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 dorsal leak from spinal anaesthesia for an elective anterior spinal fusion. 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. Losartan 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 TGFβ 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.

Disclosures: The authors have declared no conflicts of interest.

2. A CASE OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN A PATIENT WITH SLLE

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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 SLLE, 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, rising 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 oedematous 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 76.6% of cases of PRES in SLE have an acute trigger, such as infection, 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 withdrawn. 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 normal. Urine dipstick showed protein (1+) and blood (3+). Blood tests 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 10⁹/l with a rise in creatinine (352 µmol/l), ALT (850 U/l) and AST (293 U/l). Anti-dsDNA was 627 U/ml and complement was low. Serum ferritin was ~2000 µg/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 EiSpot, echocardiogram and abdominal ultrasound were unremarkable. Bone Marrow aspiration showed haemophagocytosis.
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 Methotrexate and prednisolone 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 recovered to normal. After two infusions a week apart, the treatment 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 mas of systemic features and head and neck manifestations such as facial pain, decreased visual acuity, nasal discharge, and epistaxis. Other symptoms depend on system involved, NKTL carries high mortality. Provocative tests are usually performed with MAS secondary to EVB infection but not SLE. We report the successful use of Rituximab therapy in the treatment of resistant MAS secondary to acute SLE.

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

4. NATURAL KILLER T-CELL LYMPHOMA: FATAL MICROM OF GIANT CELL ARTERITIS

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**Background:** Natural killer T-cell lymphoma (NKTL) is a type of non-Hodgkin lymphoma (NHL). It is very rare; in Western populations, the prevalence of nasal lymphomas is estimated at 0.17–1.5% of all NHL. 45% of which are thought to be NKTL in origin. It can present with systemic features and head and neck manifestations such as facial pain, decreased visual acuity, nasal discharge, and epistaxis. Other symptoms depend on system involved, NKTL carries high mortality. Provocative tests are usually performed with NKTL.

**Methods:** He presented with 2 weeks history of temporal headache, scalp tenderness, jaw ache, fatigue and weight loss. He had been treated in primary care for sinustitis when he reported cold like symptoms, nasal discharge and nose bleed. These symptoms had resolved with antibiotics. Blood test including FBC, renal, liver profile and ANCA were normal, but CRP and ESR were elevated (27 mg/l, 47 mm/h respectively). He was commenced on 40 mg Prednisolone. Temporal artery biopsy results were negative. His symptoms improved, but his mental state deteriorated. He was admitted under mental health act to a psychiatric hospital, diagnosed with steroid induced psychosis and given a rapid steroid reducing regime.

**Results:** After the steroid reduction his symptoms recurred. 4 months after initial presentation he re-presented with severe headache, swelling and redness of the right periorbital region and was admitted for further investigations. Blood tests revealed mild anaemia, high ESR 92 mm/h and CRP 22 mg/l. CT and MRI scan of his brain, orbit and head showed a thickened temporal artery and a right temporal lobe with evidence of infarction. He continued on oral prednisolone and inpatient rehabilitation. His symptoms resolved with antibiotics. Blood test including FBC, renal, liver profile and ANCA were normal, but CRP and ESR were elevated (27 mg/l, 47 mm/h respectively). He was commenced on 40 mg Prednisolone. Temporal artery biopsy results were negative. His symptoms improved, but his mental state deteriorated. He was admitted under mental health act to a psychiatric hospital, diagnosed with steroid induced psychosis and given a rapid steroid reducing regime.

**Conclusions:** Natural killer T-cell lymphoma is a rare malignancy whose symptoms were considered typical of GCA. He responded to steroid therapy initially, but then re-presented with periorbital symptoms suggestive of alternative diagnosis.

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patient at 39 nmol/l 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), aspirin and low molecular weight heparin, which reduced levels of serum Gb3 and normalized her heart function. She subsequently suffered a myocardial infarction which was associated with increased anti-cardiolipin (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 while 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 reaction of multisystem sarcoidosis. Aim of this case report is to disseminate knowledge concerning successful treatment of multisystem sarcoidosis involving pelvic bone with INFliximab. Methods: Case presentation: 33-year-old lady referred to rheumatology for multisystem sarcoidosis. Intavenous zolendronic acid helped with osteoporosis. A 19-year-old female, with no past medical history, presented to rheumatology with nail fold infarcts and purpuric macules on the dorsal-ventral junction of his fingers. In view of his clinical presentation, a diagnosis of chronic progressive multisystem granulomatous disease (CADM) was considered. She was started on infliximab and MTX. She improved on this combination of treatment and managed to reduce steroids gradually.

Conclusions: 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-CADM-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 cracks with oxygen saturations of 92% on air, synovitis of the hands and right knee. He had two aphthous 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 eccematosus 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 40 mg. 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 subset which are associated with MDA5 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. CT pulmonary angiography demonstrated a left sided small vessel pulmonary embolus. A standard thrombophilia screen was unremarkable, except for positive anti-GBM, anti-cardiolipin and a low PT. Standard anti-nuclear and anti-ENA antibodies were negative. There was no evidence of other underlying autoimmune or connective tissue disease. Although the initial presentation was felt to be less severe than previous episodes, there was still significant concern about the risk of further embolism without adequate anticoagulation. Unfortunately, the patient was non-compliant with treatment. Despite clopidogrel, the patient continued to have two further episodes of deep vein thrombosis and multiple pulmonary emboli. It was felt that there was a significant risk of fatal pulmonary embolism if treatment was not intensified.

Methods: Rituximab was commenced, the standard anti-GBM, anti-cardiolipin and anti-ENA antibodies were negative. There was no evidence of other underlying autoimmune or connective tissue disease. Although the initial presentation was felt to be less severe than previous episodes, there was still significant concern about the risk of further embolism without adequate anticoagulation. Unfortunately, the patient was non-compliant with treatment. Despite clopidogrel, the patient continued to have two further episodes of deep vein thrombosis and multiple pulmonary emboli. It was felt that there was a significant risk of fatal pulmonary embolism if treatment was not intensified.

Results: Rituximab was commenced at 375 mg/m2 on days 1 and 15, and monthly for a further 5 months. Rituximab was well tolerated and the patient has not had further episodes of PE.

Conclusions: Rituximab may be an effective alternative to conventional anticoagulation in patients with APS with recurrent thromboembolic disease who are non-compliant with standard anti-coagulation.

Disclosures: The authors have declared no conflicts of interest.
screening was positive, 1:80 (speckled) and anti-dsDNA antibodies titres were mildly raised (51 U/ml, NR 0–22), but complement levels were normal and there were no clinical features of systemic lupus. ANA was weakly positive. A biopsy of a pustular rash on the patient’s right leg subsequently demonstrated marked thrombosis of dermal venules with perivascular inflammation, consistent with a diagnosis of Behçet’s disease.

Conclusions: Idiopathic intracranial hypertension (IIH) is defined by clinical criteria that include symptoms and signs of raised intracranial pressure (headache, papilloedema, visual loss), elevated intracranial pressure with normal CSF composition, and no other cause of intracranial hypertension evident on neuroimaging or other evaluation. The rare complication of the condition is intracranial mass lesions, lesions causing reduced CSF absorption (subarachnoid haemorrhage, granulation adhesions post meningitis), hydrocephalus, choroid plexus papillomas causing increased CSF production, or conditions obstructing venous outflow (including venous sinus 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 steroids and terfenadine). None of these associations of IIH were present in our case. In our patient, there appears to be an association of Behçet’s disease with IIH, independent of other known variables.

Disclosures: The authors have declared no conflicts of interest.

11. SEROPOSITIVE NON-EROSSIVE RHEUMATOID ARTHRITIS PRESENTING WITH THE CUTANEOUS ROPE SIGN (INTERSTITIAL GRANULOMATOUS DERMATITIS) AND SUBCLINICAL SYNOVITIS RESPONSIVE 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 autoimmune disease particularly RA and lupus. We present a case of a 36-year-old male RA patient presenting with the rope sign revealing the response of RA 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 electrician presented to dermatology outpatient with a 5-year 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 perivasculary and perineural lymphocytic infiltrate in the superficial dermis and a fibrinous deep dermis with infiltrating interstitial histocytes. A diagnosis of IGD was made and 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) depomedrone 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 palpatable 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 dermatology 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.

12. A CASE OF ULCERATIVE LUPUS PROFUNDUS RESPONDING TO RITUXIMAB

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Background: Lupus profundus/panniculitis 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. Ulceration of these lesions is rare. 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 31-year-old 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 ulcercated lesions remained very resistant to treatment despite prednisolone 60mg/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, paniculitis with fat necrosis and fibrinoid necrosis 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 10mg/day.

**Conclusions:** This case illustrates efficacy and safety of rituximab in the treatment of refractory discoid LE and ulcercated lupus profundus developing in a patient with discoid LE 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, arthralgia 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 Akrinona (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.

### 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 is no medication that is known to cause this reaction.

**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, polyarthralgia, short 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, HHS 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 enteric bacteria and cryptosporidium oocysts. Blood film revealed reactive picture with eosinophils and lymphocytopenia. Urine HIAA and serum tryptase tests were performed to rule out carcinoid tumour, mastocytosis and anaphylaxis.

Results: The array of clinical symptoms and laboratory findings led to 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 DRESS syndrome in patients with rash multiorgan failure in addition to infections and CTDs. Prompt recognition and steroid initiation appears to be effective steps in managing of this condition.

Disclosures: The authors have declared no conflicts of interest.

16. AN UNEXPECTED CAUSE OF SEVERE HYPOKALEMIA 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 pseudohypoaldosteronism.

Case: 51-year-old lady presented with new onset rhabdomyolysis and muscle paralysis due to severe hypokalaemia of unexpected cause. She was well known for her sicca symptoms and postural hypotension. At presentation, she had a marked myopathy with power 2/5 in all muscle groups in both upper and lower limbs. Initial admission, she was found to have a marked myopathy with power 2/5 in all muscle groups in both upper and lower limbs. Initial investigations revealed the presence of liquorice. With blood film revealed reactive picture with eosinophils and lymphocytopenia. Urine HIAA and serum tryptase tests were performed to rule out carcinoid tumour, mastocytosis and anaphylaxis.

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

Disclosures: The authors have declared no conflicts of interest.

17. SUCCESSFUL TREATMENT OF SCHNITZLER’S SYNDROME WITH ANAKINRA, COMPLICATED BY THE DEVELOPMENT OF ANTI-NUCLEAR ANTIBODIES

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Background: Schnitzler’s syndrome is a rare, autoimmune condition characterized by a chronic urticarial skin rash and monoclonal IgM gammapathy together with 2 of intermittent fever, arthralgia, bone abnormalities on imaging, lymphadenopathy, hepatitis or splenomegaly, neutrophilia and/or a raised ESR. Recently cases have been reported documenting successful treatment of Schnitzler’s syndrome with the IL-1 receptor antagonist (IL-1-RA), anakinra.

Other rheumatological conditions are often treated with biologic drugs targeting the TNF pathway. In some patients, efficacy and usage of these drugs is limited by the development of anti-nuclear antibodies (ANA). This has not previously been reported following treatment with IL1-RA.

Methods: Written consent for publication was obtained from the patient.

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. Individual 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 definitive urticular vasculitis.

In investigations, BCR, ANA, ENA, dsDNA, immunoglobulins, CRP 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.

Further investigation revealed an IgM kappa monoclonone (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.

At review 1 year later, she had developed generalised fatigue, intermittent fever and marked arthralgia and was referred to rheumatology. ESR was 58 mm/h (1–15) and CRP 55 mg/l (0–10). ANA not detected. A diagnosis of Schnitzler’s syndrome was made and anakinra 100 mg s/c od prescribed. Within 48 h, her rash and arthralgia completely resolved. Prednisolone was withdrawn.

Dermatology Life Quality Index improved dramatically. Inflammatory markers and neutrophil count normalized.

9 months after starting anakinra she developed significant titres of positive ANA with a coarse speckled pattern on indirect immunofluorescence using Hep-2 cells. dsDNA and ENA antibodies remained negative. She has no clinical symptoms of an autoimmune condition.

Conclusions: Schnitzler’s syndrome shares many similarities with other cryopyrin-associated periodic syndromes and this case adds further evidence to the use of IL1-RA to treat these diseases. The development of ANA is a well recognized complication of treatment with anti-TNF but has not previously been reported following treatment with IL1-RA. The clinical significance of the antibody formation in this case remains unclear but will be closely monitored.

Disclosures: The authors have declared no conflicts of interest.

18. CETROLIZUMAB-INDUCED ACUTE LIVER FAILURE

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Background: Certolizumab pegol is a pegylated tumour necrosis factor-α (TNF-α) specific Fab fragment of a human monoclonal antibody. It was first licensed by NICE in 2010.

Methods: We present a case of a 65 year old, diagnosed with RA in 1996, she was initially commenced on SSZ and prednisolone. Sulphasalazine was later substituted for MTX due to poor efficacy. The dose was gradually escalated as the patient’s disease became more active to 25 mg once weekly. In June 2011, her disease remained active. The DAS28 was 6.43 therefore HCQ was commenced, which failed to adequately control her RA, so in January 2012 certolizumab was commenced.

Results: Liver function tests (LFTs) were normal prior to treatment with certolizumab. However, within 4 months of treatment the patient had developed an asymptomatic hepatosplenitis with an ALT of 226. The patient became clinically icteric 6 months after treatment.
Renal disease is common in granulomatosis with polyangiitis (GPA). Therefore any renal mass should be taken seriously. GPA presenting with renal masses, stretching back as far as 1978. On review of the literature we have found 16 examples of GPA with renal masses. The diagnosis of DILU requires a high degree of suspicion, pattern recognition, establishing a temporal relationship and excluding other causes of renal 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 hepatocyte 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 in 1000 patients per year (38 cases among 576 000 treated patients over 8 years).

Renal core biopsy revealed fibrosis and non-necrotizing, non-liquefactive granulomatous 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 isonazid and pyridoxine to cover for latent tuberculosis. Treatment with azathioprine with ultrasound at 8 months revealed that the renal mass had resolved. The inflammatory markers and c-ANCA had normalised and both renal function tests and urine analysis were unremarkable. Of these, 12 (75%) were unilateral and 4 bilateral. Twelve (75%) of the 16 were ANCA positive (although 3 reports did not specify ANCA status) and 6 (37.5%) of the 16 had normal urine analysis. Interestingly, of the 16 cases in the literature, 9 (56.3%) received either partial or total nephrectomy.

Renal masses can occur in the context of GPA and can be inflammatory or neoplastic in nature. This case highlights the importance of obtaining a clear diagnosis in patients presenting with a renal mass to avoid potentially unnecessary surgical intervention and the timely initiation of appropriate treatment.

Disclosures: 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, corneal irritation, arthralgia of knees and elbows and night sweats, together with microscopic haematuria.

Her history was significant for chronic fatigue syndrome and a raised CRP. She had been treated with DILU, with no clinical improvement.

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)

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 for 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 etravirine, tenofvir and lamivudine was treated with 40 mg of triamcinolone into the right knee for OA, 4 weeks later she presented with weight gain and increased appetite. She was cushingoid and random cortisol low (67 nmol/l) with attenuated diurnal variation. She had 4 sets of negative blood cultures but was found to have a positive Quantiferon TB Gold. Chest radiograph and transthoracic 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. She was treated with cyclosporine and prednisolone, followed by AZA as maintenance therapy together with isonazid and pyridoxine to cover for latent tuberculosis.

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 oral 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.

Disclosures: The authors have declared no conflicts of interest.

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

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The bilirubin peaked at 479 µmol/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.

Diagnosis of acute liver failure 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 cetolizumab. Currently this patient’s RA is in remission and LFTs have returned to normal. Current treatment is prednisolone 5 mg and ursodeoxycholic acid.

Conclusions: DILU has been described with other anti-TNFα agents (adalimumab, infliximab, etanercept). However, this is the first case described with respect to cetolizumab. The diagnosis of DILU 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 hepatocyte 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 in 1000 patients per year (38 cases among 576 000 treated patients over 8 years).

Renal core biopsy revealed fibrosis and non-necrotizing, non-liquefactive granulomatos glomerulonephritis. The diagnosis of DILU 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 hepatocyte damage.
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 lymphangiitis 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, trinitus 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 conjunctival injection but general examination was otherwise unremarkable.

Investigations revealed anaemia, normal renal, liver and bone function tests, reduced folate (20(3)g/l), ESR 61 mm/h and CRP 3 mg/l. She had positive ANA, anti-Ro, anti-La, RHF, ACL and anti-TG. 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 neutrophil exudate but negative immunofluorescence assays.

Diagnoses of primary Sjögren’s syndrome, with lupus spectrum features and with coeliac disease were made. The patient commenced 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 measures.

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, HCQ 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>
</tr>
<tr>
<td>Weight, kg</td>
<td>65.6</td>
<td>56.3</td>
<td>61.2</td>
</tr>
<tr>
<td>SF36, BILAG</td>
<td>37, 25</td>
<td>nd, 17</td>
<td>64, 2</td>
</tr>
<tr>
<td>Anti-TG (0–6 U/ml), U/ml</td>
<td>128</td>
<td>9.2</td>
<td>5.4</td>
</tr>
<tr>
<td>RF (0–30 U/ml), U/ml</td>
<td>196</td>
<td>52</td>
<td>nd</td>
</tr>
<tr>
<td>IgG (4.1–13 mg/dl)</td>
<td>28.8, 4.03</td>
<td>9.9, 2.7</td>
<td>9.2, 2.9</td>
</tr>
<tr>
<td>IgA (0.8–3.7 mg/dl), mg/dl</td>
<td>2.7</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Prolactin dose, mg.d (IU)</td>
<td>30, 10</td>
<td>7.5</td>
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Disclosures: The authors have declared no conflicts of interest.

24. AN UNUSUAL CASE OF BILATERAL PAROTID AND SUBMANDIBULAR GLAND INVOlVEMENT IN ANCA ASSOCIATED VASCULITIS, 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 concerns regarding secondary infection. Magnetic Resonance Imaging confirmed progressive glandular destruction and air within the cavity, raising the possibility of actinomyces infection. The ESR remained elevated and ANCA weakly positive and a further submandibular gland biopsy again demonstrated features consistent with granulomatous infection. Infection with actinomyces 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.

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**IMAGING**

25. **EARLY RESPONSE TO ABATACEPT PLUS MTX IN MTX-IR RA PATIENTS USING POWER DOPPLER ULTRASONOGRAPHY: AN OPEN-LABEL STUDY**

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**Background:** The global power Doppler ultrasound (PDUS) scoring system combining synovial hyper trophy, joint effusion and PD signal developed by the OMERACT-EULAR-US Task Force has good intra- and inter-observer reliability in metacarpophalangeal (MCP) and non-MCP joints, and demonstrates consistency between PDUS machines. We present the first international, Phase IIb study using the global PDUS synovitis score to assess early impact of i.v. abatacept on synovial inflammation.

**Methods:** This 6-month, single-arm, open-label study enrolled active MTX-IR RA patients defined as DAS28 (CRP) >3.2 or >3.6 and swollen joints and CRP >ULN. Patients had a total synovitis PDUS score >1 for ≥2 MCPs and ≥1 for ≥1 other MCP (out of MCP 2–5 bilaterally, i.e. 8 joints) at screening and baseline (BL). The primary objective was to evaluate early response to abatacept, defined by improvement of synovitis assessed by global PDUS of affected MCP joints bilaterally. Global PDUS was scored over 8 MCP joints (range 0–24 units) at BL, Days 7, 15, 29, 43 and 57, then monthly by a PDUS reader blinded from clinical assessments. Early signs of improvement were defined as the earliest time point when 95% CI for mean change from BL in global PDUS score did not contain 0 for that and all later time points. DAS28 (CRP) and safety were assessed for all patients who received ≥1 dose of abatacept.

**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) (atral fibrillation, burstsis, dementia, endomethiasis, pleural effusion and pulmonary fistula, and hyperension), 62 (69.6%) 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.

**Disclosures:** P.B., Bristol-Myers Squibb—Grant/Research Support, Abbott, Pfizer, MSD, Roche, GenoSite, GE, ESAOTE, ACR, EULAR—Speaker’s Bureau. K.V., Bristol-Myers Squibb—Grant/Research Support, Abbott, Pfizer, MSD, Roche, GenoSite, GE, ESAOTE, ACR, EULAR—Consultant, Speaker’s Bureau. W.K., Bristol-Myers Squibb—Consultant. C.G., Abbott, Pfizer, MSD, Roche, GenoSite, GE, ESAOTE, ACR, EULAR—Consultant. F.W., Bristol-Myers Squibb—Employee. All other authors have declared no conflicts of interest.

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**TABLE 1. Demographic, clinical and PDUS data**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Females (%)</th>
<th>83.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (S.D.), years</td>
<td>56.4 (14.1)</td>
<td></td>
</tr>
<tr>
<td>BL characteristics, mean (S.D.)</td>
<td>7.3 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>5.29 (1.11)</td>
<td></td>
</tr>
<tr>
<td>DAS28 (CRP)</td>
<td>12.6 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Global PDUS score</td>
<td>72.9 (14.2)</td>
<td></td>
</tr>
</tbody>
</table>

**Mean (95% CI) change from BL in global PDUS score (LOCF)**

| Day 7 | -0.7 (-1.2, -0.1) |
| Day 169 | -4.8 (-5.8, -3.9) |
| Day 169 | -0.55 (-0.70, -0.39) |
| Day 169 | -2.13 (-2.39, -1.86) |

**Patients (%), day 169**

| Remission (DAS28 <2.6) | 40/98 (40.8) |
| Low disease activity status (DAS28 ≤3.2) | 56/98 (57.1) |
| Clinically meaningful improvement | 72/97 (74.2) |

**Mean (95% CI) change from BL in PDUS synovitis 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, burstsis, dementia, endometriosis, pleural effusion and pulmonary fistula, and hyperension), 62 (69.6%) an AE, and 20 (19.2%) an infection.

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

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1Pharmacy and Pharmacology, University of Bath, Bath, 2Department of Twin Research and Genetic Epidemiology, King’s College London, London, UK and 3Department of Medical Biochemistry and Molecular Biology, University of Oulu, Oulu, Finland

**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 (VLP), 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, VLP 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 VLP in the lumbar spine.

**Methods:** We conducted a classic twin study of VLP changes of 880 ~ MPRIs in 155 monozygotic (MZ) and 285 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 parameters. 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>P-value</th>
<th>95% CIs estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEP</td>
<td>ACE</td>
<td>0.006</td>
<td>0.81</td>
<td>(1, 1)</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>0.006</td>
<td>0.81</td>
<td>(1, 1)</td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>0.006</td>
<td>0.81</td>
<td>(1, 1)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.006</td>
<td>0.81</td>
<td>(1, 1)</td>
</tr>
</tbody>
</table>

VEP: vertebral end plate.
Gout Impact Scale (GIS) had good content validity with different clinical stages. However, subscales of the GIS showed poor internal consistency 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 (e.g., attack frequency and intensity, inter-critical pain, and number of affected joints) and comorbidities were associated with poor HRQOL. Evidence for the impact of tophi, serum uric acid and allopurinol on HRQOL was less robust. Limitations of existing studies include cross-sectional design, recruitment from specialist clinic settings and frequent use of generic instruments.

Conclusions: Most studies have used the generic HAQ-DI and SF36. Gout-specific characteristics and comorbidities contribute to poor HRQOL. There is a 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 prolonged 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 directly 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 assessed. 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 as a result of admission directly due 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.

HES data for 2011 estimated the inpatient cost for this DGH to be £62400. Using the same daily inpatient costing our results show an estimated 12 month cost for patients admitted due to gout to be £148200 and for admissions complicated by gout to be £68400. The resultant total of £216600 being 3.5 times greater than the HES estimate.

94% (n = 60) had an established diagnosis of gout preceding their admission, but only 33% (n = 20) had a serum urate level measurement recorded in the year preceding admission, only 67% (n = 40) were on treatment for gout prior to admission and only 2.5% (n = 1) were treated according to existing management guidelines prior to admission.

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...
32. RISK FACTORS FOR HYPERURICAEAMIA AMONG A LARGE COHORT OF HIV-INFECTED MEN

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2Rheumatology, Brighton and Sussex Medical School, Brighton, UK

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 participate in 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 scrutiny of the HIV database for HIV parameters including stage of HIV infection, CD4 count, viral load, duration since diagnosis, and measured anthropometry and blood pressure. Patients gave consent for scrutiny of the HIV database for HIV parameters including stage of HIV infection, CD4 count, viral load, duration since diagnosis.

Results: Table 1 summarizes mean eGFR overtime by randomized treatment group and across the 3 study arms pooled. eGFR at week 0 was numerically (but not statistically) higher in the placebo group. Results of the model suggest that change in eGFR was not differentially affected by treatment (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.

Table 1. Mean (±SD) eGFR over time for patients with RCG and stage 3–4 CKD

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Pegloticase q2weeks</th>
<th>Pegloticase q4weeks</th>
<th>Placebo</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>40 (12); 42</td>
<td>40 (13); 41</td>
<td>43 (13); 20</td>
<td>41 (12); 103</td>
</tr>
<tr>
<td>Week 7</td>
<td>43 (14); 36</td>
<td>44 (19); 36</td>
<td>43 (13); 20</td>
<td>41 (12); 103</td>
</tr>
<tr>
<td>Week 13</td>
<td>41 (5); 36</td>
<td>40 (15); 33</td>
<td>46 (10); 19</td>
<td>42 (14); 88</td>
</tr>
<tr>
<td>Week 19</td>
<td>44 (15); 33</td>
<td>41 (15); 31</td>
<td>45 (10); 19</td>
<td>43 (15); 83</td>
</tr>
<tr>
<td>Week 25</td>
<td>42 (11); 31</td>
<td>41 (15); 30</td>
<td>47 (13); 18</td>
<td>43 (13); 79</td>
</tr>
</tbody>
</table>

Disclosures: F.O., Savient Pharmaceuticals, Inc.—Shareholder, Employee, M.W., Savient Pharmaceuticals, Inc.—Shareholder, Employee, R.Y., Takeda—Grant (Clinical Research and Drug Trial).

34. AUDIT OF ARMA 2012 STANDARDS OF CARE FOR PEOPLE WITH GOUT IN PRIMARY CARE IN EDINBURGH AND THE LOTHIANS

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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 EULAR and BSR guidelines. An audit of current care in general practitioners 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 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 50% 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 66% 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 16% and 37% were aware of the EULAR 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.
flares and ≈50% were given advice about self management of acute attacks.

Conclusions: The ARMA Standards of Care are not being met for many people. Despite improvement in the prescription of ULTs since 2008, target levels of SUA are still not achieved in a large proportion of patients and there are important deficits in patient education, training of health care professionals, diagnosis and assessment for comorbidities as well as in treatment and follow up. Standards of care for people with gout might be greatly improved by dissemination of consensus guidelines, application of care pathways and inclusion of gout in the quality outcome framework (QOF) for GPs.

Disclosures: The authors have declared no conflicts of interest.

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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1Arthritis Research UK Epidemiology Unit, School of Translational Medicine, University of Manchester, Manchester and 2Rheumatology Department, Norfolk and Norwich Hospital, Norwich, UK

Background: Mortality is increased in RA and this may be particularly 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 different weighting depending on whether the titre is low or high, suggesting they may have a differential prognosis. The aims of this study were 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 adjusted 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 20113 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 EROSIONAL DISEASE IN RHEUMATOID ARTHRITIS: A CLINICAL EXPERIENCE

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Background: Rheumatoid arthritis (RA) is a chronic progressive inflammatory arthritis 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 (s.d.) 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.
Results: A total of 35 studies were eligible for inclusion in the review, including 23,785 patients. Meta-analyses revealed the pooled mean QoL scores for the SF-36 domains to be: physical function 45.2 (95% CI 37.7, 52.8); role physical 36.9 (95% CI 29.1, 44.8); bodily pain 41.5 (95% CI 35.3, 47.8); global health 47.3 (95% CI 41.3, 53.4); vitality 48.6 (95% CI 42.9, 54.3); social function 58.1 (95% CI 50.8, 65.5); role emotional 51.5 (95% CI 43.0, 60.1); and mental health 59.6 (95% CI 54.2, 65.0). Reduced physical QoL was generally associated with increased disease activity, physical disability, pain and fatigue; reduced mental QoL was generally associated with increased disease activity, pain, fatigue, and increasing age. Furthermore, mental QoL and physical QoL were significantly associated ($r$ = 0.60, $P < 0.001). Reduced mental QoL was associated with reduced physical QoL. A sub-analysis comparing pooled mean physical and mental QoL scores before and after the shift in RA management was performed. The results indicated no difference in physical QoL, before and after the change in management: publication year at/pre 2009 physical QoL 41.7 (95% CI 30.9, 52.5); publication year post-2009 physical QoL 41.5 (95% CI 31.3, 51.7). However the same comparison for mental QoL showed improved outcomes for both physical and mental QoL, whilst not impacting physical QoL, $P = 0.001$. Changes in RA management: publication year at/pre 2009 mental QoL 57.9 (95% CI 45.8, 68.2); publication year post-2009 mental QoL 50.4 (95% CI 39.9, 60.8).

Conclusion: Early RA repair treatments, particularly the physical components of the SF-36. QoL is associated with several disease characteristics, including pain and fatigue. Furthermore, the recent change in RA management whilst not impacting physical QoL, may have implications for patients’ mental well-being. Therefore optimal care for RA patients requires a broader clinical perspective, taking into account patients’ physical and mental health needs. A specific focus on mental health may lead to improved outcomes for both physical and mental well-being.

Disclosures: The authors have declared no conflicts of interest.

38. SEROLOGICAL STATUS: A ROLE IN PERSONALIZED MEDICINE FOR RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a heterogeneous disease with diverse outcomes. Serological status such as rheumatoid factor (RF) and anti-citrullinated peptide antibody (anti-CCP) are associated with poorer outcome. Early intensive treatment regimes aiming at achieving remission have been 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), triple therapy. The trials randomised 467 patients; 61% female and their median age was 54 years. Disease activity was assessed using the DAS28. Remission was defined as DAS28 <2.6 at 24 months. Rheumatoid Factor isotypes (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 24 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 RA disease, this 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 IG A AND ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES: PREDICTORS OF RADIOGRAPHIC PROGRESSION

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1Rheumatology, King’s College London, London and 2Medical and Molecular Genetics, King’s College London, London, UK

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, (68% female, mean age 54 years). 467 baseline serum samples were analysed for RF isotypes and anti-CCP2 using commercial kits, (Euromimmun 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 IgG 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 ($beta = 2.019$, $beta = 1.975$ and $beta = 1.587$, 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 ($beta = 1.667$ 95% CI 0.265, 3.070, $P = 0.02$ and $beta = 1.389$ 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>$beta$ 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>
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<tr>
<td>RF IgA+</td>
<td>1.970</td>
<td>3.371</td>
<td>0.079</td>
<td>0.008</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>0.027</td>
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<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>
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<td>0.077</td>
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<td>&lt;0.001</td>
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<td>AGA</td>
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<td>0.074</td>
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<tr>
<td>DAS28</td>
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<td>1.268</td>
<td>0.300</td>
<td>0.002</td>
</tr>
<tr>
<td>Steroid treatment</td>
<td>-2.041</td>
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<td>0.001</td>
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</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: Treatment of RA differs between ethnicities due to differences in disease presentation and treatment response.

Methods: We analysed the baseline characteristics of 206 patients with RA who had been recruited into the Department of Rheumatology, Queen Elizabeth Hospital, Birmingham, UK.
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 TNF 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 (82 vs 53 years, respectively; \( P < 0.001 \)) and heavier (76 kg vs 67 kg, respectively; \( P < 0.001 \)). Compared with Caucasians, Asians had a higher ESR (42 vs 36, respectively; \( P = 0.04 \)), which was confirmed after adjusting for age, weight, SJC, TJC and smoking (\( \beta = 11.74, P = 0.003 \)); 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 36, respectively; \( P = 0.04 \)), which was confirmed after adjusting for age, weight, SJC, TJC and smoking (\( \beta = 10.9; P = 0.05 \)), 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. PIPJ 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 night PIP involvement more commonly seen among Caucasians (53% vs 70% and 70% vs 54%; \( P = 0.07 \)). 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 PIPJ 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

Elena Nikiphorou,1 Lewis Carpenter2, Keenanar Jayakumar1, Csilla Solymossy3, Josh Dixey and Adam Young3
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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 of progressive joint damage. X-rays of hands and feet (Larsen) are the gold standard imaging modality to quantify joint damage.

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. Length of 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, 3years 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 which 159 (28%) had at least one procedure 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 a Larsen score \( > 10 \) within the first 3 years increased the risk of hand and foot surgery by more than 2 fold (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 (OxTrend). 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 (\( P = 0.17 \)). 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 (66/99, 74%) (\( P = 0.85 \), \( \chi^2 \)). Smokers also had lower DAS28 scores at presentation (4.6) as compared with ex-smokers (5.5) and non-smokers (5.6) (\( P = 0.17 \)) and again at 12 months (2.24 vs 2.98 and 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 early arthritis data from other centres.

Further work is required to investigate genetic susceptibility to RA across ethnicities as well as evaluate differences in attitudes of 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 and demographic 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 (4.36 (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 year 1, 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 at baseline 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—2.5) vs 3 years (2.3, IQR 1—4). 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 0.25, 95% CI 0.07, 0.94), and were less likely to sustain remission over the year following (0% vs 7.1%, 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 at 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

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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. ≥ 170 IU) was present in 22 patients, this group represented the ‘cases’ and will be referred to as the ‘discordant antibody group’. 42 ‘controls’ were selected from patients with a very strongly-positive RF levels (arbitrarily >30 fold higher than the upper normal limit (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

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: The 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 ‘discordant 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).
Clinical features: Palindromic rheumatism was significantly more likely to precede the diagnosis of RA in the discordant antibody group [8 of 22 (36%)] compared with the strongly-positive RF group [1 of 42 (2%)] P = 0.008. There was a significantly increased prevalence of large joint and an asymmetrical presentation were also 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 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 Davies3, Kath Watson1, British Society for Rheumatology Biologics Register Control Centre Consortium1, Will Dixon1, Deborah Symmons1,3 and Kimme L. Hyrich1**

**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-naïve comparator cohort treated with non-biologic drugs (nbDMARDs) were recruited from 2001–2008. All were followed by clinician and patient questionnaires b-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 CVAs 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 (PS) which included baseline age, sex, female, current smoking status, smoking in the past year, ethnicity, smoking and registration date. Cumulative time on nbDMARD was calculated from the first time a subject was exposed to a nbDMARD until the date of diagnosis of isCVA or the date of last follow-up. Results: There were 130 verified incident isCVA occurred: 21 in 3271 nbDMARD treated subjects and 48 in 11 931 anti-TNF treated subjects (95% CI 0.22, 7.56) respectively.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>nbDMARD (n = 11642)</th>
<th>Anti-TNF (n = 3271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>60 (12)</td>
<td>56 (12)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>2420 (74)</td>
<td>8964 (77)</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>2.0 (0.6)</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: anti-TNF adjusted* (OR 95% CI)</td>
<td>0.88 (0.46, 1.71)</td>
<td>1.41 (0.18, 11.05)</td>
</tr>
</tbody>
</table>

#### Conclusions:

There was no difference in the risk of isCVA 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 18 (38%). There was no difference in risk of NHL between the cohorts; P adjusted HR 1.15 (95% CI 0.53, 2.48). There is no evidence that anti-TNF increases the risk of lymphoma over the background risk associated with RA, but further follow-up is needed to establish if the picture changes with prolonged treatment.

**Disclosures:** BSRBR-RA, Abbott Laboratories, Amgen, Merck, Pfizer Limited, Roche, Swedish Orphan Biovitrum, 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**

**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-naïve 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 scores of propensity score (PS) 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 censored at 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 3388 nbDMARD treated subjects and 48 in 11 931 anti-TNF (157 vs 90 per 100 000 person-years). After adjusting using PS 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 18 (38%). There was no difference in risk of NHL between the cohorts; P adjusted HR 1.15 (95% CI 0.53, 2.48). There is no evidence that anti-TNF increases the risk of lymphoma over the background risk associated with RA, but further follow-up is needed to establish if the picture changes with prolonged treatment.

**Disclosures:** O.T., Abbott Laboratories, Amgen, Merck, Pfizer Ltd, Roche, Swedish Orphan Biovitrum (SOBI), UCB Pharma Ltd—Research Grant. All other authors have declared no conflicts of interest.
48. **RELATIONSHIP BETWEEN ANTI-TNF THERAPY AND RISK OF MYOCARDIAL INFARCTION IN SUBJECTS WITH RHEUMATOID ARTHRITIS: RESULTS FROM THE BSRBR-RA**

Audrey Low\(^1\), Mark Lunt\(^1\), Louise Mercer\(^1\), Ellen Bruce\(^1\), British Society for Rheumatology Biologics Registers Control Consortium\(^1\), Will Dixon\(^1\), Kimme Hyrich\(^1\) and Deborah Symmons\(^1,2\)

**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 modulation 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 BSRBR-RA is an ongoing national prospective observational cohort study. Subjects with RA starting anti-TNF (etanercept, infliximab, adalimumab) and a biologic-naïve comparator observational cohort study. 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.

**Conclusions:** Risk of MI in subjects on anti-TNF therapy (etanercept, infliximab, adalimumab) and a biologic-naïve comparator observational cohort study. Subjects with RA starting anti-TNF (etanercept, infliximab, adalimumab) and a biologic-naïve comparator observational cohort study. 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.

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**Table 1. Results**

<table>
<thead>
<tr>
<th>Follow-up (person-years)</th>
<th>n</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>Female, %</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>RA duration, median (IQR), years</td>
<td>6 (10)</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></td>
</tr>
<tr>
<td>Lymphoma: PD adjusted HR (95% CI)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>1.5–3 years: 0.97 (0.40, 2.37)</td>
<td>-3 years: 1.31 (0.45, 3.79)</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, antiplatelet use, NSAIDs/COX2 inhibitors use.

**Disclosures:** BSRBR-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.

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

Saadia P. Malik\(^1\), Clive Kelly\(^2\), Jennifer Hamilton\(^3\), Carol Heycock\(^2\), Vadivelu Saravanan\(^3\) and Martin Rynne\(^2\)

**Rheumatology, Freeman Hospital, Newcastle and \(^2\)Rheumatology, Queen Elizabeth Hospital, Gateshead, UK**

**Background:** 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 standardised pro forma. Where case notes were not available, 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.

**Results:** The database contained 11466 patient-years from 2100 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 interstitial lung disease and one patient died from bone marrow failure thought to be related to disease rather than therapy. Therapy was felt 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.

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

Helen E. Harris\(^1\), Fiona Tweedie\(^1\), Yiannis Skaparis\(^2\), Marie White\(^1\), Nicola Scott\(^1\) and Kay Samson\(^2\)

**Fife Rheumatic Diseases Unit, NHS Fife, Kirkcaldy, Department of Medicine, University of Dundee, Dundee and \(^2\)Smoking 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 seropositive 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% had knowledge about each of the 5 campaign messages. 62 smokers identified before the campaign were contacted again following the campaign and found to have modest changes in their attitudes to smoking (Table 1). 32% 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 ex-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 FSG 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>
<thead>
<tr>
<th>Knowledge of link (all)</th>
<th>Pre (%)</th>
<th>Post (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on treatment (all)</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Smokers planning to stop</td>
<td>6.7</td>
<td>9</td>
</tr>
<tr>
<td>Smokers thinking about stopping</td>
<td>47.5</td>
<td>51</td>
</tr>
<tr>
<td>Smokers NOT intending to stop</td>
<td>45.8</td>
<td>40</td>
</tr>
</tbody>
</table>

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—Speakers fees, N.S., Pfizer—Educational grant to fund telephone work, Y.S., Pfizer—Educational grant for telephone work on J.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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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. We therefore introduced 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 department 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 attributable to osteoporosis (within 5 years) was > 15%.

Results: Mean age was 58.6 years (s.d. 14.4, range 20–85 years, 69 women). All patients had confirmed RA and had been prescribed at least 7.5 mg prednisolone. Twenty-three patients had high RA disease activity at presentation and were commenced on high dose corticosteroids (COBRA regimen). Forty-four patients had another risk factor for fragility fractures other than RA and GC treatment, while 16 had more than two risk factors. The most frequent additional fracture risks were previous fracture and smoking in patients with newly diagnosed RA. DXA scans were carried out in 92 patients. The mean time from RA diagnosis to DXA scan was 3.2 weeks (s.d. 2.81). The mean FRAX risk (calculated with femoral neck T scores) for a major osteoporotic fracture was 13.9% (s.d. 9.6) and for hip fracture 3.6% (s.d. 5.5).

Following fracture risk assessment bone protection medication was recommended in 31 patients. Treatment was recommended in 2 patients <50 years (n = 23), in 6 patients 50–64 years (n = 32) and in 23 patients 65 years or older (n = 37). Six patients were on a bisphosphonate prior to being diagnosed with RA. Of these 3 patients were recommended to continue bisphosphonate treatment following DXA.

Conclusions: A small minority of patients newly diagnosed with RA, and aged under 50 were recommended treatment to reduce fracture risk. In contrast more than 2/3 of those over 65 were advised such treatment. These results serve to highlight the benefits of DXA scanning in such patients to help refine fracture risk. The scans also allow clinicians to avoid recommending unnecessary treatment in the short time interval between commencing treatment for RA and fracture risk assessment may be helpful to attenuate adverse effects of GCs on bone.

Disclosures: The authors have declared no conflicts of interest.

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

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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 recently recruited 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 patients with a RA diagnosis) were defined by time at onset: 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 appointed to 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 general population. 

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 they 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: Raising 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?

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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 6 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, 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 25 years. In total 110 patients (48%) were male, giving a male:female ratio of 1:1.09 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 (67%) than females (60%) [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, RA 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 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.

Table 1. Changes in percentages of deaths occurring as a result of interstitial lung disease, median age at death from ILD, and median survival in those dying from ILD, as related to year of onset in clusters of 6 years

<table>
<thead>
<tr>
<th>Year of onset of RA-ILD</th>
<th>% of patients dying from ILD</th>
<th>Median age at death from ILD in years</th>
<th>Median survival in months from ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987–1993</td>
<td>67</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>1994–1999</td>
<td>42*</td>
<td>68*</td>
<td>36</td>
</tr>
<tr>
<td>2000–2005</td>
<td>54</td>
<td>72*</td>
<td>50*</td>
</tr>
<tr>
<td>2006–2012</td>
<td>30**</td>
<td>76*</td>
<td>48*</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01 from baseline.

Disclosures: The authors have declared no conflicts of interest.

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

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

Background: Rheumatoid arthritis (RA) is associated with clinically relevant interstitial lung disease (ILD) in approximately 5% of patients. In a previous study by the ERAS the prognosis had been poor, with a mean survival of 3 years following diagnosis of RA-ILD. However, 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 6 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 1:1.1 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.

Table 1. Baseline characteristics and 5-year outcome

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number</td>
<td>1006</td>
<td>880</td>
<td>638</td>
</tr>
<tr>
<td>% female</td>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>54 (42–67)</td>
<td>55 (44–67)</td>
<td>58 (47–70)</td>
</tr>
<tr>
<td>Number (%) of CV deaths</td>
<td>36 (3.6)</td>
<td>34 (3.9)</td>
<td>26 (4.1)</td>
</tr>
<tr>
<td>Crude CV mortality (per 1000 PY)</td>
<td>7.5</td>
<td>8.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Crude CV mortality (per 1000 PY)</td>
<td>1.13 (0.82, 1.57)</td>
<td>1.29 (0.92, 1.81)</td>
<td>1.51 (1.03, 2.22)</td>
</tr>
<tr>
<td>CV SMR (95% CI)</td>
<td>1987 ACR RA patients CV SMR (95% CI)</td>
<td>0.72 (0.41, 1.27)</td>
<td>1.30 (0.79, 2.16)</td>
</tr>
<tr>
<td>2010 ACR/EULAR RA patients CV SMR (95% CI)</td>
<td>1.07 (0.71, 1.62)</td>
<td>1.27 (0.80, 2.01)</td>
<td>1.59 (0.92, 2.73)</td>
</tr>
</tbody>
</table>

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 Stannett2 and Richard Hull3

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

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 active acute arthritis and that the
support/ information needs may be higher in this group. We felt further analysis of the data collected could examine this further.

Methods: We analysed every contact by telephone, email, letter or online, elicited 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 (6.6%) reported they had at least one additional health problem and 59% 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 anxiety. 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 experienced 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. High 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

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Background: Rheumatoid arthritis (RA) is characterized by an increased prevalence of cardiovascular disease (CVD) as well as a combination of physiological factors (maximal oxygen uptake -VO2max) which is also a strong predictor of CVD. Exercise is known to improve 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 = 0.043), DAS28 (P = 0.006) and HAQ (P = 0.003).

Preliminary 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 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. OSTEOPOROTIC FRACTURE IN RHEUMATOID ARTHRITIS: A STUDY OF INCIDENCE, PREDICTIVE FACTORS AND ECONOMIC BURDEN FROM TWO UK INCEPTION COHORTS

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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.

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 (median 10 and 3 years). Yearly assessments recorded co morbidities and in-patient hospital episodes, including fracture sites, and orthopaedic interventions (OPCS codes). Clinical databases were supplemented and validated with national databases, the National Joint Registry (data available from 2003–2011), Hospital Episode Statistics (data 1997–2011) and the National Death Register (data 1986–2011). Only patients who moved abroad or were not registered with a general practitioner would be absent from national databases. Treatment regimens followed guidelines of the era, mainly conventional DMARD therapies, ± steroids, and latterly biologics.

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 5years (IQR 5–15) and average length of stay (LoS, the main driver for indirect costs) was median 15days 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 in 1st year: high rheumatoid factor positivity in the 1st year (OR 2.9, 95% CI 1.1, 2.9), erosions (OR 2.4, 95% CI 1.4, 4.0), steroid use (OR 2.7, 95% CI 1.1, 6.5), high haemoglobin (OR 1.9, 95% CI 1.1, 3.1), low haemoglobin (OR 1.99, 95% CI 1.2, 3.1), the latter an unusual finding.

Conclusions: Osteoporotic fracture complications RA a 6.5% over 25years, mainly hip fractures, which were a moderately common complication of RA and most required major orthopaedic interventions and health costs. Risk factors for hip fracture included disease severity measures, prompting more active therapies needed for RA and bone protection.

Disclosures: The authors have declared no conflicts of interest.

58. NATURAL HISTORY, DISEASE CHARACTERISTICS AND AUTOANTIBODY POSITIVITY IN PATIENTS WITH BRONCHIOLITIS OBliterans: IS THE LUNG AN INITIATING SITE OF AUTOIMMUNITY IN RHEUMATOID ARTHRITIS?

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Background: Rheumatoid arthritis (RA) patients have a 10-fold increased prevalence of symptomatic bronchiectasis (BR) compared with the general population and HRCT studies report radiological BR in 25–29%. To date the association remains unexplained. Previous
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 and whose BR symptoms preceded RA (BRR). We then 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 BRRRA and RABB groups (Table 1). Duration of BR was significantly shorter in the RABR group averaging 8 years compared with 41 years in the BRRR 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, 33 (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 BRRA. Further investigation is required, there is increasing evidence to suggest that BR might initiate RA by the production of autoantibodies in susceptible individuals.

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of patients with BRRA and RABR</th>
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<tbody>
<tr>
<td>BRRA</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
</tr>
<tr>
<td>Years with BR, median (IQR)</td>
</tr>
<tr>
<td>Years with RA, median (IQR)</td>
</tr>
<tr>
<td>DAS28-CRP, median (IQR)</td>
</tr>
<tr>
<td>Erosive disease, n (%)</td>
</tr>
<tr>
<td>MRC dyspnoea score, median (IQR)</td>
</tr>
<tr>
<td>Chest infections in past 12 months, median (IQR)</td>
</tr>
<tr>
<td>FEV1% predicted, median (IQR)</td>
</tr>
</tbody>
</table>

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

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

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1Sport and Exercise Sciences, University of Birmingham, 2Rheumatology Department, Dudley Group of Hospitals NHS Foundation Trust, Dudley, 3School of Sport, Performing Arts and Health, Wolverhampton University, Wolverhampton, UK and 4Department of Rheumatology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

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 dilatation and GTN-induced dilatation) 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.

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 (3%) 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 non-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.

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**RHEUMATOID ARTHRITIS: PATHOGENESIS AND ANIMAL MODELS**

61. **INTRA-ARTICULAR INJECTION OF MESENCHYMAL 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 intraperitoneally in animal models of RA and lead to different therapeutic effects, varying from significant improvement to no effect so far overall the results remain inconclusive. The reason for this may be the route of administration; IA administration of MSCs may be more beneficial than the intravenous/intrapitoneal route, applying them directly to the affected tissues.

**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. For a control, the same volume of PBS was injected into the left knee joint. 20 h after induction infiltration, 10 μl of serum free IMDM, containing 50 000 mMSCs labelled with red fluorescent cell tracer CM-Dii were injected intra-articularly into the right knee joint. Control animals were injected with only serum-free IMDM. Joint diameters were measured at days 1, 2, 3, 5, 7, 14, 21 and 28. At the end of the experiments, animals were killed and joints were collected for histology.

**Results:** Knee joint diameter (swelling) was measured as a clinical indication of joint inflammation and this parameter, was statistically significantly less in MSC treated mice compared with control treated animals 72 h after arthritis induction (P < 0.05). This difference continued for ~7 days post IA mBSA administration (P < 0.05). Three and 7 days after arthritis induction CM-Dii-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 injection of 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/C023/0811] and Institute of Orthopaedics Ltd, Oswestry.

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

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62. **MACROPHAGES IN HYPOXIC RHEUMATOID JOINTS 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 remodelling potential leading to inflammation and joint destruction. Macrophages respond to hypoxia by up regulating the hypoxia inducible transcription factor-2 (HIF-2) 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 (FR-1, CD147, 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%), FR-1, Tie2 and CD206. A similar pattern was observed in patients with severe disease where sections expressed more HIF-2, FR-1 and 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 FR-1, Tie2 and CD206, important in tissue remodeling and angiogenesis. We are currently investigating these gene expression patterns in these subpopulations using laser capture micro-dissection and gene arrays.

**Disclosures:** The authors have declared no conflicts of interest.
64. RELATIONSHIP OF BAFF-BINDING RECEPTORS WITH SERUM BAFF LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS RELAPSING AFTER RUTIMUB

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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 disease symptoms in patients with RA. B-cell return 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, transmembrane activator and calcium signal modulating cyclophilic ligand interactor (TACI) and B-cell maturation antigen (BCMA). Serum BAFF levels rise after BCDT but the relationship with BAFFR-receptor expression has not been investigated.

Methods: We included 10 Healthy Controls (HC) and 20 RA patients at relapse (R) within 3 months after BCDT (Concordant Relapse; C-R) and 10 relapsing within 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) at ≥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, %BAFF-R+B cells were significantly lower in naive 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.

Conclusions: Binding of soluble BAFF to BAFFR delivers a survival signal to (particularly) naive B cells, but is also thought to give a negative signal through TACI on post-GC B cells. Loss of BAFFR expression is also necessary in order for post-GC B cells to differentiate to ISC. The relatively higher percentage of post-GC B cells and plasmablasts in patients with C-R indicates rapid differentiation into ISC. Raised BAFF levels at relapse were associated with lower %BAFFR+ and %TACI+B cells. Resumption of disease following BCDT period of clinical remission reflects differentiation or expansion of auto-reactive B-cells. Raised BAFF levels may therefore be altering BAFF-binding receptor expression with consequences for survival and selection of auto-reactive B cells.

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^-5 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-baFF 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 true for HDAC3, 5, and 9, leading 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.

67. MEMBRANE-BOUND AND SOLUBLE BAFF EXPRESSION BY HUMAN RHEUMATOID FIBROBLAST-LIKE SYNOVIOCYTES IN RESPONSE TO TLR STIMULATION

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Background: B-cell activating factors of TNF family (BAFF) is associated with the survival and maturation of B cells. BAFF is widely expressed in the RA synovium which is characterized by the presence of synovial niches of auto reactive B cells and sustain in situ autoantibody production. Importantly, B-cell niches remain functional in an in vitro model in the absence of naive B-cells, suggesting that autocrine mechanisms support ongoing B-cell activation in the RA synovium. BAFF exerts its functional role both as a membrane bound protein and in soluble form. Here we investigated whether resident synovial fibroblasts and synovial fibroblasts (RASF) are capable of producing either forms of BAFF and thus contribute to local B-cell activation.

Methods: mRNA BAFF in RASF stimulated with TLR2, TLR3 and TLR4 ligands was assessed by quantitative Taqman PCR. RA dermal fibroblasts (rRASF) and OA SF (oRASF) were used as controls. The cytoplasmic, membrane bound and/or soluble forms of BAFF were investigated by 1) Western blot using total and membrane-enriched protein extracts, 2) flow cytometry, 3) ELISA and 4) immunocytochemistry.

Results: In vitro stimulation of TLR3, and to a significantly lesser extent TLR4, but not TLR2 on RASF led to strong induction of BAFF mRNA. In response to TLR3, soluble BAFF was time-dependently released in the supernatant of RASF (~600 pg/ml) and, to a lesser extent, OASF and rRASF. RASF constitutively expressed both cytoplasmic and membrane bound BAFF as demonstrated by WB, FACS and immunocytochemistry which was upregulated upon TLR3 stimulation and was significantly increased as compared with rRASF.

Conclusions: Here we provide conclusive evidence that the RA synovium is a pivotal source of the B-cell survival factor BAFF at both in vivo and in vitro. Determination 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.

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 attach, 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 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 expressed CD248 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 only had cartilage. In addition, we detected 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.

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 for new or 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. NICE and ACR thresholds were used. Gender, age, BMI, smoking, family history of DM, hypertension, prior cumulative dose of oral GC, current DMARDs and ever NSAID use were potential confounders. Incidence rates for DM were calculated for different patterns of GC exposure. Crude and adjusted hazard ratios (HR), compared with non-use, were estimated using Cox regression.

**Results:** 23 736 adult RA patients were included. 70% were female with a median age of 59 (IQR 49–71). Median follow-up time was 74 months (IQR 30–108). 2462 patients were diagnosed with type II DM during follow-up: incidence 14.0 events/1000 person years (PY) in unexposed patients and 21.9 events/1000 PY in time following GC exposure. The crude HR was 1.33 (95% CI 1.20, 1.48). This equates to one additional case of DM per year for every 212 patients currently receiving GCs. Each 5 mg increase of current oral GC was associated with a 1.14 increased risk of DM (HR 1.14, 95% CI 1.11, 1.17). Patients currently taking between 10 and 30 mg/day had an adjusted HR of 2.30 (95% CI 1.65, 2.50) compared with non-use, equating to one additional case of DM for every 64 patients treated. A 5 mg increase in average daily dose was associated with a 3.34 increased risk (HR 1.36 95% CI 1.26, 1.48), suggesting prolonged exposure increased risk.

**Conclusions:** Oral GC therapy is a significant and clinically important risk factor for incident Type II DM in patients with RA, the risk increasing with dose and duration of treatment. Screening for DM might be warranted in patients taking oral GC therapy, particularly at high doses or for prolonged time. Further work is planned to investigate current practice around screening for DM in patients receiving GC therapy, and examining the outcomes of DM in patients taking GC therapy.

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

### Table 1. Clinical and functional outcomes at 5 years of ADA treatment (observed analyses)

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**References:**

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70. **LONG-TERM EFFECTIVENESS AND SAFETY OF ADALIMUMAB IN PATIENTS WITH MODERATE VS SEVERE RHEUMATOID ARTHRITIS**

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1Clinic for Rheumatology and Clinical Immunology, Charité—Universitätsmedizin Berlin, Berlin, Germany; 2Rheumatology, Azienda Ospedaliera di Firenze, Firenze, Italy; 3Hospital General Universitario Elche, Alicante, Spain; 4Immunology Development, AbbVie GmbH and Co. KG, Ludwigshafen and 5Data and Statistical Sciences, AbbVie GmbH and Co. KG, Ludwigshafen, Germany

**Background:** Patients with moderate RA despite DMARDs may gain benefit from anti-TNF therapy; however, severe disease activity is often refractory or requires further anti-TNFs. This analysis compared treatment responses and adverse events (AEs) between patients with moderate vs severe RA.

**Methods:** ReAct enrolled patients with active RA (DAS28[ESR] > 3.2) despite DMARD treatment for open-label adalimumab (ADA) therapy for 12 weeks; patients were eligible to enrol in ReAct in the first 12 months of completing ReAct. This post hoc analysis stratified patients by baseline (BL) disease activity, defining moderate activity as DAS28 >3.2 to ≤5.1, and severe activity as DAS28 >5.1. Analyses on observed data (without imputation) calculated treatment responses (ACR criteria), the percentage of patients with DAS28 and SDAI low disease activity (LDA) and remission, and functional ability (Disability Index of the HAQ, HAQ-DI).

**Results:** Of 6610 patients enrolled in ReAct, 3435 (52%) elected to continue in ReAct; of these, 1805 (53%) completed the study. At BL of ReAct, 1267 (19%) had moderate and 5343 (81%) had severe disease activity. Patients with severe activity had slightly increased mean age and disease duration; as expected, these patients had higher levels of disease activity (e.g., swollen/tender joint counts, ESR/CRP levels, and HAQ-DI) compared both groups, treatment responses were maintained through 5 years. After 5 years of ADA, ACR20/50/70 responses were greater among patients with severe disease, while more moderate disease patients achieved LDA and remission (Table 1). Correspondingly, absolute values of DAS28 and HAQ-DI 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 leading to discontinuation (8.2 vs 8.7 E/100PY, serious AEs (13.3 vs 15.3 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 progression and preserving function, these findings support the use of anti-TNF in patients with moderate RA. There were no noticeable differences in the safety profile for ADA between patients with moderate and severe disease activity.

**Disclosures:** GB, no better than search Grants, Consultation Fees, Speakers’ Bureau. S.K., AbbVie—Contract Employee; Stocks. H.K., AbbVie—Employee, Stocks or Options. AbbVie—AbbVie sponsored the study, contributed to its design, and participated in the collection, management, and interpretation of the data, and in writing and approval of the final version. F.N., Roche—Research Grants. K.U., AbbVie—Employee, Stocks. All other authors have declared no conflicts of interest.

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 intolerable or current use, current daily dose, and duration of treatment. Screening for DM might be warranted in patients taking oral GC therapy, particularly at high doses or for prolonged time. Further work is planned to investigate current practice around screening for DM in patients receiving GC therapy, and examining the outcomes of DM in patients taking GC therapy.

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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. Moreover, the use of folinic acid dose was increased from 5 mg weekly to 5 mg on 6 days a week in 39% cases by 6 months to reduce MTX related side effects. 23% patients had made at least 1 helpline call relating to MTX use and 44% patients had 1 or more discussions about MTX with their rheumatologists at their appointments.

**Conclusions:** Protocol driven tight control of RA at our Rheumatology department through monthly review, commencing moderate doses of MTX at baseline, not only allowed rapid escalation of MTX dose aiming for remission but also led to higher retention rates than historically seen at 1 year.

**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 aquarter 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 therapy. A reason could be lack of awareness regarding the disease known to lost to follow ups and have poor compliance with their medications. A reason could be unawareness regarding the disease and the benefits of compliance. The primary objective of this prospective 24 weeks controlled study was to assess the impact of RA disease and management related education on adherence to recommended compliance with MTX dose.

**Methods:** At two centres 122 consecutive adult patients with RA were 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 another 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% and 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 may 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. 592 patients with active RA (≥6/68 swollen joints, ≥6/68 tender joints, CRP ≥1.0mg/dl, RF and/or anti-CCP antibody-positive) despite ≥3months of MTX (15-25mg/week) participated in this multicentre, randomized, double-blind, placebo (PBO)-controlled phase III study. Patients were randomized (2:1) to i.v. GLM 2mg/kg or PBO at weeks0,4 and 12; all patients continued stable MTX doses. The primary remission was defined by 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: 4.6% vs 2.0%, respectively; P < 0.05 and week 24: 7.3% vs 2.0%, respectively; P < 0.01).

Moderate (approx.10%-15%) increases in week 24 DAS28-CRP remission and ACR/EULAR remission in these patients. 592 patients with active RA (≥6/68 swollen joints, ≥6/68 tender joints, CRP ≥1.0mg/dl, RF and/or anti-CCP antibody-positive) despite ≥3months of MTX (15-25mg/week) participated in this multicentre, randomized, double-blind, placebo (PBO)-controlled phase III study. Patients were randomized (2:1) to i.v. GLM 2mg/kg or PBO at weeks0,4 and 12; all patients continued stable MTX doses. The primary remission was defined by 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: 4.6% vs 2.0%, respectively; P < 0.05 and week 24: 7.3% vs 2.0%, respectively; P < 0.01).

Moderate (approx.10%-15%) increases in week 24 DAS28-CRP remission rates were observed among subgroups of patients defined by HAQ score ≤0.25 (24% vs ≤0.625 (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 2mg/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):
NSAIDs at baseline: yes/no 57/323 (18) / 13/72 (18)
DMARDs at baseline: yes/no 38/206 (18) / 32/189 (17)
Oral corticosteroids at baseline: yes/no 38/251 (16) / 32/144 (22)
HAQ score (median 1.625)
CRP (mg/dl):
Anti-CCP: negative/positive 6/32 (19) / 64/362 (18)
RF: negative/positive 6/30 (20) / 64/365 (18)
Functional class: I/II/III 9/33 (27) / 48/284 (17) / 13/78 (17)
Swollen joint count (median 12):

75. RHEUMATOID ARTHRITIS RESPONSIBILITY DEAL

Jamie Hewitt

1National Rheumatoid Arthritis Society, Maidenhead, UK

Background: Rheumatoid arthritis (RA) is a complex disease to manage. To improve clinical outcomes, patients and those making decisions that affect their care and services—healthcare professionals, healthcare managers and policymakers—need to work together and take greater personal responsibility in their individual roles. To find out what patients in England, people believe are important, the National Rheumatoid Arthritis Society (NRAS) hosted a call and invited comments from everyone with an interest and connection to the disease. We then summarized the information into a series of pledges that people could endorse.

Methods: NRAS drafted a series of open-ended questions asking consultees which personal responsibilities patients, healthcare professionals, NHS service managers and policymakers should commit to taking to improve clinical outcomes for RA. The questions were then piloted, adjusted and distributed electronically to 4,679 individuals—including all NRAS members with an email address, other supporters of NRAS and rheumatology community stakeholders. Responses were then grouped into thematic headings from which the pledges were derived. NRAS then conducted a literature review to examine the medical evidence and public policy frameworks that inform the treatment of RA across the UK and used this information to provide a background context and accompanying justifications to the pledges.

Results: In total 691 consultation responses were returned. The largest numbers of responses received were from patients or those caring for people with RA (97%) with a high level of female respondents (85%). The largest age categories for consultees were 55–64 (34%) closely followed by 45–54 (27%) and 65 and over (19%). The majority of respondents were from England (87%), with smaller numbers from Scotland (8%), Wales (4%) and Northern Ireland (1%).

Themes identified for patients in the consultation are the need to improve knowledge of their disease, undertake greater self-management and work openly with healthcare teams. For healthcare professionals, consultees want them to continue to improve their knowledge about RA, optimize the RA patient journey through healthcare services, and listen more to patients. In respect of NHS service managers, consultees wish them to focus on improving the capacity and ability of healthcare professionals to deliver evidence-based, high quality care and look at new ways to meet the needs of patients. Finally, for policymakers, consultees want them to increase their understanding of RA, raise the profile of the disease among other policymakers, and develop policies that raise the standards of care and quality of life.

Conclusions: The consultees identified better communication skills and education about RA (including self-management and continuing professional development) as important ways that patients, healthcare professionals and policymakers can take greater personal responsibility to improve clinical outcomes.

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 (20.2%) 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, 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 (0.28 ± 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.


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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 diseases 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.

Six severe 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. IgM 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 low IgG or IgM levels are low.

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

78. TOCILIZUMAB IN METHOTREXATE-INTOLERANT OR CONTRAINDED PATIENTS—A COST-UTILITY MODEL

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 contraindicated to MTX. The objective was to evaluate the cost-effectiveness of monotherapy TCZ in DMARD-IR patients intolerant of or contraindicated to MTX in the UK (UK).

Methods: A cost-effectiveness 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 measurement 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 inferred 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 independently 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 contraindicated to MTX.

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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

Michael E. Weinblatt1, Roy Fleischmann1, O. Davies2, K. Luijten3 and Desiree van der Heijde4
1Brigham and Women’s Hospital, Boston, MA, 2University of Texas South Medical Centre, Dallas, TX, USA, 3UCB Pharma, Brussels, Belgium and 4Department of Rheumatology, Leiden University Medical Centre, Leiden, Netherlands

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 an 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 400 mg/ PBO at weeks 0,2,4, then CZP 200 mg/PBO at weeks 6,8,10 plus current treatment), patients received open-label CZP 200 mg 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, 0.3–0.9, 1.2, 1.5 and 1.8 units) and SJC NR (percentages of %CFB at week <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 28. Patients with a SJC change of ≥29% by week 12 had a 1.5% chance of achieving LDA at week 28. For any given threshold in DAS/ SJC, the failure to respond up to a later timepoint was associated with a lower chance of 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 CSA28 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 pt 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 naive 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>% (n/n)</th>
<th>Week 6</th>
<th>% (n/n)</th>
<th>Week 12</th>
<th>% (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 (ESR) change from BL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.3</td>
<td>16.6 (27/166)</td>
<td>9.3 (6/65)</td>
<td>2.2 (1/42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.6</td>
<td>17.9 (48/268)</td>
<td>12.2 (14/115)</td>
<td>1.4 (1/70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.9</td>
<td>18.9 (66/349)</td>
<td>10.9 (19/174)</td>
<td>1.2 (2/163)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.2</td>
<td>20.9 (193/930)</td>
<td>13.8 (199/145)</td>
<td>1.0 (3/304)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>21.5 (113/526)</td>
<td>14.8 (51/344)</td>
<td>6.3 (14/224)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.8</td>
<td>22.4 (132/588)</td>
<td>17.1 (75/439)</td>
<td>10.5 (34/323)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SJC % change from BL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>29.6 (88/300)</td>
<td>19.8 (10/19)</td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>23.7 (130/548)</td>
<td>17.7 (82/25)</td>
<td>11.9 (29/244)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>27.1 (184/660)</td>
<td>23.0 (130/564)</td>
<td>18.9 (99/471)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a:*5% probability of LDA at week 28.

Table 1. Results

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of pregnancy events (n)</th>
<th>Live births</th>
<th>Miscarriages</th>
<th>Elective termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct exposure to CZP from global safety database</td>
<td>US General Population (National Vital Statistics Data—1900-2004)</td>
<td>139</td>
<td>390 000</td>
<td>103/139 (74.1%)</td>
</tr>
</tbody>
</table>

62. SAFETY UPDATE ON CERTOLIZUMAB PEGOL IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS WITH LONG-TERM EXPOSURE

X. Mariette1, Ronald F. van Vollenhoven2, V. Bykerk3, M. de Longueville4, C. Arendt4, K. Luijtens4 and J. Cush5

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Background: The safety of certolizumab pegol (CZP) in RA has been evaluated in 10 randomized controlled trials (RCTs) and 7 open-label extensions (OLEs). An update of long-term safety data of CZP in RA is provided.

Methods: Data were collected from all clinical trials of CZP in RA (cut-off date of 30 Nov 2011). Adverse events (AEs) were defined as occurring after the first dose and within 84 days of last dose. Serious adverse events (SAEs) were defined conservatively with the addition of opportunistic infections (OIs), malignancies and medical events important to the investigator. Serious infectious events (SIEs) were defined according to the regulatory definition with addition of the need for i.v. antibiotics. Search terms for OIs were defined by 6 external experts and validated by the steering committee (UC/VBR/WX/ XM). External experts manually reviewed all cases of death, SIEs (including OIs) and malignancies. Deaths were categorized as primarily associated with cardiovascular (CV), infectious, malignant or other causes; malignancies were classified as non-melanoma skin cancer (NMSC), solid tumours or lymphoma. Incidence rates (IR) and event rates (ER) per 100 pt-years (PY) are reported.

Results: 4049 RA patients had received CZP in all studies, totaling 9277PY. Mean exposure to CZP was 2.1 years (min 0.04, max 7.8); median exposure was 0.77. SIEs were the most common SAEs. In total, 43 tuberculosis (TB) infections occurred in 43 patients, of which 39 occurred in Central/Eastern Europe (CEE). 58 deaths occurred in CZP patients (IR 0.63) as a result of 19 CV events, 13 infections, 13 malignancies and 18 other causes. 65 CZP patients in all studies developed malignancies (ER 0.78), with 60 patients developing solid tumours (IR 0.70) and 5 developing lymphoma (IR 0.05). External experts manually reviewed all cases of death, SIEs (including OIs) and malignancies. Deaths were categorized as primarily associated with cardiovascular (CV), infectious, malignant or other causes; malignancies were classified as non-melanoma skin cancer (NMSC), solid tumours or lymphoma. Incidence rates (IR) and event rates (ER) per 100 pt-years (PY) are reported.

Results: Data were collected for 169 patients retrospectively.

(i) 44% were prescribed combination DMARD therapy on diagnosis.
(ii) 41% initiated therapy within 3 months of diagnosis.
(iii) 54% had CRP done monthly, 6% didn’t have CRP checked despite being reviewed monthly, 25% had CRP checked on each clinic visit (visits weren’t monthly), 15% had the CRP checked infrequently or not at all.
(iv) 27% had DAS assessments done monthly, 14% didn’t have DAS28 calculated despite, 31% had DAS checked each visit (visits weren’t monthly), 28% had DAS28 checked infrequently or not at all.
(v) 43% were reviewed monthly.

Conclusions: In conclusion, we compared the audit with a previous audit done in 2009 to assess improvement in service provided in Wales and to identify our shortcomings.

Disclosures: The authors have declared no conflicts of interest.

TABLE 1. Results

<table>
<thead>
<tr>
<th>RCTs</th>
<th>All CZP doses, n = 2965</th>
<th>All studies (RCTs and OLEs), n = 4049</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total exposure (PY)</td>
<td>373</td>
<td>9277</td>
</tr>
<tr>
<td>Mean exposure, days</td>
<td>110</td>
<td>782</td>
</tr>
<tr>
<td>Median exposure, days</td>
<td>111</td>
<td>267</td>
</tr>
<tr>
<td><strong>AEs</strong></td>
<td><strong>233.9</strong></td>
<td><strong>188.8</strong></td>
</tr>
<tr>
<td><strong>ERa</strong></td>
<td><strong>3.0</strong></td>
<td><strong>3.3</strong></td>
</tr>
<tr>
<td><strong>IRa</strong></td>
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<td><strong>0.8</strong></td>
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<tr>
<td><strong>n</strong></td>
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<td><strong>11.0</strong></td>
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<tr>
<td><strong>pcts</strong></td>
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<td><strong>68.1</strong></td>
</tr>
<tr>
<td><strong>%</strong></td>
<td><strong>66.1</strong></td>
<td><strong>56.9</strong></td>
</tr>
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<td><strong>11.0</strong></td>
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<tr>
<td><strong>ERa</strong></td>
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<td><strong>0.7</strong></td>
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<tr>
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<td><strong>0.7</strong></td>
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<td><strong>ERa</strong></td>
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<tr>
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<td><strong>pcts</strong></td>
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<td><strong>%</strong></td>
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*All P-values were significant at the 0.05 level.

Treat emergent AEs of oesophageal candidiasis were included as OIs. bPer 100 PY.

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

Aisha Khan1, Zoe Maclaren2 and Sayam Dubash3

1Rheumatology, Princess of Wales Hospital, Bridgend, 2Rheumatology Department, Wrexham Maelor Hospital, Wrexham and 3Rheumatology Department, Hinchingbrooke Hospital, Cambridge, UK

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 have had their disease activity 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 have had key components of disease activity measured monthly until treatment has controlled the disease to a level agreed with the person.

Results: Data were collected for 169 patients retrospectively.

(i) 44% were prescribed combination DMARD therapy on diagnosis.
(ii) 41% initiated therapy within 3 months of diagnosis.
(iii) 54% had CRP done monthly, 6% didn’t have CRP checked despite being reviewed monthly, 25% had CRP checked on each clinic visit (visits weren’t monthly), 15% had the CRP checked infrequently or not at all.
(iv) 27% had DAS assessments done monthly, 14% didn’t have DAS28 calculated despite, 31% had DAS checked each visit (visits weren’t monthly), 28% had DAS28 checked infrequently or not at all.
(v) 43% were reviewed monthly.

Conclusions: In conclusion, we compared the audit with a previous audit done in 2009 to assess improvement in service provided in Wales and to identify our shortcomings.

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

Venkant C. Chalam1, Tom Sheeran1, Tom Price1, Sangeetha Bakkar1, Diarmuid Mulherin1, Cauline Molloy1, Fiona Keay1, Caroline Heritage1 and Barbara Douglas1

1Canock Rheumatology Centre, Canock, UK

Background: Oral MTX is the gold standard first-line therapy for RA patients. The place in therapy for subcutaneous (SC) MTX is less clear. Oral MTX is the gold standard first-line therapy for RA patients. 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 dose SC MTX 15.6 mg/week; 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 95% 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 1.2. After 3 months, the proportion of patients with DAS28 ≥5.1 and ≥3.2 fell from 95% 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.

Disclosures: The authors have declared no conflicts of interest.

References


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

Roy Fleischmann1, Michael E. Weinblatt2, Michael H. Schiff3, Stephen Carpenter4, Venkat C. Chalam1, Tom Sheeran1, Tom Price1, Sangeetha Bakkar1, Cauline Molloy1, Fiona Keay1, Caroline Heritage1 and Barbara Douglas1

1Canock Rheumatology Centre, Canock, UK

Background: This study assessed how use of an objective multi-biomarker disease activity (MBDA) test for RA affects treatment decisions by their HCPs (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 95% 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.

Methods: At routine office visits, 101 patients with RA were assessed by their HCPs (N = 6). 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 95% 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.

Results: A total of 646 patients were randomized and treated with ADA (n = 318) or ADA (n = 328) on background MTX. Pt characteristics were balanced. A similar proportion of patients achieved a HAQ-DI response from baseline to year 1 (80.4% patients in the ADA arm vs 57.0% patients in the ADA arm). Improvements in pt pain (mean % ± SE) were 46.5 ± 4.2% vs 35.6 ± 4.1% at 6 months, and 53 ± 6.1% vs 39.2 ± 6.0% at 1 year for ADA and ADA, respectively. Improvements in PtGA were for ADA 40.2 ± 7.3% vs 29.6 ± 7.3% (p = 0.004), for ADA 46.1 ± 3.5% vs 41.2 ± 3.4% for ADA and ADA at 6 months and 1 year, respectively. Fatigue decreased from baseline by –22.4 ± 1.5% vs –19.9 ± 1.5% at 6 months, and –23.2 ± 1.5% vs –21.4 ± 1.5% at 1 year for ADA and ADA, respectively. Improvements in all domains of the SF-36, including PCS and MCS, observed at 6 months were maintained at 1 year. For RAPID3, the ADA- and ADA-treated groups demonstrated improvements (mean ± SE) of –2.7 ± 0.1 vs –2.5 ± 0.1 at 6 months and –2.9 ± 0.1 vs –2.7 ± 0.1 at 1 year.

Conclusions: In this first head-to-head comparison, subcutaneous abatacept demonstrated significant improvements with similar kinetics of response in PROs and HRQoL measures over 1 year, which were comparable to ADA.


86. IMPACT OF A MULTI-BIOMARKER DISEASE ACTIVITY TEST ON RHEUMATOID ARTHRITIS DECISION AND THERAPY USE

Wan Ying Li1, Eric H. Sasso1, Daniel E. Bemeling2, Guy Cavet2 and Keri Ford1

1Medical, Crescendo Bioscience Inc, South San Francisco, CA, and 2Research, Biosimply, El Cerrito, CA, USA

Background: This study assessed how use of an objective multi-biomarker disease activity (MBDA) test 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 and their HCPs’ perceived value of MBDA test result. The main outcome measure was the percentage of cases in which the HCP changed the planned treatment after 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 19% and other immunomodulatory agent 19%. After HCP 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
dosage, frequency or route of administration. The total frequency of use of the major classes of drug therapy changed by <5%. Treatment plans changed 63% of the time when the MBDA test result was perceived as being not consistent or somewhat consistent with the HCP assessment of disease activity. Study limitations include sample size and a lack of control group or longitudinal follow-up. Conclusions: The addition 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.

Disclosures: C.R., Crescendo Bioscience, Inc.—Employee, D.E., Crescendo Bioscience, Inc.—Consultant, K.F., Crescendo Bioscience, Inc.—Former Employee, W.L., Crescendo Bioscience, Inc.—Employee, E.S., Crescendo Bioscience, Inc.—Employee.

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 or remission. Patients whose scores fall between 3.2 and 5.1 have no access to biologic therapy despite inappropriately 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<2.9, Group 2 DAS 2.9-3.09; Group 3 DAS 3.1-4.19, Group 4 DAS 4.2-5.09; Group 5 DAS >5.1. Patients in group 4 and 5 had their DAS scores reassessed at up to 6 months.

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

Groups 1 and 2 (good control); 166 patients (53.2%) of whom (4.2%) had their DMARD therapy increased and 2 (2.8%) decreased.

Group 4: 39 patients (12.5%) of whom 19 (48.7%) had DMARD therapy increased and none decreased.

Group 5: 37 patients (11.9%) of whom 32 (86.4%) had DMARD therapy increased or were started on a biologic agent and none decreased.

Follow up data were available in 20 group 4 patients and 21 group 5 patients mean follow up of 14.7 days. In group 4 the mean change of DAS was −0.16 (range +1.42 to −2.90), (ns). In group 5 the mean change in DAS was −1.17 (range +0.94 to −4.18), (P = 0.05).

7 patients in group 5 had moved onto biologic therapy between assessments and none of the group 4 patients had.

Using the EULAR DAS response criteria in group 4, 3 patients had a good response, 4 moderate response and 13 no response. Of these 6 had deteriorated as judged by an increase in DAS of >0.6. In group 5; 3 had a good response, 9 a moderate response and 9 no response with 3 deteriorating. The 6 best responses were seen in patients who had initiated biologic therapy.

Conclusions: This small real life study showed that 53% of our patients sampled have reasonable disease control and that treatment escalation decisions correlate well with disease activity. Paradoxically however, patients in group 4 with moderately active disease who (in the UK) are not biologic eligible, are clearly disadvantaged with less change in DAS on follow up and greater numbers showing a deterioration compared with the more severe group. Further follow up is required, it is worrying that despite the drive for earlier aggressive treatment, this group with be lost in the therapeutic pathway and in the fullness of time will have worse a outcome than those with a more severe disease.

Disclosures: The authors have declared no conflicts of interest.

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

Eilane Morrison1, Ann Tierney2, Hilary Wilson2 and John Hunter3
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 (BSR) 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,

Disclosures: The authors have declared no conflicts of interest.

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

Bronwen Mackenzie-Green1, David Collins1, Elizabeth Price1 and Lyn Williamson1
1Rheumatology, Great Western Hospital, Swindon, UK

Background: Those with a more severe disease benefit from aggressive treatment, this group with be lost in the therapeutic landscape. In the UK) are not biologic eligible, are clearly disadvantaged with less change in DAS on follow up and greater numbers showing a deterioration compared with the more severe group. Further follow up is required, it is worrying that despite the drive for earlier aggressive treatment, this group with be lost in the therapeutic pathway and in the fullness of time will have worse a outcome than those with a more severe disease.

Conclusions: This small real life study showed that 53% of our patients sampled have reasonable disease control and that treatment escalation decisions correlate well with disease activity. Paradoxically however, patients in group 4 with moderately active disease who (in the UK) are not biologic eligible, are clearly disadvantaged with less change in DAS on follow up and greater numbers showing a deterioration compared with the more severe group. Further follow up is required, it is worrying that despite the drive for earlier aggressive treatment, this group with be lost in the therapeutic pathway and in the fullness of time will have worse a outcome than those with a more severe disease.

Disclosures: The authors have declared no conflicts of interest.
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, F = 563, M = 138) have RA. RA patients with RA, the median age (n = 701) is 57 years (range = 19–86 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 biologics 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 the SRG 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

Margaret H. Ma1 and David L. Scott1
1Academic Department of Rheumatology, King’s College London, London, UK

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 therapy was not assessed. High 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 efficacy 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). The authors have declared no conflicts of interest.

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

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<td>ACR20</td>
<td>Combo DMARDs 6 2.75 (1.79, 4.22) 9 5.14 (4.12, 8.348)</td>
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<td>anti-TNF/MTX 9 8.02 (4.47, 14.38)</td>
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<tr>
<td>ACR50</td>
<td>Combo DMARDs 6 5.07 (3.01, 8.29) 9 8.02 (4.47, 14.38)</td>
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<td>anti-TNF/MTX 9 8.02 (4.47, 14.38)</td>
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<tr>
<td>ACR70</td>
<td>Combo DMARDs 5 4.85 (2.34, 10.05) 9 5.58 (0.98, 10.09)</td>
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<td>anti-TNF/MTX 9 5.58 (0.98, 10.09)</td>
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<tr>
<td>Withdrawal due to inefficacy</td>
<td>Combo DMARDs 9 1.51 (1.02, 2.25) 7 0.13 (0.15, 0.17)</td>
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<tr>
<td></td>
<td>anti-TNF/MTX 7 0.13 (0.15, 0.17)</td>
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<tr>
<td>Withdrawal due to toxicity</td>
<td>Combo DMARDs 9 1.59 (1.08, 2.36) 7 0.94 (0.62, 1.41)</td>
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<tr>
<td></td>
<td>anti-TNF/MTX 7 0.94 (0.62, 1.41)</td>
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<tr>
<td>HAQ</td>
<td>Combo DMARDs 3 –0.19 (-0.27, -0.10) 1 –0.35 (-0.56, -0.14)</td>
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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 (82%) 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 DMARDs. Two patients had discontinuation of treatment due to adverse events (recurrent mouth ulcers and diverticulitis). 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 = 0.011) 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 was observed as -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-2 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 ± 3 (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 anti-TNF with MTX is the preferable treatment regime in patients who have failed 1 DMARD. A direct head-to-head study is required to confirm these findings.

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-TNF agents. The remaining 40 patients had received an average of 1.9 previous anti-TNF agents. 3 of these patients had also received anakinra.

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 primary 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 a loss of heart failure (n = 1) and at patient’s request (n = 1). Of the 13.4% of patients who were sera-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 persistent 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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8Clinical 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 pt 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 pt experience. Patient experience is not 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 option 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 care pathway for a long term condition.

Disclosures: M.B., UCB Celltech, Merck—Honoraria, Conference Attendance, Roche, Pfizer—Honoraria, Conference Attendance, Monies for Computer Software, Menarini, Proctor and Gamble—Conference Attendance, Eli-Lilly—Conference Attendance, Servier—Meeting Attendance, I.S., Roche—Freelance Medical Writing. All other authors have declared no conflicts of interest.

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

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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 that respond to other biologics (10) and adalimumab or etanercept 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. 1000 (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 were sepsis and 9 due to malignancy. 4 patients were switched from ABA to biologics (4 months after last ABA infusion; pt was receiving tocilizumab): Pneumocystis jirovecii (4 months after last ABA infusion, pt had deep vein thrombosis); and urosepsis. 23 patients experienced serious infections; 9 malignancies; 5 serious cardiac disorders; and 3 serious vascular disorders. No TB occurred, 2 opportunistic infections were reported (cytomegalovirus and P. jiroveci). We will present full results of these pilot studies and the final PREMs questionnaire.

Conclusions: 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 care pathway for a long term condition.

Disclosures: M.B., UCB Celltech, Merck—Honoraria, Conference Attendance, Roche, Pfizer—Honoraria, Conference Attendance, Monies for Computer Software, Menarini, Proctor and Gamble—Conference Attendance, Eli-Lilly—Conference Attendance, Servier—Meeting Attendance, I.S., Roche—Freelance Medical Writing. All other authors have declared no conflicts of interest.

95. EXPECTATIONS OF NEW TREATMENT IN RHEUMATOID ARTHRITIS: THE DEVELOPMENT OF A PATIENT-GENERATED SCALE
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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 following personal characteristics: mean age 58 years (S.D.: 13.71), age range 25-96 years, 73% female, 74% Caucasian and 43% reported disabled. Table 1 shows mean of scores of the 3 identified domains at each time point. There were no mean difference in the physical domain over 1 week and Stage3: psychometric testing with 140 patients over 6 months.

Table 1. Mean scores of the three domains at each time point and kappa statistics

<table>
<thead>
<tr>
<th>Items</th>
<th>Time 1 (Mean (S.D.))</th>
<th>Time 2 (Mean (S.D.))</th>
<th>Percentage observed agreement</th>
<th>Percentage expected agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical domain</td>
<td>24.09 (8.21)</td>
<td>22.41 (11.73)</td>
<td>76</td>
<td>66</td>
</tr>
<tr>
<td>Psycho-social domain</td>
<td>18.09 (6.73)</td>
<td>15.41 (9.59)</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>Impact of new treatment domain</td>
<td>29.83 (6.97)</td>
<td>26.07 (13.81)</td>
<td>78</td>
<td>66</td>
</tr>
</tbody>
</table>

*aWeighted kappa, all six scales were included.

Disclosures: The authors have declared no conflicts of interest.

96. WEEKLY SUBCUTANEOUS ABATACEPT CONFERS COMPARABLE ONSET OF TREATMENT RESPONSE AND MAGNITUDE OF EFFICACY IMPROVEMENT OVER 6 MONTHS WHEN ADMINISTERED WITH OR WITHOUT AN INTRAVENOUS ABATACEPT LOADING DOSE
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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 AMPLE 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 AMPLE. 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 AMPLE (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 1.60 in ACQUIRE and AMPLE, respectively. Efficacy was observed 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, 44.5, 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.

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 (±SD) changes from baseline to Day 169 in DAS28 were −2.57 (1.30) and −2.09 (1.58) in ACQUIRE and AMPLE, 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 equivalence of i.v. loading, target therapeutic concentrations 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.


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

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**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 disease activity for 16 weeks or 6 months, or on TCZ monotherapy. 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. Mean (±SD) proportion of patients continuing treatment in the AMBITION LTE. During the LTE, MTX/other DMARDs could be added in patients not achieving a 50% reduction in disease activity for 16 weeks or 6 months, or on TCZ monotherapy.

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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 prescribable 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 cinematic 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 test conditions (P = 0.633) with mean ± S.D. scores of 6.1 (2.0), 6.4 (2.3) and 7.0 (2.4) for SFO, FDM and SLS FOs respectively. Device fit scores were also equivalent (P = 0.633) 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 = 0.014, P = 0.009). No adverse reactions were reported.

Conclusions: PFOs designed to optimize foot function demonstrated better mechanical 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>Table 1. Selected mechanical function variables with differences</th>
</tr>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Peak rearfoot dorsiflexion</td>
</tr>
<tr>
<td>Mean rearfoot inversion</td>
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</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 Buckle1, Axel Finckh², Tom W. Huizinga³, J. Scali4, Rieke Alten5, Joel M. Kremer6, Laura Pitts7, Emma Vernon8 and Ronald F. van Vollenhoven9
1Rheumatology, Leiden University Medical Centre, Leiden, Netherlands and 2Medical, 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 produce 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. Given 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 monotherapies, 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 [Crl]: 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, 1.64]) and [RR = 0.52 (95% CrI: 0.3, 0.82)], 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 aTNF. 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 an aTNF + MTX.


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

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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% CrI 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 of aTNF (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...
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>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>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>Stroke 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>Hepatic SAEs</td>
<td>0</td>
<td>0.10 (0.02, 0.29)</td>
<td>0.04 (0.02, 0.20)</td>
<td>0.03 (0.01, 0.13)</td>
</tr>
<tr>
<td>Gl perforations</td>
<td>0.20 (0.06, 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>

[95% CI 4.1, 4.8]); the most common serious infection was pneumonia (0.95/100 PY; 95% CI 0.80, 1.12). Overall rates/100PY (95% CI) of MI SAEs and stroke SAEs were 0.25 (0.18, 0.35), 0.31 (0.23, 0.42), and 0.04 (0.01, 0.09) respectively. The GI perforation rate was 0.20/100PY (95% CI 0.13, 0.29). There were 194 confirmed malignancies, including 65 non-melanoma skin cancer (NMSC) cases (overall rate/100PY (95% CI) of 1.29 (1.12, 1.49); excluding NMSC: 0.86 (0.72, 1.02). Standardized incidence ratio for malignancies (all sites) was 1.19 (0.99, 1.42).

Conclusions: The safety profile of TCZ remained stable over a mean treatment duration of 3.7 years and no new safety signals emerged. AE rates described are consistent with those reported in the RA population and the overall rate of malignancies does not exceed reported background rates.

We used a strategy of fixed 6-monthly retreatment at half-dose following an initial full dose cycle in responders and non-responders, and looked for changes in clinical response.

Methods: Patients received 2 x 1000 mg rituximab at month 0 (C1), 2 x 500 mg rituximab at month 6 (C2) and 2 x 500 mg at month 12 (C3) regardless of C1 response. All patients were positive for RF and/or anti-CCP. 17/41 were taking concomitant MTX and 9/41 other DMARDs. All rituximab cycles were given with 2 x 100 mg methylprednisolone. Two patients were taking concomitant oral prednisolone. DAS28 was measured at baseline and at 3–6 months after each cycle and compared with baseline of the first cycle.

Results: To date, 41 patients received C1, 34 C2, 17 C3 and 14 C4 with outcome data. For all patients, mean (s.d.) DAS28 at baseline and 3–6 months after each cycle is shown in Figure 1. There was no significant difference between C1 and C2 and a trend to reduction in DAS28 after C2–C3; and 1, 3 and 10/14 patients in C4 (7/21/71%). 3/5 patients with Non response in C1 responded to C2.

Disclosures: The authors have declared no conflicts of interest.

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

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Background: The best long-term treatment strategy for rituximab has not been established. Retreatment at a fixed interval of 6 months maintains stable disease activity1 and half-dose is equally effective in first-cycle responders1. In first-cycle non- or moderate responders, responses may improve further after a second cycle at full dose2,3.

Conclusions: Some C1 non-responders responded to retreatment with half-dose at 6 months, but response rate across all patients was similar. Incremental improvements in C1 non- or moderate responders were seen more frequently after a second half-dose retreatment. This suggests that dose reduction may delay achievement of optimal responses in C1 non- or moderate responders, and these patients should have two full-dose cycles before reducing doses. Future work will analyse B-cell depletion in this cohort.

Disclosures: The authors have declared no conflicts of interest.