.9% vs 1.6%, respectively; P < 0.005 and week 24: 7.3% vs 2.0%, respectively; P < 0.001). Moderate (approx.10%–15%) increases in week 24 DAS28-CRP remission rates were observed among subgroups of patients defined by HAQ score ≤0.24 (24%) vs > ≥0.24 (12%), baseline physical Functional Class I (27%) vs Class II and III (17% each), swollen joint count ≤12 (23%) vs >12 (14%), tender joint count ≤24 (25%) vs >24 (11%), and CRP ≤1.5 mg/dl (29%) vs >1.5 mg/dl (15%).

Conclusions: In patients with active RA despite MTX, i.v. GLM 2 mg/kg – MTX yielded significantly higher DAS28-CRP remission rates and ACR /EULAR remission rates vs PBO at weeks 14 and 24. Achievement of DAS28-CRP remission appeared to be enhanced in patients with lower levels of baseline physical function impairment and lower joint counts. Confirmation of these hypothesis-generating data is needed.
Tender joint count (median 24):

MTX at baseline (mg/week):

DMARDs at baseline: yes/no 38/206 (18) / 32/189 (17)

Oral corticosteroids at baseline: yes/no 38/251 (16) / 32/144 (22)

RF: negative/positive 6/30 (20) / 64/365 (18)

Disclosures: The author has declared no conflicts of interest.

76. VALIDATION OF REMISSION OF RHEUMATOID ARTHRITIS BY TRADITIONAL DISEASE ACTIVITY SCORE AND PROVISIONAL CRITERIA BY AMERICAN COLLEGE OF RHEUMATOLOGY AND EUROPEAN LEAGUE AGAINST RHEUMATISM: ANALYSIS BASED ON PATIENT-REPORTED OUTCOMES ANALYSED FROM THREE PHASE III GOLIMUMAB CLINICAL TRIALS

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

Methods: The efficacy of golimumab (GLM) was assessed in MTX-naive RA patients (GO-BEFORE; N = 637), RA patients with inadequate response to MTX (GO-FORWARD; N = 444), and RA patients previously treated with biologic anti-TNFs agent(s) with baseline MTX use (GO-AFTER; N = 305). Pooled data from patients who received placebo (PBO) + MTX or GLM (50 or 100 mg) + MTX q4w. Patient reported outcomes were measured with the following: HAQ, SF36 PCS and SF36 MCS, Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F), and a Visual Analogue Scale (VAS, 0–10) of impact of RA on daily productivity. Descriptive statistics were provided for patient reported outcomes among patients in remission as defined by the 3 remission definitions.

Results: Greater proportions of patients treated with GLM + MTX vs patients treated with PBO + MTX achieved remission in the 3 studies by each remission definition. In the pooled analysis, the remission rate at week 24 was the highest (20.1%) by DAS28, compared with remission by SDAI (10.6%, p < 0.001) and remission by Boolean-based definition (8.6%. P < 0.001). Of patients with remission by DAS28-CRP, 67.8%, 38.4%, and 62.2% achieved normal physical function (HAQ ≤ 0.5), normal SF-36 PCS and MCS (≥50), respectively; these parameters were numerically lower than for patients with remission by SDAI (81.3%, 62.8%, 72.1%, respectively) or by Boolean-based definition (82.0%, 63.5%, 74.3%, respectively). Patients in remission by DAS28-CRP had higher HAQ scores (0.43 ± 0.49) compared with patients in remission by SDAI (0.26 ± 0.41) or Boolean-based criteria (0.28 ± 0.44). Similar results were observed in measures of FACT-F and productivity VAS scores. Among MTX-naive patients in GO-BEFORE who achieved remission by DAS28, 71.3% achieved normal physical function compared with 86.9% of those in remission by SDAI and 86.5% of patients in remission by Boolean-based definition. Among anti-TNFs-experienced patients in GO-AFTER, 62.1% of those in remission by DAS28-CRP achieved normal physical function compared with 65.0% of those in remission by SDAI and 66.7% of patients in remission by Boolean-based definition.

Conclusions: While disease remission has been adapted as a target in the management of RA, more stringent remission criteria proposed by ACR/EULAR can provide optimal patient-reported outcomes.

77. INFECTIONS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH RITUXIMAB ARE ASSOCIATED WITH MULTIPLE RISK FACTORS INCLUDING LOW IgM LEVELS

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Background: Studies show that the infection rate following rituximab therapy (RTX) in patients with RA is similar to other drugs. However, repeated cycles of RTX can lead to low immunoglobulin G (IgG) levels, which is a known risk factor for infection. Age and cardiorespiratory disease are also risk factors for infection following RTX in RA. The BSR guidelines advise monitoring Ig levels and withholding RTX if there is an underlying condition that might predispose to serious infection, although only specifically refer to IgG levels below 6 g/l. We audited the infection rate in our cohort of patients treated with RTX, the frequency of Ig monitoring and examined whether any of the observed infections could have been prevented.

Methods: Data from 23 patients with RA who had received RTX between January 2010 and June 2012 were obtained from the hospital records. The age, date of RTX infusions, Ig levels pre and post-RTX, comorbidities and development of infection requiring admission were recorded for each patient.

Results: All patients were female, with a mean age of 55.9 years (range 20 to 84), Ig levels were tested in 11/23 patients (47.8%) pre-RTX and in 20/23 (87.0%) post-RTX.

No infections were observed in 5 patients, with a rate of 17.5 infections per 100 patient years. The infections were pneumonia (3), cellulitis and infected skin ulcer (1), septic arthritis (1) and candidaemia (1). The mean time to first infections after RTX was 6.2 months. The mean age was higher in the patients with infections (P < 0.01). Chronic heart and/or lung disease was present in 4/5 patients that got infections.

The mean IgG and IgM levels were lower in the patients with infections (both P < 0.01) but only 1/5 patients with infections had an IgG level below 6 g/l at the time of infection. IgM levels were below 0.5 g/l in 4/5 patients at the time of infection. Pre-RTX IgG levels were only available for 2/5 patients with infections, both of whom had levels above 11 g/l. IgG levels were normal for all patients with infections and the mean levels did not differ from the patients that did not get infections.

Conclusions: The infection rate in our cohort of patients was much higher than has been reported in other studies. The mean IgG level was lower in the group that got infections, confirming that they are important in protecting against infection but it was below 6 g/l in only one of the patients, suggesting that better monitoring of IgG pre-RTX would have resulted in only a small improvement in the infection rate. Our data support studies that have shown that infections are increased in older patients, when there is heart or lung disease and low IgG levels, but we also found that infections were associated with low IgM levels.

We believe that the BSR guidelines should advise caution with using RTX in elderly patients, when there is known heart or lung disease or when IgG or IgM levels are low.

Disclosures: M.L., Abbott—Honoraria. All other authors have declared no conflicts of interest.

78. TOCILIZUMAB IN METHOTREXATE-INTOLERANT OR CONTRAINDIATED PATIENTS—A COST-UTILITY MODEL FOR THE UNITED KINGDOM

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Background: Tocilizumab (TCZ) is licensed for the treatment of adult RA that has responded inadequately to one or more DMARDs (DMARD-IR patients). Whilst typically given with MTX, TCZ is also licenced for monotherapy treatment in patients who are intolerant of or contraindiated to MTX. The objective was to evaluate the cost-effectiveness of monotherapy TCZ in DMARD-IR patients intolerant or contraindiated to MTX in the UK (UK).

Methods: A cost-utility model was developed to reflect the healthcare system and treatment pathway in the UK. In the model, disease severity is represented by the health assessment questionnaire (HAQ) score, a surrogate health outcome which can be translated to utility scores and ultimately quality adjusted life years (QALYs). The model captures the progression of the HAQ score for each individual patient in an individual simulation process. ACR response rates are used as a measure of response to treatment as these are readily available from TCZ trials as well as from RCTs of the other therapies included in this model.

Benefits were expressed as QALYs. Costs were calculated from a National Health Service and Personal Social Services perspective and included treatment costs as well as patient-condition-related costs. The analysis calculated incremental costs and benefits associated with the addition of TCZ in first line to the standard care pathway involving certolizumab pegol, etanercept and adalimumab. Efficacy data for comparator biologic monotherapies were available from monotherapy trials of adalimumab (van de Putte et al 2004), certolizumab pegol (Fleischmann et al 2009), and etanercept (Moreland et al 1999). TCZ efficacy was informed by results from the ADACTA study (Gabay et al 2012), a new head-to-head superiority trial of TCZ and adalimumab monotherapy in RA. The economic model used inputs derived through a mixed treatment comparison that indirectly compared TCZ mono-therapy with the standard of care biologic monotherapy treatments used in the UK (Roche data on file).

Results: Base case results estimated incremental costs of approximately £20,230 and incremental QALYs of 0.88. The incremental cost-effectiveness ratio (ICER) was £22,950 per QALY gained. The model was most sensitive to patient weight (which drives drug cost) and the parameters used in the HAQ-to-utility estimation equation. A probabilistic sensitivity analysis produced a very similar ICER of £23,200 per QALY gained.

Conclusions: The results of this analysis suggest that TCZ mono-therapy represents an efficacious and cost-effective addition to the current standard of care in the UK, for treating RA patients who are intolerant of or contraindiated to MTX.


79. OUTCOMES OF PREGNANCY IN SUBJECTS EXPOSED TO CERTOLIZUMAB PEGOL

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Background: Certolizumab pegol (CZP) is an Fc-free, PEGylated, anti-TNF approved in the EU for the treatment of RA, and in the US RA and Crohn’s disease. Pre-clinical and clinical data suggest a lack of active transfer of CZP through the placenta. However, there have been few reports of pregnancy outcomes following exposure to CZP to date. This work provides additional information regarding the primary pregnancy outcomes in women exposed to CZP.

Methods: The global CZP safety database was searched for all medically confirmed cases of pregnancy through March 6, 2012. The proportion of live births, spontaneous miscarriages, and elective terminations for women directly exposed to CZP before or during pregnancy was compared with those expected for the general US population of pregnant women.

Results: Of 294 reported pregnancy events, 152 had known outcomes, 89 had unknown outcomes and 53 were ongoing. Of the 152 pregnancies ended in spontaneous miscarriage. 15 pregnancies resulted in elective termination. These results are similar to those reported in the general population in the US (see Table 1). In 193 live births there were 2 reported cases of congenital disorder (Rate in the general US population is 3%); 1 baby had mild, unilateral hydronephrosis on antenatal ultrasound and was described as healthy upon birth. The other baby had vesicoureteric reflux.

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Tuesday 23 April 2013, 10.30–11.30

81. TIMING AND MAGNITUDE OF INITIAL RESPONSE TO CERTOLIZUMAB PEGOL IN A BROAD POPULATION OF PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS PREDICTS LIKELIHOOD OF LDA AT WEEK 28

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Background: Most patients with active RA have a rapid response to certolizumab pegol (CZP), and lack of improvement in DAS28 by week 12 predicts future failure to achieve low disease activity (LDA). We investigated whether the timing/magnitude of week 12 DAS28 (ESR) nonresponse (NR) and swollen joint count (SJC) NR to CZP can predict the likelihood of achieving LDA at week 28 in a broad RA population, including patients with prior anti-TNF, from the REALISTIC study.

Methods: Following the 12week double blind phase (CZP 400mg PBO at weeks 0,2,4, then CZP 200mg/PBO at weeks 6,8,10 plus current treatment), patients received open-label CZP 200mg Q2W for ≥16 weeks. The proportion of patients who achieved LDA (DAS28 < 3.2) at week 28 was assessed according to the level of DAS28 NR (i.e. DAS28 change from baseline [CFB] <0.3, 0.6, 0.9, 1.2, 1.5 and 1.8 units) and SJC NR (quantiles for %CFB at week 12 < −29%, −60%, −85%). Missing data were imputed using last observation carried forward.

Results: CZP-treated patients (N = 851) had a mean baseline DAS28 of 6.4 and SJC of 11.8. Overall, 81.1% of patients had <1.2 CFB DAS28 response and 89.3% had ≥29% CFB in SJC by week 12. LDA was achieved by 27.4% of the original CZP ITT population at week 28. Failure to achieve LDA at week 28 was dependent on the magnitude and timing of DAS28 and SJC change up to week 12. Patients with DAS28 changes ≤0.3 up to week 6 and <1.5 up to week 12, had <10% chance of having LDA at week 28 (Table 1). Patients without a SJC change of 29% by week 12 had ≥10% chance of achieving LDA at week 28. For any given threshold in DAS/SJC change up to week 12, the failure to respond up to a later timepoint was associated with a lower chance of achieving LDA at week 28. At BL 37.6% of CZP patients had received prior anti-TNF therapy; 79.6% of these patients had <1.2 CFB DAS28 response at week 12, similar to the proportion of naive patients (82.1%). Failure to achieve a DAS28 change of ≥1.2 by week 12 was associated with <5% chance of achieving LDA at week 28 for both groups.

Conclusions: The majority of patients responded to CZP treatment by week 12 in this broad population. Likelihood of LDA at 28 weeks could be predicted early in the course of treatment with CZP based on the timing and magnitude of initial DAS28/SJC change in patients both naïve and exposed to prior anti-TNF.

Table 1. Proportion of CZP patients achieving LDA at week 28 by DAS28 and SJC change up to week 12

<table>
<thead>
<tr>
<th>Week 2</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td>% (n/N)</td>
</tr>
<tr>
<td><strong>DAS28 (ESR) change from BL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.3</td>
<td>16.6 (27/166)</td>
<td>9.3 (6/66)</td>
</tr>
<tr>
<td>0.3–0.6</td>
<td>17.9 (48/268)</td>
<td>12.2 (14/115)</td>
</tr>
<tr>
<td>0.6–0.9</td>
<td>19.8 (66/340)</td>
<td>19.0 (19/104)</td>
</tr>
<tr>
<td>0.9–1.2</td>
<td>20.9 (83/403)</td>
<td>18.9 (28/150)</td>
</tr>
<tr>
<td>1.2–1.5</td>
<td>21.5 (113/526)</td>
<td>14.8 (51/344)</td>
</tr>
<tr>
<td>≥1.5</td>
<td>18.7 (220/1196)</td>
<td>17.1 (35/206)</td>
</tr>
<tr>
<td><strong>SJC % change from BL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤−29</td>
<td>29.6 (86/300)</td>
<td>13.8 (19/138)</td>
</tr>
<tr>
<td>&lt;−60</td>
<td>60.2 (237/394)</td>
<td>17.7 (62/351)</td>
</tr>
<tr>
<td>&lt;−85</td>
<td>27.1 (184/680)</td>
<td>23.0 (130/564)</td>
</tr>
</tbody>
</table>

*%5 probability of LDA at week 28.
Disclosures: O.D., UCB Pharma—Employee, Stock Holder, R.F., Genentech Inc, Roche, Abbott, Amgen, UCB Pharma, Pfizer, BMS, Lilly, Sanofi-Aventis, Lexicon, MSD, Novartis, Biogen Idec, Astellas, Astrazeneca, Jansen—Research Grant, Roche, Abbott, Amgen, UCB Pharma, Pfizer, BMS, Lilly, Sanofi-Aventis, Lexicon, Novartis, Astellas, Astrazeneca, Jansen—Consultation Fees, K.L., UCB Pharma—Employee, D.V., Abbott, Amgen, Astrazeneca, BMS, Centocor, Chugai, Eli-Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma, Wyeth—Consultation Fees, Research Grants, Imaging Rheumatology by—owner. M.W., Abbott, UCB Pharma—Research Grants, UCB Pharma, Abbott, Amgen, Pfizer, Centocor—Consultancy Fees. All other authors have declared no conflicts of interest.

83. MANAGEMENT OF RHEUMATOID ARTHRITIS IN WALES: AN ALL-WALES AUDIT

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Background: We undertook an All Wales audit in 2012 to assess whether we were following NICE guidelines (CG79) especially in prescription of DMARDs and monitoring of disease. We also compared the audit with a previous audit done in 2009 to assess improvement in service provided in Wales and to identify our shortcomings.

Methods: Data were collected from each rheumatology centre in Wales. The NICE criteria assessed in our audit included (i) percentage of people with newly diagnosed active RA who were offered combination DMARDs therapy as first line treatment; (ii) percentage of people with recent-onset active RA who had their CRP measured monthly until treatment has controlled the disease to a level agreed with the person; (iii) percentage of people with recent-onset active RA who had had their DAS calculated despite, (iv) 27% had DAS assessments done monthly, 14% didn't have DAS checked despite, 31% had DAS checked each visit (visits weren’t monthly), 15% had them checked infrequently or not at all.

Results: Data were collected for 169 patients retrospectively.

Conclusions: In comparison with the audit done in 2009 there seemed to be marked improvement in DMARD initiation within 3 months 19% vs 44% respectively. In both audits difficulties were noticed in monitoring disease activity due to reasons mentioned above. Establishment of early RA clinics may help achieve these targets and many units are in the process of establishing them.

Disclosures: The authors have declared no conflicts of interest.
84. A RETROSPECTIVE STUDY OF THE EFFECTS OF SWITCHING FROM ORAL TO SUBCUTANEOUS METHOTREXATE ON DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Oral MTX is the gold standard first-line therapy for RA patients. The place in therapy for subcutaneous (SC) MTX is less clear, even though it has proven to be effective in patients who fail to respond or tolerate oral MTX and allows them to continue on MTX for longer, thus delaying the need for biologic therapy [1]. Perhaps one reason for this is the lack of outcome data using DAS28, which is widely used in clinical practice and in NICE [2] and BSR [3] guidelines to determine eligibility for biologic therapy (≥5.1 and ≥3.2, respectively). The aim of this audit was to evaluate the response to treatment, as measured by DAS28, in RA patients following a switch from oral to SC MTX and to assess the impact on clinical management.

Methods: A retrospective medical record review of all RA patients who had switched from oral to SC MTX and had DAS28 at baseline and at 3 and/or 6 months was undertaken.

Results: 27 patients (63% female; average age 61.6 years; average disease duration 20.8 years; 78% on other DMARDs) had DAS28 values at 3 months (n = 22) and/or 6 months (n = 18). For those with 3 month data, DAS28 fell 0.8 points, from 5.06 at baseline to 4.2, with 36% having DAS28 improvement of ≥1.2. After 3 months, the proportion of patients with DAS28 ≥5.1 and ≥3.2 fell from 55% at baseline to 50% and from 95% at baseline to 73%, respectively. For those with 6 month data, DAS28 fell 1.9 points, from 5.5 at baseline to 3.6, with over 60% having DAS28 improvement of ≥1.2. After 6 months, the proportion of patients with DAS28 ≥5.1 and ≥3.2 fell from 67% at baseline to 11% and from 100% at baseline to 44%, respectively.

Conclusions: This study shows that SC MTX was effective in lowering DAS28. After 6 months’ SC MTX, 89% and 56% of patients were below the NICE and BSR threshold for biologic therapy, respectively. Since SC MTX can improve clinical outcomes, this treatment strategy should be a considered before use of biologic therapy in RA patients who do not respond to or tolerate oral MTX.

Disclosures: The authors have declared no conflicts of interest.

References

85. CHANGES IN PATIENT-REPORTED OUTCOMES IN RESPONSE TO SUBCUTANEOUS ABATACEPT OR ADA LIMUMAB IN RHEUMATOID ARTHRITIS: RESULTS FROM THE AMPLE (ABATACEPT VS ADALIMUMAB COMPARISON IN BIOLOGIC-NAÍVE RA SUBJECTS WITH BACKGROUND METHOTREXATE) TRIAL

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Background: This study assessed how use of an objective multi-biomarker disease activity test (MBDA) for RA affects treatment decisions made by health care providers (HCPs) in clinical practice.

Methods: At routine office visits, 101 patients with RA were assessed by their HCPs (N = 6), and they provided samples for MBDA testing. HCPs completed surveys before and after viewing the MBDA test result, recording dosage and frequency for all planned RA medications at physician global assessment of disease activity. Frequency and types of change in treatment plan that resulted from viewing the MBDA test result were determined. The primary outcome was the percentage of cases in which the HCP changed the planned treatment as viewing the MBDA test result.

Results: Prior to HCP review of the MBDA test, disease modifying anti-rheumatic drug (DMARD) use by the 101 patients included MTX in 62% of patients; HCQ 29%; TNF-inhibitor 42%; non-TNF-inhibitor biologic 19%; and other drugs at lower frequencies. Review of MBDA test results changed HCP treatment decisions in 38 cases (38%), of which 18 involved starting, discontinuing or switching a biologic or non-biologic DMARD. Other changes involved drug...

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87. STUCK IN THE MIDDLE WITH DAS: UNDERTREATMENT OF MODERATE RHEUMATOID ARTHRITIS

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1Rheumatology, Great Western Hospital, Swindon, UK

Background: In the UK access to biologic agents for the management of RA is restricted to patients with a DAS28 score of 5.1 or greater. Scores of 3.2 or less are accepted as representing good disease control. Patients whose score falls between 3.2 and 5.1 have no access to biologic therapy despite inadequately controlled disease and may be vulnerable to worse outcomes. We sought to ascertain the burden of disease activity in our clinics using DAS28 as a surrogate marker and to assess outcome for patients with higher scores.

Methods: For 4 weeks all RA patients attending outpatient clinics had DAS28CRP calculated and treatment decisions reviewed. Patients were grouped into 5 groups: Group 1 DAS28 <3.2, Group 2 DAS28 3.2-3.9, Group 3 DAS28 4.0-4.9, Group 4 DAS28 5.0-5.9, Group 5 DAS28 >5.1. Patients in group 4 and 5 had their DAS28 scores reassessed at up to 6 months.

Results: 333 patients were reviewed and DAS28 calculated on 312.

Group 1: 2 patients (0.6%) had their DMARD therapy increased and 2 (0.6%) had their DMARD therapy decreased.

Group 2: 37 patients (11.9%) of whom 32 (86.4%) had their DMARD therapy increased and 3 (8.1%) had their DMARD therapy decreased.

Group 3: 70 patients (22.4%) had their DMARD therapy increased, 2 (2.8%) had their DMARD therapy decreased and 9 (2.8%) had their DMARD therapy unchanged.

Group 4: 39 patients (12.5%) of whom 19 (48.7%) had their DMARD therapy increased, 15 (38.5%) had their DMARD therapy unchanged and 3 (7.7%) had their DMARD therapy decreased.

Group 5: 37 patients (11.5%) of whom 32 (86.4%) had their DMARD therapy increased, 2 (2.8%) had their DMARD therapy unchanged and 3 (8.1%) had their DMARD therapy decreased.

Conclusion: This small real life study showed that 33% of patients receiving biologic therapy had their DMARD therapy increased during follow up. 22% of patients had their DMARD therapy reduced and 2.8% had their DMARD therapy unchanged.

Disclosures: The authors have declared no conflicts of interest.

88. SHOULD MSK ULTRASOUND ASSESSMENT BE DONE ROUTINELY PRE-BIOLOGICS IN INFLAMMATORY ARTHRITIS MANAGEMENT?

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Background: Musculoskeletal ultrasound (US) has proven to be more sensitive method of detecting synovitis than clinical examination. It may provide a useful role in routine assessment for established IA patients rather than being not consistent or somewhat inconsistent with the HCP assessment of disease activity. Study limitations include sample size and a lack of control group or longitudinal follow-up.

Conclusions: The add-on of the MBDA test to clinical assessment led to meaningful changes in the treatment plans of 38% of RA patients being cared for by HCPs in office practice. Even though treatment was potentially improved, the overall quantity of drug use was minimally affected.


89. REGISTRY, AUDIT AND OBSERVATIONAL STUDY OF GREATER GLASGOW AND CLYDE RHEUMATIC PATIENTS RECEIVING BIOLOGIC THERAPY: BASELINE FEATURES AND ADVERSE EVENT PROFILE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Elaine Morrison1, Ann Tierney2, Hilary Wilson3 and John Hunter4

1Rheumatology, Southern General Hospital, Glasgow, 2Centre for Rheumatic Diseases, Glasgow Royal Infirmary, Glasgow, 3Rheumatology, Stobhill Hospital, Glasgow and 4Rheumatology, Gartnavel General Hospital, Glasgow, UK

Background: Our aims were (i) to establish a registry and collaborative audit of all Greater Glasgow and Clyde (GGandC) patients already receiving or starting biologic therapy in routine clinical practice; (ii) to provide detailed local data to the participating clinicians; (iii) to share data, including adverse events, between units; and (iv) to ensure good clinical governance in our biologic prescribing.

Methods: In 2007 we established a multi-disciplinary clinical group to contribute to the project. Six units participated (Southern General Hospital, Gartnavel General Hospital, Stobhill Hospital, Glasgow Royal Infirmary, Victoria Infirmary and Inverclyde Royal Hospital). Biologics are prescribed in accordance with the British Society for Rheumatology guidelines. All GGandC rheumatic patients receiving biologics are included but only data from those with RA are being presented here. Patient demographic data are collected at baseline. DAS28 and HAQ are calculated at baseline, 3 months,
6 months and thereafter 6 monthly. Past medical history, weight and smoking status are recorded. **Results:** Of 1118 rheumatic patients registered, the majority (n = 701, 63.2%) have RA. Of patients with RA, the median age (n = 701) is 57 years (range = 19–96 years) and median disease duration (n = 474) is 11 years (range = 1–56 years). Median baseline DAS28 (n = 474) was 6.2 (range 3.89–8). Most patients with RA receive biologic therapy in years 1–10 after disease onset. Median number of previous DMARDs (n = 576) is 3 (range 1–9). Reported adverse event profile is similar to previous studies. Most patients discontinue therapy due to lack of effect rather than an adverse event. Social deprivation index shows that 33% of all the rheumatic patients on our registry are Carstairs 6 and 7 (most socially deprived).

**Conclusions:** The majority of our patients with RA receiving a biologic have a high baseline DAS28 and long disease duration. There is good concordance of prescribing with BSR guidelines. There is a high prevalence of social deprivation in our patient group. Despite this, the reported adverse event profile is similar to that in the literature. **Disclosures:** The authors have declared no conflicts of interest.

**90. SYSTEMATIC REVIEW COMPARING COMBINATION DMARD THERAPY WITH ANTI-TNF PLUS METHOTREXATE IN DRUG-RESISTANT RHEUMATOID ARTHRITIS**

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**Background:** We have previously shown that combination DMARD therapy is comparable to anti-TNF therapy in combination with MTX in early RA. In this systematic review, we aim to compare these 2 intensive regimes in RA patients with any disease duration who have been refractory to DMARD monotherapy.

**Methods:** A systematic literature search of Cochrane Library, EMBASE and Ovid Medline identified 19 relevant RCTs. The following outcome measures were assessed: ACR 20, ACR 50, ACR 70, patient withdrawal for adverse events, patient withdrawal for inefficacy and mean change in HAQ. Review Manager 5.1 was used for meta-analysis.

**Results:** There were no direct head to head studies comparing DMARD therapy with anti-TNF and MTX. Consent-TNF indirect comparisons were made between RCTs of DMARD combinations and anti-TNF with MTX when compared with DMARD monotherapy. Both combination DMARDs and anti-TNF/MTX gave more ACR50, 50 and 70 responders. In combination DMARD studies, there were more withdrawals for inefficacy and toxicity when compared with DMARD monotherapy. In anti-TNF with MTX RCTs, there were less patient withdrawals due to inefficacy and no difference in patient withdrawal due to toxicity when compared with DMARD monotherapy. Both anti-TNF and combination DMARDs both gave greater improvements in HAQ compared with DMARD monotherapy, however, the improvement may be more pronounced in anti-TNF with MTX studies (Table 1).

**Conclusions:** Unlike in early RA studies, this systematic review showed that anti-TNF with MTX seems to have more efficacious and a less toxic than combination DMARD therapy in patients resistant to DMARD monotherapy. This implies that anti-TNF with MTX should be the preferable treatment regime in patients who have failed 1 DMARD. A direct head-to-head study is required to confirm these findings.

**Table 1. Combination DMARDs or anti-TNF/MTX vs DMARD monotherapy**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Studies</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Combo DMARDs</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>anti-TNF/MTX</td>
<td>9</td>
</tr>
<tr>
<td>ACR50</td>
<td>Combo DMARDs</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>anti-TNF/MTX</td>
<td>9</td>
</tr>
<tr>
<td>ACR70</td>
<td>Combo DMARDs</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>anti-TNF/MTX</td>
<td>9</td>
</tr>
<tr>
<td>Withdrawal due to efficacy</td>
<td>Combo DMARDs</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>anti-TNF/MTX</td>
<td>7</td>
</tr>
<tr>
<td>Withdrawal due to toxicity</td>
<td>Combo DMARDs</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>anti-TNF/MTX</td>
<td>7</td>
</tr>
<tr>
<td>HAQ</td>
<td>Combo DMARDs</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>anti-TNF/MTX</td>
<td>1</td>
</tr>
</tbody>
</table>

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

**91. TOCILIZUMAB IS EFFECTIVE FOR THE TREATMENT OF ANTI-TNF- AND RITUXIMAB-REFRACTORY RHEUMATOID ARTHRITIS**

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**Background:** A significant proportion of patients with RA continue to have active disease and accrue joint damage despite the use of DMARDs and biologics including anti-TNF agents and B-cell depletion therapy with rituximab. We have evaluated whether this group of patients respond to treatment with tocilizumab as data on sequential use of tocilizumab after rituximab are deficient.

**Methods:** Nineteen patients with seropositive (rheumatoid factor and/or anti-cyclic citrullinated peptide antibody) and 6 with seronegative RA (based on American College of Rheumatology diagnostic criteria) were included. The mean age of patients was 54 years and the mean disease duration was 9 years. All had an active disease with a mean DAS28-ESR score (DAS-ESR, DAS28) of 6.1, which was refractory to at least two conventional DMARDs; two anti-TNF agents and rituximab used sequentially. All patients received tocilizumab, (3–48 months after rituximab), intravenously (8 mg/kg every 4 weeks). Clinical, laboratory and functional parameters were monitored every 3 months for the duration of follow up of 12 months. Statistical analysis was performed using paired ‘t’ test.

**Results:** At 12 months, 23 patients (92%) had sustained response (DAS28 improved by >1.2) and 10 (40%) were good responders (European League Against Rheumatism response criteria) with DAS28 ≤3.2. None of the patients required an increase in the dose of background DMARDs. Two patients had discontinued treatment due to adverse events (recurrent mouth ulcers and infections).

At 3 and 12 months, the mean ± s.d. of: DAS28 reduced from 6.1 ± 1.3 to 3.7 ± 1.4 (P < 0.001) and 2.5 ± 0.8 (P < 0.0001); tender joint count decreased from 13.8 ± 10.1 to 5.6 ± 7.6 (P < 0.01) and 1.4 ± 2.3 (P < 0.003); and swollen joint count decreased from 5.7 ± 3.7 to 3.2 ± 2.7 (P = 0.2) and 0.8 ± 0.8 (P = 0.009), respectively. A significant improvement in patient reported outcomes visual analogue -global (P = 0.02) and -pain (P = 0.02) scores was noted only by 9 months. An improvement in functional activity was noted in SF-36 (P = 0.01), but not FACIT-52 or HAQ scores at 12 months. Also, at 3 and 12 months, the mean ± s.d. of: ESR decreased from 41 ± 33 to 8 ± 11 (P = 0.0002) and 8 ± 9 (P = 0.001); and CRP from 23 ± 33 to 2 ± 3 (P = 0.001), 2 ± 2 (P = 0.001), respectively. There was no significant increase in the level of cholesterol or alanine aminotransferase. The neutrophil and platelet count reduced significantly, but remained within the normal range and did not result in adverse events.

**Conclusions:** Sequential use of tocilizumab appears to be well tolerated, safe and effective for anti-TNF- and rituximab-refractory RA. Whereas very rapid control of CRP was achieved within 1 month, clinical outcome measures continued to improve beyond 3 months. Monitoring of cholesterol, full blood count and liver function tests is warranted.

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

**92. EFFICACY AND LONG-TERM SAFETY OF RITUXIMAB IN RHEUMATOID ARTHRITIS: 8 YEAR FOLLOW-UP OF THE FIRST 52 PATIENTS TREATED IN THE BELFAST TRUST RHEUMATOLOGY UNIT**

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**Background:** B-cell targeted therapy using rituximab, an anti-CD20 monoclonal antibody, is an effective treatment for RA. Trials suggest that rituximab is well tolerated over time.

**Methods:** We present an observational case analysis of longevity, efficacy and safety data on the first 52 patients with active RA treated in our unit with rituximab.

**Results:** Our cohort of patients (40 female and 12 male) received their first dose of rituximab between September 2004 and May 2008 (273 patient-years). Patients were clinically assessed and adverse events documented at least every 6 months. 12 patients had received no previous anti-TNFs agents. The remaining 40 patients had received an average of 1.9 previous anti-TNFs agents. 3 of these patients had also received anakinira.

As of October 2012, 44% (n = 23) of patients were receiving ongoing treatment with rituximab (average number of cycles per patient = 6.4), 21% of patients (n = 11) had stopped due to temporary failure of rituximab, 8 of whom subsequently responded to other
biologic drugs: tocilizumab (n = 4), abatacept (n = 2) and etanercept (n = 2). 13% had stopped due to secondary failure of rituximab (n = 7) (average number cycles per patient = 4.1), 5 of whom subsequently responded to other biologic drugs: tocilizumab (n = 4) and adalimumab (n = 1). 12% (n = 6) had gone into clinical remission and required no further biologic treatment after 1 cycle (n = 3) and after 2 cycles (n = 3). The remainder of patients had their rituximab treatment stopped due to serum IgG levels of <30 mg/L (n = 1) and at patient’s request (n = 1). Of the 13.4% of patients who were sero-negative (n = 7), 5 had primary failure of rituximab and the other 2 remain on treatment at 6 years.

Overall 34.6% (n = 18) of patients developed a persistently (>6 months) low IgM and 10% (n = 5) developed a persistently low IgG. A further 17% (n = 9) developed a transiently low IgG or IgM. One patient developed a persistently panhypogammaglobulinaemia and was taken off all biologic drugs. Of the 6 patients with persistently low IgG, 2 patients died of sepsis, 1 patient had primary failure of rituximab, 1 patient had secondary failure of rituximab (after 3 cycles) and only 1 remained on treatment (6 cycles).

There was no significant difference in infection rates in patients who developed a low IgM. There were no cases of tuberculosis or opportunistic infections.

Conclusions: Our experience confirms that rituximab is an effective long term treatment for RA, particularly in seropositive disease. It remains generally well tolerated over time. Data from our unit showed a significantly higher frequency of persistently low IgM (34.6%) and low IgG (10%) compared with a recent large pooled observational case analysis (22.45 and 3.5% respectively).

Disclosures: The authors have declared no conflicts of interest.

93. DEVELOPMENT OF PATIENT-REPORTED EXPERIENCE MEASURES FOR RHEUMATOID ARTHRITIS: RESULTS OF A PILOT STUDY

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Rheumatoid Arthritis, Royal Lancaster Infirmary, Lancaster and Clinical Sciences, University of Liverpool, Liverpool, UK

Background: Improving patient experience is a priority for the NHS: (i) the Care Quality Commission (CQC) and National Institute for Health and Clinical Excellence (NICE) published a Quality Standard that focused on improving patient experience; (ii) the NHS Patient Experience Framework (NPEF), published by the DoH, outlines the issues most important to patient experience of the NHS. It highlights the need to measure and improve the patient experience. Patient experience is currently routinely measured in RA. Commissioning for Quality in Rheumatoid Arthritis (CQRA) has previously developed quality commissioning metrics for RA. We demonstrated that implementation of the metrics can facilitate improvement of quality of care. CQRA has now developed a set of Patient Reported Experience Measures (PREMs) based on the NPEF.

Methods: CQRA carried out a scoping project to gain patients’ views and establish patient priorities on their journey through the healthcare system. Scoping covered eight areas corresponding to the evidence-based list in the NPEF. A focus group was selected as the preferred scoping method: 8–10 participants were selected and a maximum variation sample was used. Participants were members of the National Rheumatoid Arthritis Society (NRAS) aged >18 years, with active RA. A pilot study interview was conducted with one participant and analysis undertaken by recording and transcribing the focus group and interview recording. NVivo qualitative analysis software, data were encoded and emerging themes grouped together. Similarities and differences between respondents were then identified.

Results: The scoping project identified a number of key themes to be addressed in the design of a rheumatology services PREMs questionnaire. Overarching themes were: respect for patient-centred values, preferences, and expressed needs; coordination and integration of care; information, communication, and education; physical comfort; emotional support; involvement of family and friends; transition and continuity of care; and access to care. A PREMs questionnaire was developed through CQRA workshops using outputs from the scoping project together with the NICE clinical guideline on RA management, mapped against the NPEF. The questionnaire has been piloted in NRAS members, refined and re-piloted in four RA units.

We will present full results of these pilot studies and the final PREMs questionnaire.

Disclosures: Following the development of RA quality commissioning metrics, CQRA has developed and piloted a PREMs questionnaire. Implementation of the PREMs and metrics will enable commissioners and providers to improve the quality of services delivered to RA patients and to improve patient experience of care under an integrated approach for a long term condition.

94. REAL-WORLD EFFICACY AND SAFETY OF ABATACEPT TREATMENT FOR RHEUMATOID ARTHRITIS: 12-MONTH INTERIM ANALYSIS OF THE ACTION STUDY

Hubert Nusslein1, Rieke Alten2, Mauro Galeazzi3, Hannes M. Lorenz4, Dimitrios Boumpas5, Michael T. Nurfomohamed6, William Bensen7, Gerd R. Burmester8, Hans-Hartmut Peter9, Franz Rainer10, Karel Pavelka11, Melanie Chartier12, Coralie Poncet13, Christiane Rauch14 and Manuela Le Bars15

1Institute of Rheumatology, University Medicine, University of Siena, Italy, 2Division of Rheumatology, University Hospital Heidelberg, Heidelberg, Germany, 3Rheumatology, Clinical Immunology and Allergy, Panepistimiopolis Hospital, Athens, Greece, 4VU University Medical Centre, Jan van Breemen Research Institute, Amsterdam, Netherlands, 5Department of Medicine, St Joseph’s Hospital and McMaster University, Hamilton, ON, Canada, 6Department of Rheumatology, University Medical Center Freiburg, Freiburg, Germany, 7Department of Internal Medicine, Hospital Barmerzheker Brueder, Graz, Austria, 8Institute and Clinic of Rheumatology and Charité Universitätsmedizin, Berlin, 9Centre of Chronic Immunodeficiency, University Medical Centre Freiburg, Freiburg, Germany, 10Department of Biostatistics, Docs International, Sèvres, France, 11Medical Affairs Immunoscience, Bristol-Myers Squibb, Munich, Germany and 12Medical Affairs, Bristol-Myers Squibb, Rueil-Malmaison, France

Background: Randomized controlled trials (RCTs) of abatacept (ABA) in patients with RA have demonstrated sustained, long-term efficacy, high pt retention and consistent safety. We evaluate 1-year retention, efficacy and safety of ABA in routine RA clinical practice (according to label at enrolment) in Europe and Canada.

Methods: Abatacept in Routine Clinical practice (ACTION) is an ongoing, non-interventional, prospective cohort of ABA-treated RA patients with data available, according to whether patients received ABA as a first biologic, or after failure of 1 or 2 anti-TNFs. Earlier usage of ABA resulted in higher retention (Table 1). 106 serious adverse events were reported in 12 months for patients on treatment with data available, according to whether patients received ABA as a first biologic, or after failure of 1 or 2 anti-TNFs. Safety is reported for all patients enrolled, up to data cut-off.

Results: 1138 patients were enrolled and 1120 were evaluable. 1900 (89.3%) had previously failed biologic treatment, 982/1000 (98.2%) had failed ≥1 anti-TNF, 120 (10.7%) had not received biologic treatment prior to ABA. Baseline characteristics are shown (Table 1). Retention rates, reasons for discontinuation and EULAR responders at Mth 12 are presented for ABA when used as the first biologic, first switch agent, and after ≥2 anti-TNFs. Earlier usage of ABA resulted in higher retention (Table 1). 106 serious adverse events were reported in 60/1138 (5.3%) patients (21 discontinuations). 11 deaths were reported, 2 severe infections univ. to AB. Efficacy responses are reported over 12 months for patients on treatment with data available, according to whether patients received ABA as a first biologic, or after failure of 1 or 2 anti-TNFs. Earlier usage of ABA resulted in higher retention (Table 1). 106 serious adverse events were reported in 60/1138 (5.3%) patients (21 discontinuations). 11 deaths were reported, 2 severe infections (infections and vascular disorders. No TB occurred, 2 opportunistic infections were reported (P. jiroveci and cytomegalovirus). 3 patients experienced serious infections; 9 malignancies; 5 serious cardiac disorders; and 3 serious vascular disorders. No TB occurred, 2 opportunistic infections were reported (P. jiroveci and cytomegalovirus).

95. EXPECTATIONS OF NEW TREATMENT IN RHEUMATOID ARTHRITIS: THE DEVELOPMENT OF A PATIENT-GENERATED SCALE
Heidi Lempü,1,2 Daria Hofmann2, Aderonke Adû2, Carron Congreve3, Joanne Dobson3, Diana Rose3, Carol Simpson1, Til Wykes1, Andrew Cope1, David L. Scott1,2 and Fowzia Ibrahim1
1Academic Rheumatology, School of Medicine, King’s College London, London, 2Rheumatology, King’s College Hospital NHS Foundation Trust, London and 3Health Service and Population Research Department, Institute of Psychiatry, King’s College London, London, UK

Background: Partnerships with patients are understood as essential for the development of evidence-based care in the UK and across the globe and may offer one solution to the slow translation of clinical science into meaningful treatment. Service user partnerships in research exist in mental health but there have been few advances in other disciplines. Our objective was to develop a patient-generated expectancy measure for new treatments in Rheumatoid Arthritis, using a participatory method.

Methods: Stage1: three repeated focus groups and two expert panels with RA patients conducted by a Patient Researcher. Stage2: feasibility study of draft scale with 22 consecutive outpatient attendees over 1 week and Stage3: psychometric testing with 140 patients over 4 months.

Results: Patients identified 21 dimensions of new treatment expectations, grouped into (i) physical (ii) psycho-social and (iii) expectations relating to impact of treatment. This resulted in a scale assessed in a feasibility study and psychometric assessment. 140 patients were recruited into stage 3. 64 returned the questionnaires so far with similar: 27.4, 42.5, 58.5, 60.1, 66.0, 70.1 and 66.0%, respectively.

Conclusions: Participatory research methods are useful in involving patients actively in research and to produce collaboratively a feasible, valid and acceptable measure in RA. Our results illustrated that patients’ expectations were high in relation to the impact of treatment, compared with the physical and psycho-social expectations. The scale will be included in a longitudinal observational study, with newly diagnosed patients, to assess sensitivity to change for expectations when in receipt of new treatment over time.

96. WEEKLY SUBCUTANEOUS ABATACEPT CONFRONS COMPARABLE ONSET OF TREATMENT RESPONSE AND MAGNITUDE OF EFFICACY IMPROVEMENT OVER 6 MONTHS WHEN ADMINISTERED WITH OR WITHOUT AN INTRAVENOUS ABATACEPT LOADING DOSE
Michael Schiff1, Rieke Alten2, Michael E. Weinblatt3, Peter Nash4, Roy Fleischmann5, Patrick Durez6, Jeffrey Kaine7, Ingrid Delaet8, Sheila Kelly9, Michael Maldonado10, Salil Patel11 and Mark Genovese10
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Background: The aim of this analysis was to compare clinical and functional responses with subcutaneous (SC) abatacept administered with or without an intravenous (i.v.) loading dose, in patients with active RA and inadequate response to MTX.

Methods: Patients from the intent-to-treat populations of the ACQUIRE and AMPLER studies randomized to SC abatacept plus MTX were included in this analysis. All patients received fixed-dose SC abatacept 125 mg/week; in ACQUIRE, patients also received an i.v. loading dose administered in AMPLER. For this post-hoc analysis, assessments included ACR 20 and Health Assessment Questionnaire-Disability Index (HAQ-DI) response (improvement of ≥0.3) over 6 months, with patients who discontinued considered non-responders. Mean changes from baseline over 6 months in DAS28-CRP were assessed in patients with DAS28 >5.1 at baseline (last observation carried forward), to account for differences in baseline disease activity between the two studies.

Results: A total of 736 patients from ACQUIRE (i.v. loading dose) and 318 patients from AMPLER (no i.v. loading dose) were included. All patients were biologic naïve at baseline, with mean disease duration of 7.6 and 1.9 years, DAS28 (CRP) 6.2 and 3.5, and HAQ-DI 1.72 and 1.6 in ACQUIRE and AMPLER, respectively. Efficacy was compared at Days 15, 29, 57, 85, 113, 141 and 169. For patients treated with SC abatacept with an i.v. loading dose, ACR 20 response rates were 24.6, 45.4, 58.0, 66.6, 69.3, 72.4 and 74.8%, respectively. For patients treated without an i.v. loading dose, ACR 20 response rates were similar: 27.4, 42.5, 58.5, 60.1, 66.0, 70.1 and 66.0%, respectively.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>ABA first biologic, n = 120</th>
<th>ABA first switch (1 previous anti-TNF), n = 481</th>
<th>ABA after 2 previous anti-TNFs, n = 501</th>
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</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>59.0 (13.8), n = 120</td>
<td>7.0 (7.8), n = 118</td>
<td>86 (71.7), n = 120</td>
</tr>
<tr>
<td>RA duration, mean (s.d.), years</td>
<td>1 (CV risk or comorbidity, n (%)</td>
<td>21 (7.6), n = 118</td>
<td>38 (71.7), n = 120</td>
</tr>
<tr>
<td>MHI 12 outcomes</td>
<td>Retention, Kaplan-Meier estimate, % (95% CI)</td>
<td>Good EULAR response, %</td>
<td>34.5, 42.5, 58.5, 60.1, 66.0, 70.1 and 66.0%, respectively.</td>
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</tbody>
</table>

Disclosures: The authors have declared no conflicts of interest.
HAQ-DI response rates were also similar: 31.7, 45.1, 53.5, 59.5, 63.2, 64.4 and 68.3%, respectively, with the i.v. loading dose, and 31.8, 42.8, 54.4, 58.5, 60.1, 61.9 and 61.0%, respectively, without. For the overall populations, mean (i.v.) changes from baseline to Day 19 in DAS28 were –2.57 (1.30) and –2.09 (1.38) in ACQUIRE and AMPLER, respectively. For patients with baseline DAS28 >5.1, mean changes in DAS28 over time were also comparable for both studies.

**Conclusions:**
Time to onset and magnitude of ACR 20 and HAQ-DI responses and DAS28 improvements were similar for patients treated with SC abatacept with or without i.v. loading who have RA and an inadequate response to MTX. Previous pharmacokinetic data show that the incidence of i.v. loading, target therapeutic concentration are achieved in the majority of patients by Week 2 of SC abatacept treatment. The findings from this post-hoc analysis suggest that SC abatacept can be given effectively without an i.v. abatacept loading dose.

**Disclosures:**

**97. LONG-TERM EFFICACY OF TOCILIZUMAB MONOTHERAPY IN PATIENTS WITH RA: AMBITION EXTENSION 240 WEEK DATA**

Graeme Jones1, Anthony Sebba2, Denise Lepley3, Jenny Devenport3, Corrado Bernasconi4, Devi Smart5, Chiedzo Mpofu4 and Juan J. Gomez-Reino 6

**Background:** The AMBITION study was the first trial to demonstrate clinical superiority of tocilizumab (TCZ) monotherapy over MTX monotherapy. In patients MTX-naive or MTX-free for 6 months, treatment with TCZ 8 mg/kg monotherapy resulted in statistically greater ACR 20/50/70 responses than MTX at 24 weeks. This post-hoc exploratory analysis evaluates the long-term efficacy of patients who remained on TCZ monotherapy in an ongoing long-term extension (LTE) of AMBITION.

**Methods:** Patients randomized to TCZ 8 mg/kg in AMBITION (n = 286) who entered the LTE were included. During the LTE, MTX/other DMARDs could be added in patients not achieving a 50% reduction in the number of tender and swollen joints from baseline (core study). Efficacy assessments and DMARD status were evaluated up to 240 weeks.

**Results:** Of 243 patients on TCZ monotherapy who entered the LTE, 57.2% (n = 139) remained on monotherapy [102 (73%) reached 240 weeks], 9.9% (n = 24) added a DMARD before LTE entry, and 32.9% (n = 80) added a DMARD after LTE entry [18.5% (n = 49) <3 weeks post-entry and 14.4% (n = 35) >3 weeks post-entry]. DMARDs included MTX (93%), HCQ (3%) LEF (2%) and parenteral gold (2%). Mean SJC, TJC and DAS28 (data not shown) decreased sharply during the first weeks and levels continued to decrease or were maintained thereafter (Table 1). Similar trends in improved disease state were observed (40.1% and 16.7% of patients achieved DAS28 <2.6 and clinical disease activity index (CDAI) remission by week 24 respectively); rates increased or were maintained thereafter; absolute numbers achieving these endpoints increased to weeks 92 and 120. Absolute numbers of patients achieving DAS28 <3.2 and CDAI low disease activity increased to weeks 92 and 96 (data not shown), respectively.

**Conclusions:** TCZ monotherapy provided durable efficacy in a large proportion of patients continuing treatment in the AMBITION LTE.

**Disclosures:**

**98. NITRIC OXIDE LEVELS IN RHEUMATOID ARTHRITIS IMPROVES AFTER IL-6 BLOCKADE**

Inderjeet Verma1,2, Jaspreet Kaur1,3, Ashit Sngle2,3, Pawan Krishan1, Kanchan Vohra1, Ladbans Kaur4, Nidhi Garg1,2 and Inderjeet Verma1,2

**Background:** Nitric oxide (NO) plays a central role in inflammatory joint diseases and has been shown to correlate with inflammatory disease activity in these rheumatic diseases. Hence, it is a potential therapeutic target. In recent years, IL-6 antagonist, tocilizumab has emerged as an important therapeutic agent in treatment of RA. However, there is no study to evaluate the impact of tocilizumab on NO. So we aim to investigate the serum nitrite levels in patients with RA before and after 12 weeks treatment with IL-6 antagonist, tocilizumab, and to correlate with inflammatory disease activity measures and endothelial dysfunction in RA patients.

**Methods:** Eleven anti-IL-6-naïve RA patients (mean age 51.64 ± 1.44 years; disease duration 11.36 ± 2.5 years) with high DAS28 (>5.1) despite treatment with stable doses of conventional DMARDs were investigated. Inflammatory disease activity [DAS28 and HAQ-Disability Index (HAQ-DI) scores, ESR and CRP], serum nitrite concentration, serum thio-barbituric acid reactive substances (TBARS) concentration, and endothelium-dependent and -independent vasodilation of the brachial artery were measured before and after 12 weeks of therapy with tocilizumab 8 mg/kg intravenous infusion every 4 weeks. Serum nitrite levels and FMD were also estimated in 10 age- and sex-matched healthy controls.

**Results:** In healthy volunteers, mean serum nitrite level was 5.0 ± 0.11 μmol/l. Serum nitrite levels in RA patients at baseline were significantly higher compared with healthy volunteers (P < 0.01). Level of serum nitrite significantly decreased from 7.41 ± 0.18 to 6.13 ± 0.19 (P < 0.001), and FMD from 8.21 ± 0.88% to 14.60 ± 0.96 % (P < 0.001), ESR from 57.45 ± 8.9 to 25.27 ± 5.11 mm in the first hour (P < 0.005), and CRP from 34.87 ± 8.01 to 13.38 ± 5.60 mg/dl (P < 0.004) after treatment. DAS28 and HAQ-DI scores were significantly reduced, from 6.59 ± 0.24 to 4.47 ± 0.24 (P < 0.005) and from 2.17 ± 0.14 to 1.08 ± 0.09, respectively with tocilizumab in RA patients. There was a significant correlation of serum nitrite with FMD, CRP and DAS28 both at baseline (P < 0.05) and after 12 weeks therapy (P < 0.05) with tocilizumab in RA patients.

**Conclusions:** Nitric oxide production is enhanced to a greater extent in patients with RA compared with controls and decrease in nitrite level

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>24</th>
<th>42</th>
<th>62</th>
<th>72</th>
<th>120</th>
<th>168</th>
<th>216</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJC  (66 joints), mean (i.c.)</td>
<td>19.0 (10.36)</td>
<td>8.8 (3.04)</td>
<td>2.7 (4.88)</td>
<td>1.8 (3.09)</td>
<td>2.1 (3.74)</td>
<td>1.7 (3.26)</td>
<td>1.5 (3.18)</td>
<td>1.3 (3.37)</td>
<td>1.0 (3.29)</td>
</tr>
<tr>
<td>TJC  (48 joints), mean (i.c.)</td>
<td>32.5 (13.39)</td>
<td>10.5 (12.48)</td>
<td>6.2 (8.45)</td>
<td>4.8 (7.41)</td>
<td>4.2 (5.38)</td>
<td>3.7 (5.34)</td>
<td>3.0 (5.61)</td>
<td>2.8 (6.70)</td>
<td>2.4 (6.70)</td>
</tr>
<tr>
<td>DAS28 &lt;2.6, n (%)</td>
<td>0 (0)</td>
<td>55 (40.1)</td>
<td>65 (53.7)</td>
<td>69 (60.0)</td>
<td>70 (68.3)</td>
<td>73 (68.2)</td>
<td>62 (60.2)</td>
<td>58 (66.7)</td>
<td>50 (62.5)</td>
</tr>
<tr>
<td>DAS28 &lt;3.2, n (%)</td>
<td>0 (0)</td>
<td>74 (57.1)</td>
<td>90 (74.9)</td>
<td>89 (74.9)</td>
<td>89 (74.9)</td>
<td>87 (74.6)</td>
<td>76 (68.0)</td>
<td>68 (78.2)</td>
<td>66 (81.0)</td>
</tr>
<tr>
<td>CDAI remission (&lt;2.8), n (%)</td>
<td>0 (0)</td>
<td>23 (16.7)</td>
<td>36 (29.0)</td>
<td>52 (43.0)</td>
<td>43 (38.4)</td>
<td>43 (39.4)</td>
<td>39 (37.9)</td>
<td>37 (41.1)</td>
<td>31 (41.1)</td>
</tr>
<tr>
<td>CDAI low disease activity (&lt;10, n (%)</td>
<td>85 (70.2)</td>
<td>67 (51.0)</td>
<td>69 (59.8)</td>
<td>71 (59.0)</td>
<td>70 (60.2)</td>
<td>71 (60.2)</td>
<td>69 (60.2)</td>
<td>69 (60.2)</td>
<td>69 (60.2)</td>
</tr>
</tbody>
</table>

**Table 1. Efficacy over time in patients on TCZ monotherapy**
after the treatment is associated with improvement in disease activity and improvement of endothelial dysfunction. Serum nitrite level may not only act as good predictor of inflammatory disease activity but also predicts response to therapy in RA.

Disclosures: The authors have declared no conflicts of interest.

99. FUNCTIONALLY OPTIMIZED ORTHOSES FOR EARLY RHEUMATOID ARTHRITIS FOOT DISEASE: A FIRST-ON-MAN, PHASE I STUDY OF MECHANISMS AND PATIENT EXPERIENCE

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1Institute for Applied Health Research, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK
2Background: Novel foot orthoses (FOs) were functionally optimized using patient-specific dynamic foot function data and produced using additive manufacturing (AM) techniques. Selected plantar foot pressure and 3 dimensional (3-D) motion analysis parameters mapped to critical early stage foot impairments in an RA population were developed for computer aided (CAD) FO design. Two AM techniques [selective laser sintering (SLS) and fused deposition modelling (FDM)] were used to manufacture personalized orthoses (PFOs) based on identical CAD designs, PFOs were developed and tested in comparison with standardized, hand-manufactured prescribed custom FOs (SFOs) and shod for mode-of-action and patient experience.

Methods: FOs were tested in random order for a period of 7 days in a series of 15 patients with early RA of ≤2 years duration. Mode-of-action was determined from 3-D kinematic and kinetic analyses and plantar pressure distribution. Patient experience monitored FO comfort, fit and short-term symptom and activity benefits were determined through a series of Numerical Rating Scales (NRS) and 5-point Likert scales.

Results: Motion control was significantly greater for selected mechanical variables in SLS or FDM FOs in comparison with SFOs (Table 1). Peak internal dorsiflexion and inversion ankle complex moments indicate no significant differences between PFO and SFO (P = 0.269 and P = 0.428 respectively). No significant differences between PFOs and SFOs for plantar pressure distribution were observed. SLS PFOs decreased medial and lateral forefoot peak pressure in comparison with shod (P = 0.018 and P = 0.022 respectively). Patient reported device comfort scores (range 0–10) were also equivalent (P = 0.517) with mean ± s.d. scores of 6.6 (2.4), 7.3 (1.6) and 7.5 (2.1) for SFO, FDM and SLS FOs respectively. Short-term symptom benefits and activity levels were significantly better in SLS in comparison with SFOs devices (P = 0.025 and P = 0.046 respectively). Both SLS and FDM devices were subject-rated as more effective than SFOs (P = 0.009). No adverse reactions were reported.

Conclusions: PFOs designed to optimize foot function demonstrate better technical mode-of-action than SFOs for early RA-associated foot impairments. Short-term use provides a safe and optimal patient experience.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison Mean/median differences</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak forefoot inversion</td>
<td>SLS-SFO -1.8 (0.4)</td>
<td>-2.8, -0.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean forefoot inversion</td>
<td>SLS-SFO 0.7 (0.3)</td>
<td>0.0, 1.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Peak rearfoot dorsiflexion</td>
<td>SLS-SFO 1.4 (0.3)</td>
<td>1.5 (0.4)</td>
<td>0.4, 2.4, 0.3, 2.6</td>
</tr>
<tr>
<td>Mean rearfoot dorsiflexion</td>
<td>FDM-SFO -0.7</td>
<td>-</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Disclosures: The authors have declared no conflicts of interest.

100. COMPARATIVE EFFICACY OF BIOLOGICS AS MONOTHERAPY AND IN COMBINATION WITH METHOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS WITH AN INADEQUATE RESPONSE TO CONVENTIONAL DMARDS: A NETWORK META-ANALYSIS

Felicity Buckley1, Axel Finckh2, Tom W. Huizinga3, Fred Dekkerscheer4 and Jerome P. Jansen1
1Consultancy, MAPC Consultancy, Boston, MA, USA
2Rheumatology, University Hospital of Geneva, Geneva, Switzerland
3Rheumatology, Leiden University Medical Centre, Leiden, Netherlands and 4Medical, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background: A number of (network) meta-analyses indirectly compare the efficacy of biologic agents for RA. However, comparisons of the efficacy of a biologic agent as monotherapy vs a biologic agent combined with DMARDs are rare and none include all currently approved biologic agents.

Methods: A systematic literature review was undertaken to identify RCTs that assessed biologic agents as monotherapy or in combination with DMARDs in adult RA patients with an inadequate response to traditional DMARDs (DMARD-IR). 22 RCTs were included. Bayesian network meta-analysis models were used to simultaneously synthesise the results of the included RCTs and obtain effect estimates of the biologic agents in their usual dose, alone and combined with MTX in terms of ACR20/50/70 response at 24 weeks vs placebo. As demonstrated previously, the effects of anti-tumour necrosis factor therapies (aTNFs) were assumed to be exchangeable. This, and the limited data identified for these therapies as monotherapy in DMARD-IR patients, aTNF data were pooled.

Results: Using random effects modelling, in this DMARD-IR population, tocilizumab (TCZ) + MTX was shown to be comparable to other biologics + MTX for ACR20/50/70 response for MTX. The probability of ACR20/50/70 response for TCZ was found to be greater than for aTNFs. With TCZ as monotherapy, an ACR20/50/70 response similar to that of TCZ + MTX was observed [RR 0.98 (95% credible interval [CRI] 0.70, 1.71)], [RR 0.92 (95% CRI 0.62, 1.56)], and [RR 1.04 (95% CRI 0.58, 2.08)], respectively. aTNFs as monotherapy were likely to be less effective than aTNFs + MTX in terms of ACR20 and ACR50 response [RR 0.71 (95% CRI 0.48, 1.46)] and [RR 0.52 (95% CRI 0.3, 0.8)] respectively.

Conclusions: Based on a network meta-analysis involving indirect comparison of trial findings, it was observed that for DMARD-IR patients: the efficacy of TCZ + MTX was in line with the efficacy of other biologic agents + MTX. In monotherapy, TCZ was associated with a higher ACR response than was observed with aTNFs. ACR response of TCZ as monotherapy was similar to that of TCZ + MTX, whereas aTNF as monotherapy was likely to show a lower ACR response than aTNF + MTX.


101. LONG-TERM SAFETY OF TOCILIZUMAB IN RA PATIENTS TREATED FOR A MEAN DURATION OF 3.7 YEARS

Mark Genovese1, Anthony Sebb2, Andrea Rubbert-Roth3, Juan J. Scali4, Rike Aten5, Joel M. Kremer6, Laura Pitts7, Emma Vernon1 and Ronald F. van Vollenhoven1

Immunology and Rheumatology, Stanford University Medical Centre, Palo Alto, CA, 1Rheumatology, University of South Florida, Tampa, FL, USA, 2Internal Medicine, University of Cologne, Cologne, Germany, 3Rheumatology, University of Cologne, Cologne, Germany, 4Rheumatology, Schloßpark Klinik, University Medicine Berlin, Berlin, Germany, 5Rheumatology, Albany Medical College, Albany, NY, USA, 6Medical, Roche Products Ltd, Welwyn Garden City, UK and 7Medical, Karolinska Institute, Stockholm, Sweden

Background: Tocilizumab (TCZ) has demonstrated efficacy in improving signs/symptoms, reducing joint damage and improving physical function in RA patients. This analysis assessed the long-term safety of TCZ in adult RA patients (up to 5.8 years) (y) TCZ exposure.

Methods: Safety data were pooled for all patients who received ≥1 TCZ dose in 5 placebo-controlled trials (OPTION, TOWARD, RADIATE, AMBITION and LITHE), a clinical pharmacology study and long-term extension studies.

Results: 4009 patients were included with a mean (median [range]) treatment duration of 3.7 (4.6 [0.0-5.8]) y and total observation time 14,994 p-y (PY). Over time, rates of serious adverse events (SAEs), serious infections, myocardial infarction (MI) SAEs, stroke SAEs, hepatic SAEs and gastrointestinal (GI) perforations were stable (Table 1). The overall rate of AEs leading to withdrawal was 5.0/100PY (95% CI 4.7, 5.4). Infections, laboratory abnormalities and neoplasms were the most common AEs leading to withdrawal (0.97/100PY, 0.89/100PY and 0.80/100PY). 8 patients withdrew because of anaphylaxis events. Rates/100PY (95% CI) were 14.6 (14.0, 15.3) for SAEs and 0.57 (0.45, 0.70) for deaths. The most common SAEs were infections (4.5/100 PY

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The best long-term treatment strategy for rituximab has been established. Retreatment at a fixed interval of 6 months maintains stable disease activity and half-dose is equally effective in first-cycle responders. In first-cycle non- or moderate responders, responses may improve further after a second cycle at full dose.

### TABLE 1. Event rate/100 PY (95% CI) per 12 month period

<table>
<thead>
<tr>
<th>Event</th>
<th>0–12</th>
<th>13–24</th>
<th>25–36</th>
<th>&gt;36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs leading to withdrawal</td>
<td>9.3 (8.3, 10.4)</td>
<td>4.5 (3.8, 5.3)</td>
<td>4.1 (3.4, 5.0)</td>
<td>3.2 (2.7, 3.7)</td>
</tr>
<tr>
<td>SAEs</td>
<td>16.1 (14.7, 17.4)</td>
<td>14.2 (12.9, 15.7)</td>
<td>15.7 (14.2, 17.2)</td>
<td>13.5 (12.5, 14.5)</td>
</tr>
<tr>
<td>GI perforations</td>
<td>0.20 (0.08, 0.42)</td>
<td>0.13 (0.04, 0.34)</td>
<td>0.29 (0.12, 0.57)</td>
<td>0.19 (0.1, 0.34)</td>
</tr>
<tr>
<td>MI SAEs</td>
<td>0.29 (0.14, 0.53)</td>
<td>0.17 (0.05, 0.39)</td>
<td>0.29 (0.12, 0.57)</td>
<td>0.26 (0.15, 0.43)</td>
</tr>
<tr>
<td>Hepatic SAEs</td>
<td>0.43 (0.24, 0.71)</td>
<td>0.26 (0.11, 0.52)</td>
<td>0.29 (0.12, 0.57)</td>
<td>0.28 (0.16, 0.45)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>4.6 (4.0, 5.4)</td>
<td>3.9 (3.3, 4.7)</td>
<td>5.4 (4.6, 6.3)</td>
<td>4.2 (3.7, 4.7)</td>
</tr>
<tr>
<td>SAEs</td>
<td>16.1 (14.7, 17.4)</td>
<td>14.2 (12.9, 15.7)</td>
<td>15.7 (14.2, 17.2)</td>
<td>13.5 (12.5, 14.5)</td>
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<td>0.29 (0.12, 0.57)</td>
<td>0.28 (0.16, 0.45)</td>
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<tr>
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<td>0.20 (0.08, 0.42)</td>
<td>0.13 (0.04, 0.34)</td>
<td>0.29 (0.12, 0.57)</td>
<td>0.19 (0.1, 0.34)</td>
</tr>
</tbody>
</table>

## 102. DOSE REDUCTION IN RITUXIMAB RETREATMENT MAY DELAY ACHIEVEMENT OF OPTIMAL RESPONSES

Mohammed I. Sharif, Sudipto Das, Paul Emery, Helen Maciver, Wendy Shingler, Philip Helliwell, Katharina Sokoll, and Edward M. Vital

Rheumatology, East Surrey Hospital, Surrey, University of Leeds, Leeds and Rheumatology, Bradford Teaching Hospital, Bradford, UK

**Background:** The best long-term treatment strategy for rituximab has not been established. Retreatment at a fixed interval of 6 months maintains stable disease activity and half-dose is equally effective in first-cycle responders. In first-cycle non- or moderate responders, responses may improve further after a second cycle at full dose.