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Presidents

Martin Rudwaleit
Dept. of Internal Medicine and Rheumatology
Klinikum Bielefeld
Bielefeld, Germany

John D. Reveille
Division of Rheumatology
The University of Texas Health Science Center at Houston
Houston, USA

Local Organisers

Herman Mielants
Dirk Elewaut
Filip Van den Bosch
Dept. of Rheumatology, University of Gent
Gent, Belgium

Abstracts

Invited Lectures

INV1

THE INTESTINAL MICROBIOME AND THE IMMUNE SYSTEM

Eberl G.
Lymphoid Tissue Development Unit, Institut Pasteur, Paris, France

RORγt⁺ T cells and RORγt⁺ innate lymphoid cells (ILCs) play central roles in the development of the immune system, in homeostasis of the host with its symbiotic microbiota, in defence against invasive microbes and in inflammatory pathology. The cytokines produced by RORγt⁺ cells, including the lymphotoxins $LT\alpha_1\beta_2$ and $LT\alpha_3$, GM-CSF, IL-17 and IL-22, elicit innate defence mechanisms in mucosal tissues, activate and regulate lymphocytes and antigen presenting cells, and recruit myeloid cells. We have shown that RORγt⁺ ILCs, or ILC3s, are programmed to express high levels of IL-22, and that microbiota regulate this activity during homeostasis. In contrast, the activity of RORγt⁺ T cells is induced by microbiota. RORγt⁺ T cells not only include pro-inflammatory Th17 cells expressing IL-17, but also FoxP3⁺ regulatory T cells (Tregs). We find that FoxP3⁺ RORγt⁺ Tregs express high levels of IL-10, but not IL-17, and are induced by the symbiotic microbiota through pro-inflammatory pathways that normally induce Th17 cells. However, in the colon, these pathways lead to the preferential induction of Tregs in a vitamin A-dependent pathway, and play an important role in the microbiota-controlled development of a balanced immune system.

INV3

CV RISK AND OTHER RISK FACTORS: A VIEW OF AXIAL SPA, RA, AND SLE

Nurmohamed M.T.
Dept. of Rheumatology, VU University Medical Centre, Amsterdam, The Netherlands

There is accumulating evidence that patients with inflammatory joint diseases (IJD) such as axial SpA (particularly ankylosing spondylitis (AS)) and RA suffer from an increased cardiovascular (CV) risk in comparison to the general population. The magnitude is approximately doubled in IJD whereas in SLE the risk appears to be increased at least four-fold in comparison the general population. There are several potential explanations for the higher CV risk in these patients categories but inflammation itself appears to play a pivotal role (1). Inflammation accelerates atherosclerosis directly, but also mediates CV risk factors, such as lipid profile, blood pressure, and insulin resistance.

The increased CV-risk in AS is not only due to atherosclerotic disease, but also due to the "AS-specific" cardiac manifestations. Well-known lesions are conduction defects and aortic insufficiency. Less common CV-diseases include pericarditis, cardiomyopathy, mitral valve disease and ventricular dysfunction (2). Conduction disturbances are due to inflammation-induced fibrosis of the interventricular septum, thereby affecting the atrioventricular node and prevalences are reported up to 35%, and there might be an relationship with the HLA-B27 antigen. However, these data are based on studies conducted several decades ago, hence there is a clear need for contemporary studies assessing the current contribution of AS-related cardiac manifestations towards the increased CV-risk in AS. Hypertension occurs between 50 – 100% more frequent than in the general population (3, 4). Dyslipidemia is related to disease activity and patients with active disease have decreased HDL-cholesterol and total cholesterol levels (5, 6). Furthermore, there is some evidence that patients with AS smoke twice as much in comparison to the general population.

An inverse relationship between lipid levels and disease activity, *i.e.* a higher disease activity is related with a lower TC but even more depressed HDL-cholesterol, resulting in a higher (unfavorable) atherogenic index (TC/HDL-C ratio) is also observed in RA (7). Smoking and insulin resistance are more frequent in RA in comparison to the general population, data about hypertension are contradictory whereas no conclusions can be drawn with respect to the contribution of "body mass" index and physical fitness towards the increased CV risk in RA.

It is important to realize that in an inflammatory situation the normally anti-inflammatory and ant-atherogenic HDL-cholesterol becomes pro-inflammatory and pro-atherogenic. For instance, these dysfunctional HDL particles were observed in approximately 50% of SLE patients, compared with 5–7% in healthy controls and are associated with a more than 15-fold increased risk of carotid plaque in SLE (8).

Nowadays, there is no doubt that CV risk management is necessary for patients with IJD as well as SLE. This is generally done on the basis of the 10 years absolute risk for a (fatal) CV-event, which is calculated from a CV-risk formula, such as the Framingham risk calculator and the Systematic Coronary Risk Evaluation (SCORE), which are based on CV risk factors. Statin and/or antihypertensive treatment is then only initiated above a certain threshold, *e.g.* a 10-year CV mortality risk of 10% or more or a 10 year CV morbidity of 20% or more.

EULAR recommendations for CV-RM in patients with IJD advised yearly CV risk screening For RA it is recommended to adapt existing risk functions, such as SCORE, by a multiplier of 1.5 to achieve a more appropriate estimation of the 10 years CV risk (9). Obviously, effective suppression on the inflammatory process is necessary to further decrease the CV-risk. For SLE it is recommended the LDL-cholesterol levels should below 2.6 mmol/L and blood pressure levels be lower than 130/80 mmHg. When there are no contraindications, aspirin should be given to patients with a history of CV events (including myocardial infarction, angina or stroke), the presence of antiphospholipid antibodies, hypertension, diabetes, hypercholesterolemia, or smoking (10). Also for SLE the EULAR recommends yearly CV-risk screening (11).

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INV5

MAPPING THE IL-23/IL-17 AXIS

Elewaut D.
Dept. of Rheumatology, University Hospital Ghent, Ghent, Belgium

Inflammatory responses in rheumatic diseases are steered by hierarchical cytokine cascades. In spite of the marked therapeutic success of TNF blockade in SpA and PsA, there is a particular need for new mode of action drugs. Evidence has emerged that in SpA and PsA, IL-17 and IL-17 steering responses may represent another dominating cytokine cascade. In the skin, IL-17 blockade in psoriasis has marked efficacy and in PsA significant impact on arthritic disease. Also in axial disease, blocking IL-17 driven responses induces therapeutic responses. By contrast, in inflammatory bowel disease, lack of benefit was observed. These observations highlight that IL-17 driven responses appear to be distinctly fine tuned in different organs.

INV7

THERAPIES FOR NON-RADIOGRAPHIC AXIAL SPA – FROM CLINICAL TRIALS TO CLINICAL PRACTICE

Dougados M.
Rhumatologie B, Hôpital Cochin, Paris, France

Background. The diagnosis of axial spondyloarthritis is based on the combination of axial symptoms (*e.g.* inflammatory back pain of at least 3 months duration starting before the age of 45 years), extra-spinal signs/symptoms (*e.g.* enthesitis) and laboratory (CRP) and imaging (Pelvic X-Rays and MRI) investigations. Until the use of anti-TNFs in this area, the clinicians were not considering the presence of structural damage at the sacroiliac joints level to initiate any therapy. Because the clinical trials evaluating anti-TNF in axial SpA have been focused on the sub-group with such structural damage (*e.g.* so-called ankylosing spondylitis), some national health care systems are making mandatory the presence of such structural damage to permit a patient to have access to such therapies. Because of this situation, TNF blockers in patients without such structural damage (*e.g.* non-radiographic) have been recently evaluated.
Data Available. Two kinds of information are currently available. The first ones issued from randomized perspective placebo controlled (1, 2, 3) trials sponsored by pharma companies and the second ones issued from longitudinal observations of patients suffering from recent onset spondyloarthritis (4). All these studies conclude at a clinically relevant effect of TNF blockers especially in the subgroup of patients with objective signs of inflammation at baseline (*e.g.* abnormal CRP or presence of subchondral bone edema at MRI of the sacroiliac joints).
Conclusion. The data currently available support the use of TNF blockers in patients suffering from active, NSAID refractory axial SpA even in the absence of structural damage.

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INV8

INTERPRETATION OF MR IMAGING IN AXIAL SPA: BRIDGING SCIENTIFIC STUDIES AND CLINICAL PRACTICE

Lambert R.G.W.
Dept. of Radiology & Diagnostic Imaging, University of Alberta, Edmonton, Canada

Whether research is prospective or retrospective, a study population is defined with appropriate inclusion and exclusion criteria and a sufficient number of subjects recruited to allow statistical analysis of the groups. Clinical practice starts from the opposite end of the clinical scale. A single patient presents because of a health problem and there are no exclusion criteria. At the time of referral, the patient's diagnosis or problem has often not yet been established and so a unique patient-clinician interaction develops which is rarely as neat and tidy as a clinical trial. Which diagnostic test is performed first often depends as much on availability, cost, convenience and administrative issues as it does on any practice guideline and international variation is considerable.
Sacroiliac Joint. Imaging of the sacroiliac (SI) joints has been a critical part of the diagnosis of spondyloarthritis (SpA) for many years and radiography is still in daily use for detection of the structural changes associated with inflammatory sacroiliitis which is an essential component of most diagnostic criteria for SpA. For over 20 years now, magnetic resonance imaging (MRI) has been increasingly used to visualize inflammation in the axial skeleton and the inflammatory lesions are often visible on MRI long before structural changes are detected on radiography.
The MRI manifestations of spondyloarthritis in the SI joint have been well described in many manuscripts and textbooks. A wide range of both inflammatory and structural damage changes may occur and the MRI findings in the later stages of disease are now well understood and are consistently detected on MRI by trained observers. The changes of active sacroiliitis include bone marrow oedema (BMO/BME) and bone marrow contrast enhancement (osteitis) in subchondral and periarticular bone; synovitis and capsulitis of the SI joints; and enthesitis at the attachment of ligaments and tendons. The structural damage lesions of the SI joints are most often observed as subchondral erosion and sclerosis; subchondral or periarticular fat infiltration; and bony bridging or ankylosis.
The most challenging aspect of MRI of the SI joint is the gap between the science and clinical practice for the diagnosis of early disease and in particular, the diagnosis of "non-radiographic axial Spondyloarthritis" (nr-axSpA). Inflammation of the sacroiliac joints is required for the fulfillment of the imaging criterion "active sacroiliitis on MRI" as applied in the ASAS classification criteria for axial SpA. The ASAS classification is a practical and widely used definition that has been very important in helping to advance research and therapy in early disease but in subtle or challenging cases, the definition remains controversial. How much BMO is required to be "highly suggestive"? How many lesions are required or what size do they need to be? What is the role of the structural damage lesions in the diagnosis? Fat infiltration appears to add useful contextual information enhancing reader confidence but is too non-specific to be used on its own. In one analysis, BMO and erosion were observed with similar reliability and with equal frequency in nr-axSpA but the concomitant presence of both (50.6%) was the most common observation in the SI joints. Erosion was observed less frequently in control subjects than BMO, and so MRI evidence of erosion would appear to have higher specificity for the diagnosis of SpA. However the incremental value of adding erosion to the definition remains unclear as the analysis did not take into consideration whether these subjects had or had not already met the definition by the clinical arm. Yet erosion plays a key part in the evaluation of inflammatory sacroiliitis for daily diagnosis of SpA helping to distinguish it from a variety of other conditions.
The majority of other diagnoses can usually be distinguished from SpA on the basis of clinical grounds & radiography, such as septic arthritis, stress fractures, and osteitis condensans ilii. However, their imaging manifestations can appear similar to SpA. Mild or moderate osteoarthritis (OA) of the SI joints is very commonly seen on imaging and should not be mistaken for SpA. Subchondral cysts and intra-articular gas are common in OA and the articular surfaces are relatively smooth. Bone marrow inflammation as evidenced by either BMO or fat infiltration is usually mild or absent. Anatomical variation may also cause SI joint pain and posterior accessory facets of the SI joints are quite often associated with OA in the accessory joint.
Spine. In most cases, MRI of the spine is not required to confirm the diagnosis of axial SpA or nr-axSpA. The SI joints are nearly always affected first or at the same time and only rarely is the spine involved without SI joint disease. The range of MRI findings in the spine is similar to the SI joint and again have been well documented. However one big difference is in the visualization of bone formation. In the spine, syndesmophyte formation occurs within the annulus fibrosus or longitudinal ligament and these small mineralized outgrowths of bone are not visible on MRI as they appear dark within the dark background of the fibrous structures. Bone growth or ankylosis does not become visible until the bone formation is coarse enough to contain marrow fat signal. Spine MRI shows the marrow inflammation well and it occurs in typical locations and often with a typical configuration. The most common inflammatory lesion is a focus of BMO in the anterior or posterior corner of the vertebral body adjacent to the endplate and the anterior/posterior cortex – often referred to as a corner inflammatory lesion (CIL). However CILs also occur in degenerative disc disease and it is often not possible to determine the cause of an individual CIL. Still, the size, number and distribution of CILs may render a diagnosis of SpA possible on the basis of a spine MRI alone. Some spinal lesions are less common but are highly specific for SpA such as inflammation of the costovertebral and costotransverse joints.
MRI is extremely useful as a problem solving tool in the spine being able to distinguish a variety of other causes of back pain from SpA such insufficiency fractures, infectious discitis, and degenerative conditions. It may also show characteristic findings in other locations such as inflammatory lesions of the chest wall and when performing whole body MRI, enthesopathy is often seen in the shoulder and pelvic girdles.

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INV9

GENETICS AND THE AETIOPATHOGENESIS OF ANKYLOSING SPONDYLITIS

Brown M.A.
University of Queensland Diamantina Institute, Princess Alexandra Hospital, Brisbane, Australia

Substantial progress has been made in mapping the genetic susceptibility factors involved in >90% of the risk of developing AS in subjects of white European descent. This has thrown new light on the mechanisms by which histocompatibility antigens are involved in the disease, as well as highlighting novel cytokine, antigen processing and cell types likely involved in the disease.
Studies of MHC associations of AS using imputation from large SNP-genotyped case-control cohorts have demonstrated that the HLA-associations of AS are much more complex than originally thought, with association both at *HLA-A* and *HLA-DP*, as well as at other *HLA-B* alleles other than *HLA-B27*. At *HLA-B*, risk associations achieving genomewide significance have been demonstrated with *HLA-B*40, B*51* and *B*57*, whereas a protective effect was seen at HLA-B*7. Testing for association with amino-acids encoded by HLA-genes, conditional analyses indicate that amino-acid 97 is the key determinant of the HLA-B association with AS, rather than Cys67, critical to homodimers formation.
Genetic interaction between *HLA-B27* and *ERAP1* has been identified, indicating that the two must have close functional interaction. Similar interaction has also been demonstrated with *HLA-Cw6* and *ERAP1* in psoriasis, and *HLA-B51* and *ERAP1* in Behcet's disease. Recently we have demonstrated that *HLA-B40* also interacts with *ERAP1*, with *ERAP1* variants being associated with AS in B27-negative, *B40*-positive cases, but not in *B40*-negative cases. This suggests that these HLA-alleles probably operate in a similar manner, all involving close interaction with ERAP1, to cause disease.
42 non-MHC loci have been shown to be definitely associated with AS, confirming the polygenic nature of the condition. Using data from the IGAS Immunochip study (IGAS, Nature Genetics, 2013), analysed with a larger healthy control set and in combination with genotype data from studies of psoriasis, IBD and primary sclerosing cholangitis, we have discovered a further 19 genomewide significant loci, bringing the total number of genomewide significant loci to over 60. These findings and the light they shed on the pathogenic process involved in AS will be discussed.

INV10

REVISITING MHC AND NON-MHC GENES IN SPONDYLOARTHRITIS

Breban M.
Faculty of Health Sciences Simone Veil, Inserm U 987, University of Versailles Saint-Quentin and Ambroise Paré Hospital, Boulogne-Billancourt, France

Spondyloarthritis (SpA) represent a spectrum of inflammatory osteo-articular disorders affecting both axial and peripheral joints/entheses and also frequently associated with characteristic extra-articular features, such as psoriasis, uveitis or inflammatory bowel disease. The role of genetic background is high in determining disease predisposition, as shown by a sibling recurrence risk of 40 to 80, depending on the studied phenotype. The HLA region contains the major genetic factor, *i.e.* HLA-B27.
Among different subtypes of this allele that exist over the world, a majority of those that are sufficiently frequent to be studied are being associated with SpA. Interestingly HLA-B*2706 that is not associated differ from the associated B*2704 by only one substitution in the peptide-binding groove. This non-associated alleles displays biochemical differences with associated alleles that may help to decipher the pathogenic role of this molecule. On the other hand, albeit is has been difficult to study, due to the overwhelming weight of HLA-B27 itself, it appears that other genes situated in the HLA region may confer additional risk for SpA. Besides, the MHC region, segregation analyses indicate that other loci situated outside the MHC region account for roughly half of the genetic load. Several strategies may allow to identify such other genetic factors, including case-control genome-wide association studies and family-based approaches. We have conducted a large family-based study on >200 multiplex families (each containing from 2 to 11 affected relatives), the results of which highlight several loci that appear to be linked to SpA, with substantial heterogeneity between families.

INV11

HLA-B27, ANTIGEN PRESENTATION AND ERAP1

Bowness P.
Nuffield Dept. of Orthopaedics Rheumatology and Musculoskeletal Science, Oxford, UK

We do not know why B27 causes AS, but genetic and functional studies have place antigen presentation by HLA-B27 at the heart of AS pathogenesis. After HLA-B27, the second strongest genetic association is with the ERAP1 (contributing approximately 15% of the population attributable risk). This association is only found in B27-positive AS patients (an example of eptistasis). HLA-B27 is known to bind antigenic peptides within the endoplasmic reticulum for subsequent cell surface presentation to Cytotoxic T lymphocytes (CTL). ERAP1 plays a non-redundant role in trimming these peptides, acting as a "molecular ruler" to trim off N-terminal residues. HLA-B27 may cause AS by presenting "arthritogenic" peptides to pathogenic T cells. HLA-B27 may alternatively cause AS because of its abnormal cell biology. Thus B27 can form homodimers ($B27_2$) both intracellularly and on the cell surface. The former can trigger an ER stress response -which can in turn lead to cytokine release. Cell surface $B27_2$ may have a pro-inflammatory effect in AS by interacting with Natural Killer family receptors expressed on T cells and Natural Killer Cells.
The effects of ERAP1 and of its allelic variants on peptide supply to and presentation by B27 will be discussed. The effects of ERAP1 on B27 misfolding and on B27 expression at the cell surface of free heavy chain forms will also be presented.

INV14

JUVENILE SPONDYLOARTHRITIS: CLINICAL EPIDEMIOLOGY UPDATE

Weiss P.
Children's Hospital of Philadelphia, USA

Juvenile spondyloarthritis (SpA) accounts for up to 20% of pediatric inflammatory arthritis. In addition, 10-20% of adults with ankylosing spondylitis have symptom onset in childhood. Treatment for children with juvenile SpA is suboptimal as only 15-40% are in remission, joint damage is common, on-going enthesitis is problematic, and outcomes are poorer in comparison to other categories of juvenile arthritis. In this presentation I will provide an update on the clinical epidemiology of juvenile SpA including recent work focused on enthesitis, disease activity measures, and sacroiliitis in juvenile SpA.
The classification of juvenile SpA, including the International League of Associations for Rheumatology juvenile arthritis classification criteria, and the major differences between adult and juvenile SpA will also be reviewed.
Enthesitis is a distinct feature of juvenile SpA that is not present in other forms of juvenile arthritis and is independently associated with increased pain, decreased function, and poorer quality of life in these children. I will review recent data regarding the distribution of enthesitis in children, altered pain perceptions at the entheses and the role of imaging versus standardized physical examination for the detection of enthesitis.
Children with JSpA spend a majority of time with continuous disease activity and a minority achieves remission within 5 years of diagnosis. Despite increased recognition of poorer outcomes in juvenile SpA versus other juvenile arthritis categories, there are few validated instruments to assess disease activity in these children. Progress in finding effective therapies for juvenile SpA cannot be made without highly responsive instruments to assess disease activity. I will review both the Juvenile Disease Activity Score (JADAS) which is a validated composite pediatric disease activity score for all categories of juvenile arthritis and the juvenile SpA Disease Activity (JSpADA) index which is the first validated JSpA disease activity score.
Axial symptoms are less common in juvenile SpA than adult disease. Studies in recent years have reported the prevalence of sacroiliitis in children with SpA to range from 10-40%. Predictors of sacroiliitis in these studies include hip arthritis, elevated C-reactive protein, HLA-B27 positivity, higher active joint count at diagnosis, and higher tender entheses count at diagnosis. Prior studies demonstrate that sacroiliitis in children may be sub-clinical, suggesting that imaging may play an important role in detection of axial disease. In adults sacroiliac synovitis rarely occurs in the absence of bone marrow edema on magnetic resonance imaging. Therefore, dedicated pelvic imaging using fluid sensitive sequences, including Short T1 Inversion Recovery (STIR), and without the use of contrast is considered sufficient for the detection of early sacroiliitis. I will review data examining whether fluid sensitive sequences are also sufficient for the detection of early sacroiliitis in children. Lastly, I will review data regarding the prevalence of sacroiliitis at the time of juvenile SpA diagnosis and the association of clinical features (demographics, patient-reported symptoms, laboratory values, and physical examination findings) with positive findings on MRI.

INV17

HLA-B27 MISFOLDING AND SPONDYLOARTHRITIS

Colbert R.A.
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA

HLA-B27 plays a key role in the pathogenesis of most forms of spondyloarthritis (SpA), particularly ankylosing spondylitis (AS) where it is nearly required for disease to develop. Understanding the contribution of this MHC class I allele may reveal novel approaches to ameliorating symptoms or even preventing disease. Aberrant features of HLA-B27 such as its tendency to misfold and dimerize have become the focus of considerable investigation, and have provided possible links to the IL-23/IL-17 axis, which is strongly implicated in genetic predisposition and may drive unique aspects of the SpA phenotype.
To better understand the implications of HLA-B27 misfolding we have used transgenic rats that express HLA-B27 and human β_2m (B27-Tg), which causes a gut microbe-dependent SpA-like inflammatory disease characterized by gastrointestinal inflammation, peripheral arthritis, and trabecular bone loss. Disease is specific for HLA-B27 as rats expressing comparable levels of HLA-B7 remain healthy. In addition to serving as a pro-inflammatory stimulus promoting IL-23 expression, HLA-B27 misfolding promotes TNF-α-induced osteoclast (OC) formation via overproduction of IL-1α. Preliminary results reveal that HLA-B27 expression also blocks inhibitory effects of TNF-α and IFN-γ on osteoblast function, an effect that could contribute to bone formation during TNF-mediated inflammation. Together, these data indicate that HLA-B27 misfolding may impact different cell types with relevance to the pathogenesis of SpA. In addition, HLA-B27 appears to alter the response of cells to TNF-α, a "downstream" effect that may contribute to both inflammation and bone homeostasis.
Since overexpression of HLA-B27 amplifies the consequences of misfolding, we have sought evidence for ER stress in peripheral blood mononuclear cells (PBMC) from SpA patients. Results show that cytokine stimulation leads to greater upregulation of certain unfolded protein response (UPR) target genes and activation of XBP1 splicing in PBMC from SpA patients compared to healthy controls. This response correlates with HLA-B gene upregulation, but is more pronounced when HLA-B27 is present. In $CD14^+$ monocytes isolated from PBMC we find evidence of ER stress developing over 48 hours in culture in HLA-B27-expressing patient cells without a need for IFN-γ and/or TNF-α stimulation. These data suggest that consequences of HLA-B27 misfolding can be found in patient-derived peripheral blood cells and support a role for HLA-B27 misfolding in SpA.
Genetic data suggest that in some patients with HLA-B27 and AS, ERAP1 variants are contributing to disease susceptibility. To determine how ERAP1 influences HLA-B27 we have taken several complementary approaches. First, we are assessing effects of ERAP1 knockdown (KD) on HLA-B27 expressed in U937 monocytic cells. Second, using a similar KD approach we are assessing how ERAP1 affects HLA-B27 expressed in rat cells. Third, using a genome editing we created a 29-nucleotide deletion in the first exon of the rat *ERAP1* gene that eliminates protein expression. KD of ERAP1 in U937 cells (65%) reveals greater accumulation of folded and unfolded HLA-B27 molecules as well as misfolded disulfide-linked HLA-B27 complexes. Interestingly, ERAP1 KD does not increase the accumulation of folded/unfolded HLA-B51 and HLA-B18, the other endogenous B alleles in U937 cells, indicating allele-specific effects. Similar effects of ERAP1 KD on HLA-B27 were seen in rat bone marrow-derived macrophages. Although preliminary, these results indicate that loss of ERAP1 function impacts HLA-B27 folding/misfolding, which may in turn affect the development of SpA. We are currently assessing how hemizygous/homozygous disruption of ERAP1 affects the development of disease in B27-Tg rats.

INV18

DISTINGUISHING NR-AXSPA AND AS BY IMAGING: HOW FEASIBLE AND HOW RELEVANT?

van der Heijde D.
Dept. of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Axial spondyloarthritis (axSpA) comprises both patients with radiographic SpA (radSpA, also known as AS) and nonradiographic SpA (nr-axSpA). According to the ASAS classification criteria, the only distinction between the two groups of patients is the presence of sacroiliitis on radiographs according to the modified New York criteria. Patients with nr-axSpA can have inflammation on MRI, but this is not mandatory. Comparing patients with AS and nr-axSpA reveals that there is a higher percentage of male patients and a higher level of CRP in the AS subgroup. However, other demographic data, such as the presence of SpA features including extra-articular features, are very similar across patients with axSpA irrespective of the presence of radiographic sacroiliitis. This is also the case for the level of signs and symptoms assessed by BASDAI, BASFI, and work impact.
As the only distinction is radiographic sacroiliitis, it is important to know how reliably this can be assessed. It is known for a long time that judging radiographs of the SI joints is highly variable. Moreover, training radiologists and rheumatologists in clinical practice, did not improve reliability. In the GESPIC cohort, >25% of patients had to be reclassified according to mNY criteria after a central read in comparison to a local read. In the DESIR cohort the agreement between local reading of SI joints by rheumatologists and radiologists of 25 centres across France with two central, trained readers was investigated. The overall agreement between the local and the central reading (final score obtained with third reader if necessary) was poor. However, this was similarly poor between the two central readers. This is confirming that training does not really improve the agreement between readers. But, the disagreement between the two central readers was balanced in two directions: as many patients were scored positive by one reader while negative by the other reader, as the other way round. This was different when comparing local with central reading. There was significant overreading by local rheumatologists/radiologists: >40% of the patients fulfilling the mNY criteria, did not meet the criteria according to the central readers. Only, 7.5% of the patients scored locally as not fulfilling the mNY criteria, fulfilled the criteria according to central read.
These data indicate that it is challenging to distinguish patients based on radiographic sacroiliitis. And as the clinical features are quite similar between the two groups, it is questionable if it necessary to make this distinction. However, reality is that the presence of radiographic sacroiliitis is still an important distinguishing factor in clinical practice, *e.g.* with respect to access of TNF-blocking drugs. In some countries, access is limited to patients with AS only. In other countries, patients with nr-axSpA can be treated, but only with additional mandatory objective signs of inflammation, a requirement which does not exist for patients with AS. Given the poor reliability of assessing reliability of radiographic sacroiliitis questions the validity of these diverging consequences.

INV19

ARE TNF-BLOCKERS TRUE DMARDS IN AS – HOW STRONG IS THE EVIDENCE?

Gensler L.S.
Spondylitis Clinic, University of California, San Francisco, CA, USA

The effects of Tumor Necrosis Factor (TNF) inhibitors on radiographic progression in Ankylosing Spondyitis (AS) have been debated over the last decade. Unlike rheumatoid arthritis and psoriatic arthritis, randomized controlled trials (RCTs) have not shown retardation of progression, using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Osteoproliferation strongly influences measured damage accumulation in AS, not erosive disease. Additionally progression in many patients does not occur or does not occur rapidly over the assessment period. A historic comparator control group was used against open label extension treated patients from the RCTs in several studies with similar radiographic progression in treated subjects. Most of these studies assessed effect at 2 years in patients with long-standing disease. This was potentially not be enough time to see the benefit and starting the TNF inhibitor in patients with longer duration of disease may have contributed to the lessened effect. In addition, since these studies were published, we have learned about confounders that need to be included in analyses as they too are associated with more progression, including baseline damage, inflammation and smoking. Are there other factors that have not been determined as important players in AS radiographic progression? MRI studies have helped to unravel the story – where does bone marrow

edema and fat metaplasia fit into the process of ankylosis and how do TNF inhibitors contribute to these changes? We recently attempted to readdress the question of TNF inhibitor effect on radiographic progression using a prospective cohort with longer duration between radiographs, in addition to addressing potential confounders. During this session, we will review the published literature and discuss other factors that should still be addressed in understanding the effects of TNF inhibitors on radiographic progression in AS.

INV20

INFLAMMATION AND OTHER FACTORS RELEVANT FOR RADIOGRAPHIC PROGRESSION IN AS

Landewé R.
Academic Medical Center, University of Maastricht & Atrium Medical Center Heerlen, The Netherlands

Radiographic progression in ankylosing spondylitis in essence implies the formation of new –and the growth of - existing syndesmophytes. Syndesmophytes reflect new bone formation rather than bone destruction (which is the hallmark of inflammatory diseases such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA)). Other classic radiographic features of AS include erosion (actually bone destruction), sclerosis and squaring, all occurring at the most prominent site of inflammation: the vertebral corner.
Despite these resemblances regarding the site of occurrence, it has been very difficult thus far to unequivocally link the occurrence of inflammation to the occurrence of bone formation (syndemophyte), which has challenged many to hypothesize that inflammation and radiographic progression in AS are uncoupled processes.
In the last few years, however, careful studies with sensitive methodology and analysis have been carried out that have shown that there is a definite link between inflammation and radiographic progression. Following the wake of these initial observations, other factors have now been identified that may influence this relationship further.
In this lecture the epidemiological evidence for a pathophysiological link between inflammation and new bone formation in AS will be presented, and the contribution of other factors to this relationship will be discussed.

INV21

THE MECHANISTIC POINT OF VIEW OF NEW BONE FORMATION IN AS

Lories R.
Laboratory of Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, KU Leuven, Belgium

The success of targeted therapies directed against tumor necrosis factor for patients with spondyloarthritis has shifted the focus of physicians and scientists towards the prevention of structural damage to the involved structures, in particular the sacroiliac joints and the spine, to avoid loss of function and disability. Structural damage to the skeleton as witnessed by radiography mainly consists of new bone formation potentially progressively leading to spine or joint ankylosis. This important long-term outcome parameter has been difficult to study, not alone because the time-window for change may be long but also because human tissues with direct translational relevance are rarely available.
Data from rodent models have identified growth factor signalling pathways as relevant targets. Both human and animal studies have tried to understand the link between inflammation and new bone formation. At the current moment, most evidence points towards a strong link between both, but with questions still lingering about the sequence of events, disease triggers and the interdependence of both features of disease. New discoveries such as a masterswitch T cell population that carries the IL-23 receptor and the analysis of auto-antibodies directed again noggin and sclerostin are contributing to innovative insights into the pathophysiology of disease. Long-term data with TNF inhibitors also suggest that some window of opportunity may exist to inhibit structural disease progression.
The development and increasingly general acceptance of the non-radiographic Axial SpA (AxSpA) group and its epidemiological characteristics suggests that AxSpA is not by definition a continuum. This provides support for earlier hypotheses that suggested that genetic as well as acquired/environmental factors may be distinct for their contributions to inflammation or structural damage. Such evidence also suggests that the identification of early patients who are at risk for structural damage becomes a further research priority. This observation also forces a critical evaluation of current concepts based on studies only including AS patients. By including AS patients only, there is a risk for selection-bias as the criteria applied require structural damage at the sacroiliac joints that can be visualized on conventional X-rays. This applies for instance to studies on radiographic progression and genetics. By only studying AS patients divided in groups, risk factors associated with ankylosis may be overlooked as the inclusion criteria would exclude AxSpA patients not likely to show radiographic signs of disease. In addition, remodelling in the sacroiliac joints as well as in the spine may affect progression of disease in other sites. This fits well with the view that biomechanical factors also play an important role in SpA pathogenesis. Part of the progression of ankylosis over time may therefore be a secondary phenomenon linked to initial damage.

INV23

HOW TO IDENTIFY NEW THERAPEUTIC TARGETS IN SPA?

Sieper J.
Charité, Berlin, Germany

Currently only NSAIDs and TNF-blockers have been shown to be effective in the treatment of axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS), conventional ‘disease modifying drugs (DMARD), which show a good treatment response in rheumatoid arthritis, are ineffective for axSpA. There are two major therapeutic aims in axSpA: (i) to suppress inflammation effectively and (ii) to prevent new bone formation. Several biologics targeting IL-6R, IL-1, or T cells (abatacept) did not show a response regarding signs and symptoms in therapeutic trials. Interesting new targets are IL-17 and IL-23, a blockade a which has been proven to be highly effective on psoriasis. Indeed, smaller trials in AS also indicate that these molecules are very promising new targets and the results of ongoing and/or future trials have here to be awaited for. Other potential targets are the JAK kinases (inhibited, for axample, by tofacitinib) or phosphodiestrase 4 (inhibited by apremilast) are currently tested also for the treatment of AS. Regarding inhibition of new bone formation, early and effective suppression of inflammation might be the most effective way to achieve this aim. No specific treatment is currently available to block new bone formation selectively, although several potential targets have been identified in animal models. Interestingly, NSAIDs seem to inhibit – in addition to their good anti-inflammatory effect – also new bone formation, probably through their effect on prostaglandin E2.
Only very few treatment trials are available for patients with predominant peripheral SpA, and it is currently not clear whether treatments tested for axial SpA have a similar efficacy (or inefficacy) in peripheral SpA. However, this seems to be the case for TNF-blockers.

INV24

NOVEL IMAGING MODALITIES IN SPA

Eshed I.
Dept. of Diagnostic Imaging, Sheba Medical Center, Tel Aviv University, Israel

The role of imaging in the diagnosis, management and follow-up of patients with spondyloarthritis (SpA) has become dramatically more important with the introduction of new therapies such as TNF alpha inhibitors. This is especially true with respect to the clinically difficult to evaluate axial manifestations of SpA.
With effective therapy now available, an early and accurate diagnosis is crucial resulting in an increasing clinical demand for reliable and accurate tests that can distinguish between patients that are most appropriate for biological therapy, and provide imaging insight on the immediate and long term clinical response.
The optimal imaging modality should facilitate early, sensitive and specific diagnosis, would ideally cover multiple disease target sites, would not involve ionizing radiation and of course is expected to be quick and relatively inexpensive.
MRI is currently considered the most sensitive and accurate diagnostic tool for the evaluation of early SpA by which the two main components of the disease; the active inflammatory, and the structural damage can be reliably assessed.
In the current presentation contemporary perspectives on whole body MRI imaging along with several novel imaging modalities for the diagnosis and follow-up of SpA will be discussed.

INV25

PERSONALIZED MEDICINE USING BIOMARKERS IN SPA – REALITY OR FICTION?

Maksymowych W.
University of Alberta, Edmonton, Canada

Axial Spondyloarthritis (axSpA) presents a major challenge in management because diagnosis at an early stage of disease is challenging, and neither disease activity nor prognosis can be readily assessed using currently available clinical and laboratory parameters. MRI reflects histopathological parameters of inflammation but is not readily available, especially for clinical monitoring over time. Consequently, there is a major unmet need for biomarkers that have diagnostic capacity, and can reflect disease activity and prognosis. Current methodologies validate biomarkers according to clinical parameters of disease activity such as the BASDAI, ASDAS, and CRP but these demonstrate only minimal to modest correlations with the current gold standard, MRI. No biomarker has yet been shown to be superior to the CRP in reflecting MRI parameters of disease activity. Future validation activities should aim at the assessment of changes in biomarkers in relation to changes in MRI parameters of inflammation at an early stage of disease before reparative changes are already evident on MRI as these may confound interpretation. Whole body MRI may be a more sensitive gold standard than conventional imaging of the axial spine. Several biomarkers have been proposed for prognostic utility based on associations with radiographic changes though most studies have been cross-sectional and/or analyzed in only single datasets and/or not consistently reproducible. No study has yet validated candidate biomarkers following a program of discovery in one prospective cohort followed by reproducibility in an independent prospective cohort. Elevated acute phase reactants appear to predict progression of non-radiographic axial SpA to radiographic sacroiliitis. However, prognostic capacity in individual patients is limited. Low levels of mediators associated with suppression of signaling through Wingless proteins, dickkopf and sclerostin, suggest that impaired suppression of osteoblast activity may be a factor in development of ankylosis. Biomarkers associated with degradation of turnover of cartilage and connective tissue, such as metalloproteinase (MMP) 3 and urinary type II collagen C-telopeptide, have been linked to radiographic progression in single cohort studies. A related study has shown that MMP-degraded citrullinated proteins may predict progression suggesting a potential link to smoking. It is questionable if any of these candidates have prognostic utility in individual patients although recent reports suggests that MMP3 and/or MMP-degraded citrullinated vimentin together with evidence of radiographic changes already evident at baseline may predict as many two-thirds of patients who will progress over a two-year time frame. A major limitation of studies conducted to date is that analysis has focused on baseline predictors, which may be confounded by factors such as treatment, especially anti-TNF therapy. Consequently, a response-to-treatment intervention study design has been proposed by the OMERACT Soluble Biomarker Working group for validation studies in SpA aimed at assessing whether short-term change in candidate biomarkers might predict radiographic progression. Extensive heterogeneity of disease together with the slow progression of radiographic changes means that discovery analyses should focus on homogeneous populations, characterized by imaging, while validation cohorts should select for patients at higher risk for progression according to known predictors, such as presence of baseline syndesmophytes.

Oral Presentations

O1

HLA-B27 SUBTYPE OLIGOMERIZATION AND INTRACELLULAR ACCUMULATION PATTERNS CORRELATE WITH PREDISPOSITION TO SPONDYLOARTHRITIS

Jeanty C.[1], Noteuil A.[1,2], Jah N.[2], Sourisce A.[1], Wielgosik A.[1], Fert I.[1,2], Breban M.[1,2,3], André C.[1,2]
[1]Institut Cochin, INSERM U1016, CNRS UMR8104, Faculty of Health Sciences Simone Veil, and INSERM U987; [2]University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, Université Paris Diderot, Sorbonne Paris Cité, Laboratoire d'Excellence, Paris; [3]Service de Rhumatologie, Ambroise Paré Hospital, University of Versailles Saint-Quentin-en-Yvelines, Boulogne, France

Aim. Mechanisms underlying the striking association of spondyloarthritis (SpA) with the MHC class I molecule HLA-B27 remain poorly understood. SpA-like disease develops spontaneously in B*2705 transgenic rats in correlation with high HLA-B27 expression levels. This study was undertaken to examine the effects of increased expression of HLA-B27 alleles that are differently associated with SpA on oligomerization and intracellular redistribution.
Methods. HeLa cells were transfected with complementary DNA encoding for HLA–B proteins fused to yellow fluorescent protein and/or *Renilla* luciferase and harvested at an early phase and a later phase of expression. We monitored HLA-B intracellular trafficking and localization by means of microscopy and live-cell imaging. Bioluminescence resonance energy transfer (BRET) and Western blotting were used to monitor HLA-B oligomerization.
Results. At low expression levels, BRET signals were similarly elevated for all SpA-associated HLA-B27 alleles, but were lower for the non-associated B*2706. At higher expression levels, HLA-B27 signals remained steady while those for HLA-B7 decreased sharply, reaching the level observed for B*2706. This was due at least in part to a decreased oligomer proportion without unfolded protein response. Such differential behavior was not abrogated by proteasome inhibition. With increased expression, all HLA-B proteins accumulated to a high density in cytoplasmic vesicles with labile form and size. The extent of this phenomenon was closely correlated with the level of predisposition to SpA.
Conclusion. To our knowledge, this is the first report of a correlation between the level of predisposition to SpA conferred by HLA-B27 alleles and their biochemical behavior. These findings open new perspectives for understanding the pathogenicity of HLA-B27.

O2

PEPTIDE HANDLING BY HLA-B27 SUBTYPES INFLUENCES THEIR BIOLOGICAL BEHAVIOR, ASSOCIATION WITH ANKYLOSING SPONDYLITIS AND SUSCEPTIBILITY TO ERAP1

Alvarez-Navarro C.[1], García-Medel N.[1], Sanz-Bravo A.[1], Gómez-Molina P.[1], Barnea E.[2], Marcilla M.[3], Admon A.[2], López de Castro J.A.[1]
[1]Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Madrid, Spain; [2]Faculty of Biology, Technion, Israel Institute of Technology, Haifa, Israel; [3]Functional Proteomics Unit, Centro Nacional de Biotecnología, Madrid, Spain

Introduction and Aims. HLA-B27 and ERAP1 are jointly associated with ankylosing spondylitis (AS). With a single exception, AS-associated and non-AS-associated subtypes differ in thermostability and folding. In this study we analyzed the relationship between peptide specificity, thermostability, folding, TAP suitability and ERAP1 dependency of HLA-B27 subtypes in order to understand the pathogenetic role of HLA-B27-bound peptides in AS.
Methods. MHC-peptide complexes from 7 major subtypes were isolated from C1R-HLA-B27-transfected cells and the subtype-bound peptidomes were compared after high-throughput peptide sequencing using LC-MS/MS.
Results. Peptides found only among AS-associated/high-thermostability subtypes were longer and had bulkier and more diverse C-terminal residues than those found only among non-AS/lower-thermostability subtypes. Peptides found in all AS-associated subtypes and none of the non-AS-associated ones, were very rare. Residue 116, through its influence on the hydrophobicity, size and other features of pocket F, determined peptide binding, thermodynamic properties and folding, thus emerging as a key structural hallmark of HLA-B27. The peptides found only among AS-associated subtypes were better suited for TAP transport than those from non-AS-associated ones, suggesting that AS-associated subtypes tend to bind peptides directly generated in the cytosol. Peptides found only among AS-associated subtypes showed a higher frequency of ERAP1-resistant N-terminal residues compared to the non-AS-associated ones, revealing a more pronounced effect of ERAP1 on the former group.

Conclusions. Our results define the molecular basis for the close relationship between peptide specificity, stability and folding of HLA-B27 subtypes, providing a unified view of HLA-B27 biology. They also reveal a differential influence of the disease-related ERAP1 polymorphism on AS-associated, relative to non-AS-associated subtypes.

O3

DISCOVERY OF T CELL RECEPTOR CLONOTYPES DISTINCTIVE FOR HLA B27-POSITIVE ANKYLOSING SPONDYLITIS BY DEEP REPERTOIRE SEQUENCE ANALYSIS

Faham M.[1], Carlton V.[1], Moorhead M.[1], Zheng J.[1], Asbury T.[1], Inman R.D.[2]
[1]Sequenta, Inc. South San Francisco, CA, USA; [2]Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

Introduction. More than 90% of ankylosing spondylitis (AS) patients are HLA-B27 positive (B27+). One proposed mechanism for this association is that arthritogenic peptides presented by HLA-B27 play a key role in the pathogenesis of AS. Recent studies demonstrate the utility of next-generation sequencing (NGS) for elucidation of T cell receptor (TCR) profiles and characterization of immune responses with unprecedented sensitivity.
Materials and Methods. We conducted TCRβ repertoire sequencing (LymphoSIGHT platform) to determine sequences and motifs that are shared among HLA B27+ AS patients. Previous studies have described some TCR clones that may be associated with AS and reactive arthritis. These studies were limited by traditional Sanger sequencing methods that had limited sequencing depth, resulting in a profile of the immune repertoire which was not comprehensive.
Results. LymphoSIGHT NGS was used to obtain TCRβ repertoire clonotype sequences from 200 B27+ AS patients, 47 B27- AS patients, and >200 controls with the goal of identifying common motifs among B27+ AS patients. Seven of the previously published motifs were observed to be enriched in the B27+ AS samples compared to controls. Following analysis with independent training and test sets including over 80 million clones, we identified ten novel motifs that were significantly enriched in B27+ AS patients compared to the controls. Two of the ten novel motifs were related by sequence to two of the seven published motifs, demonstrating an overlap between the published and novel motifs. The majority of the 17 positive motifs were expressed primarily in CD8+ T cells.
Conclusion. This is the first TCR NGS study in AS. Enrichment of distinct TCR motifs in AS is consistent with the hypothesized mechanism that HLA-B27 contributes to AS through presentation of distinct peptides to CD8+ CTL. This immune repertoire sequencing approach provides insight into AS pathogenesis and offers a novel molecular approach to identify common, disease-specific T cells.

O4

AUTOANTIBODY TO 14-3-3ETA IS A NOVEL BIOMARKER ASSOCIATED WITH MRI INFLAMMATION AND RADIOGRAPHIC PROGRESSION IN AXIAL SPONDYLOARTHRITIS

Maksymowych W.P.[1], Wichuk S.[1], Murphy M.[2], Marotta A.[2]
[1]University of Alberta, Edmonton; [2]Augurex Life Sciences Corp, North Vancouver, Canada

Introduction. 14-3-3η is a ubiquitous intracellular chaperone protein that may be expressed extracellularly in rheumatoid arthritis and mediate inflammatory cascades that result in expression of metalloproteinases. It may elicit autoantibodies (AAb) to a range of epitopes on the native protein. We aimed to determine whether autoantibodies to the native protein were generated in SpA and which specific autoantibody might be associated with MRI inflammation and have diagnostic and prognostic properties.
Methods. Sera from 116 patients with SpA by modified New York criteria followed prospectively and 106 healthy controls were screened against ten 14-3-3η peptides (Pan 1-10) using an electrochemiluminescent multiplex assay platform. Patients had median age of 41 years, 74% male, and median symptom duration 15.5 years. Mann-Whitney U-test was used to determine group differences and ROC analysis was used to assess diagnostic utility. Pearson correlations and multivariate regression analyses were used to examine associations with MMP-3, CRP, SPARCC MRI SIJ inflammation, baseline mSASSS and 2-year change in mSASSS.
Results. Median (SD) expression of the Pan-1 14-3-3η autoantibody was significantly higher in SpA than in healthy controls (838 U/ml (605-1287) vs. 456 U/ml (346-568), p=0.0001) and area under the ROC curve was 0.86, 95%CI (0.82-0.91). A cut-off of 803 U/ml delivered 95% specificity and 53% sensitivity (LR+ 11.2, LR- 0.5). Pearson correlations were 0.44 (p<0.00001) for MRI inflammation, 0.23 (p=0.02) for CRP, 0.18 (p=0.05) for baseline mSASSS, and 0.34 (p=0.001) for 2-year change in mSASSS. Independent predictors of MRI inflammation were symptom duration (p=0.04) and Pan 1 autoantibody (p=0.0004). Controlling for baseline mSASSS, Pan 1 was the only significant predictor of the ΔmSASSS at 2 years (p=0.002) in multivariate regression analysis.
Conclusions. 14-3-3η Pan 1 autoantibody is a novel serum marker that is differentially expressed in AS versus healthy controls. Pan 1 is significantly associated with MRI inflammation and its baseline expression is a predictor of ΔmSASSS at year 2.

O5

THE RELATIONSHIP BETWEEN INFLAMMATION, FATTY LESIONS AND SYNDESMOPHYTES IN AS: RESULTS FROM GO-RAISE

Baraliakos X.[1], Hermann K.G.[2], Xu S.[3], Hsu B.[3], Braun J.[1]
[1]Rheumazentrum Ruhrgebiet, Herne; [2]Radiology, Charité Berlin, Germany; [3]Janssen R&D, Spring House, USA

Aim. Spinal changes in AS are characterized by inflammation (INF), fatty degeneration (FAT), and syndesmophytes (SYN). Using data from GO-RAISE, we assessed how INF and FAT on MRI relate to subsequent SYN on x-rays.
Methods. 98 patients from GO-RAISE were included. All had lateral radiographs of the cervical and lumbar spine at baseline, wks104 and 208 and corresponding spinal MRI in T1 and STIR sequences at baseline, wk14, and wk104. MRIs were read by two readers blinded to time order of the images, evaluating vertebral corners on x-rays for SYN and the MRIs for INF and FAT with notation of the location by vertebral quadrant (VUq: upper, lower, anterior, posterior).
Results. There were 91 patients representing 4,368 VUq with evaluable MRI data at baseline and wk14 and corresponding vertebral corner x-ray data at wk104 and 208. Of VUq with FAT at wk14, more frequently there was also FAT at baseline and FAT persisting to wk104, and INF was more frequently absent at baseline than present. Overall, the percentage of VUq with new SYN at wk 104 or 208 was greater in VUq where FAT persisted at both baseline and wk14, compared to FAT being only present at wk14. New SYN were significantly more likely to develop in VUq with FAT at both baseline and wk14 than those that did not have persistent FAT (odds ratios >2.4). The combined presence at baseline of FAT and INF appeared to further increase the chance of SYN developing at the corresponding VUq. Conversely, for VUq without FAT or INF at baseline but wk14 FAT present, only 0-1.5% of VUq developed new SYN later.
Conclusion. This detailed analysis of spine MRI and radiographs supports the hypothesis that in AS, fatty degeneration and inflammation unit favors subsequent syndesmophyte growth and ankylosis.

O6

DISEASE ACTIVITY IN MALE SMOKERS HAS A >10-FOLD AMPLIFIED EFFECT ON RADIOGRAPHIC DAMAGE IN COMPARISON WITH FEMALE NON-SMOKERS IN ANKYLOSING SPONDYLITIS

Ramiro S.[1], van Tubergen A.[2], Landewé R.[1], Stolwijk C.[2], Dougados M.[3], van den Bosch F.[4], van der Heijde D.[5]
[1]ARC, Amsterdam; [2]MUMC, Maastricht, The Netherlands; [3]Paris-Descartes University, Paris, France; [4]GUH, Ghent, Belgium; [5]LUMC, Leiden, The Netherlands

Aim. To investigate whether smoking influence the longitudinal relationship between disease activity and radiographic damage in AS.
Methods. Patients from the Outcome in AS International Study (OASIS) were followed-up for 12 years, with biannual clinical and radiographic assessments. Two readers independently scored the x-rays according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and scores were averaged. Disease activity was assessed by the ASDAS-CRP. The relationship between ASDAS and radiographic damage was investigated using generalized estimating equations, with auto-regressive (i.e. adjusted for the 2-year previous mSASSS) models with a 2-year time-lag. Interactions were tested with baseline smoking status and if significant, analyses were repeated in strata.
Results. A total of 127 patients were included (71% males, mean (SD) age 41(12) years, mean symptom duration 18(11) years and 82% HLA-B27 positive). Smoking status modified the relationship between disease activity and radiographic damage significantly (p<0.001), and this effect extended to other strata: males (p=0.002) and patients with shorter symptom duration (<18y) (p=0.009). Overall, an increase in one ASDAS-unit led to an increase in 0.72 mSASSS-units per 2 years. In smokers, this value reached 1.94 mSASSS-units and in male smok-

ers 2.15 mSASSS-units. Comparing the magnitude of the effect of ASDAS on mSASSS in smokers vs non-smokers, smokers had a 5.5-fold amplified effect, whereas male smokers had a 13.4 fold amplified effect compared to female non-smokers. Smokers with short symptom duration had a 8.1-fold amplified effect compared to non-smokers with long symptom duration.
Conclusion. Smoking amplifies the effect of disease activity on radiographic damage (5-fold). This effect is further amplified in male smokers (13.4-fold) in comparison with female non-smokers.

O7

FACTORS ASSOCIATED WITH RADIOGRAPHIC SACROILIITIS IN SPONDYLOARTHRITIS (SPA): RESULTS FROM CROSS-SECTIONAL AND LONGITUDINAL ANALYSES IN A COHORT OF MULTIPLEX FAMILIES

Costantino F.[1,2], Zeboulon-Ktorza N.[1], Said-Nahal R.[1], D'Agostino M.A.[1,2], Breban M.[1,2]
[1]Rheumatology Division, Ambroise Paré Hospital (AP-HP), Boulogne-Billancourt; [2]INSERM U987, UFR Simone Veil, Versailles-Saint Quentin University, France

Introduction/Aim. Radiographic sacroiliitis is an important outcome in SpA and is mandatory to establish a diagnosis of ankylosing spondylitis (AS). However, few data are available on the factors associated with radiographic sacroiliitis. The objectives of the study were to identify such factors in a cross-sectional study and longitudinal study of SpA patients with positive family history.
Methods. 1,358 patients fulfilling the ASAS criteria for SpA and having at least one first- or second-degree SpA-affected relative were recruited by the Groupe Français d'Etude Génétique des Spondylarthrites (GFEGS) and followed longitudinally. Pelvic X-rays were examined blindly and independently by 2 qualified examiners, using the modified New York criteria. Definite radiographic sacroiliitis corresponded to a grade ≥2 bilateral, or grade ≥3 unilateral. Of the 448 cases without definite sacroiliitis at inclusion, 160 patients were followed-up (with new pelvic X-ray) for 2 to 15 years. Regression analysis was used to assess factors associated with definite radiographic sacroiliitis at inclusion and with progression to definite sacroiliitis.
Results. In multivariate analysis, factors positively associated with definite sacroiliitis at inclusion were male sex (p=7x10^{-8}), younger age at disease onset (p=0.04), longer disease duration (p=0.0005), HLA-B27 positivity (p=0.02), inflammatory back pain (p=0.02) and uveitis (p=9.8x10^{-5}). The only negatively associated factor was enthesitis (p=0.002). In longitudinal study, 38 of the 160 patients (23.75%) developed definite sacroiliitis after a mean follow-up duration of 8.8±3.0 years. Factors associated with progression to definite sacroiliitis in univariate analysis were a low grade radiographic sacroiliitis at inclusion (p=0.002) and occurrence of uveitis or buttock pain during the follow-up period (p=0.04 and V=0.05, respectively).
Conclusions. After an average follow-up duration of almost 9 years, 23.75% of the patients with non-radiographic SpA had developed AS. This study allowed us to identify several demographic, genetic and clinical factors associated with definite radiographic sacroiliitis.

O8

MORTALITY AND ASSOCIATED CONDITIONS IN HOSPITALIZED ANKYLOSING SPONDYLIYIS PATIENTS

Wysham K.W., Murray S.G., Yelin E.H., Gensler L.S.
University of California San Francisco, Dept. of Medicine, Division of Rheumatology, San Francisco, CA, USA

Introduction. Little data exist regarding mortality in Ankylosing Spondylitis (AS) patients. We performed a population-based study of diagnoses associated with in-patient mortality in AS.
Methods. Data were abstracted from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) between 2007-2011. We identified discharges with AS by International Classification of Disease-Clinical Modification (ICD9-CM) code 720.0. We used clinical classification software (CCS) codes to categorize diagnoses associated with mortality in AS patients and used ICD9-CM diagnoses for statistical modeling. Chi-square and Wilcoxon rank sum tests were used when appropriate to identify differences between AS patients who did and did not die. Multivariable logistic regression, including socio-demographic variables, significant covariates and comorbidities, was performed to identify independent predictors of in-hospital mortality.
Results. There were 12,493 AS admissions and 276 deaths between 2007-2011. The mean age of AS patients was 59.0±16.4 years, 71% were males and 24% were electively admitted. The mean age of those who died was 73.0±12.9 years, 78% were males and 10% were electively admitted. The median Charlson Comorbidity Index (CCI) for patients who died was 2 (IQR 0,4). "Septicemia" and "other fractures" (including cervical spine fracture [CSFX]) were the top two primary diagnostic categories in patients who died. In the multivariable model, bacteremia and CSFX were the diagnoses with the highest odds of death, 7.28 (95% CI 5.36-9.88) and 5.70 (95% CI 3.63-8.95), respectively. Of those with CSFX, 66% also had a diagnosis of fall.
Conclusions. The diagnoses most strongly associated with mortality in hospitalized AS patients, were bacteremia and CSFX, however pneumonia and concurrent comorbid conditions were also significantly associated with death. Falls appear to be associated with CSFX, although we cannot evaluate if falls cause CSFX. This is the first population-based study of in-hospital mortality in AS. Further studies should be conducted to evaluate the etiology of CSFX in AS to aid in prevention of this known complication.

Table I. Multivariable model of mortality in hospitalized AS patients.

Variable	Adjusted OR*	95% CI	p value
Age (per 1 year)	**1.05**	**1.03-1.06**	**<0.001**
Male Gender	0.97	0.71-1.33	0.866
Private insurance	0.77	0.53-1.11	0.162
Community population <50,000	**1.38**	**1.02-1.87**	**0.038**
Elective admission	**0.58**	**0.38-0.88**	**0.010**
Charlson Index (per 1 point on weighted scale)	**1.25**	**1.18-1.34**	**<0.001**
Bacteremia	**7.28**	**5.36-9.88**	**<0.001**
Pneumonia	**1.98**	**1.44-2.70**	**<0.001**
Cervical spine fracture	**5.70**	**3.63-8.95**	**<0.001**
Thoracic spine fracture	0.81	0.41-1.59	0.541
Lumbar spine fracture	1.88	0.81-4.41	0.144
Fall	0.98	0.63-1.51	0.921

*Odds ratios adjusted for all variables shown.

O9

THE EFFECT OF SMOKING CESSATION IN ANKYLOSING SPONDYLITIS – RESULTS FROM THE SCOTLAND REGISTRY FOR ANKYLOSING SPONDYLITIS (SIRAS)

Jones G.T.[1], Ratz T.[1], Dean L.E.[1], Macfarlane G.J.[1], Atzeni F.[1,2], on behalf of SIRAS
[1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, UK; [2]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy

Introduction/Aim. Smoking is associated with increased disease activity, reduced physical function, and poorer quality of life in ankylosing spondylitis (AS). However, other than as part of general health advice, specific recommendations on smoking cessation are not commonly given by physicians, nor perceived as high importance by patients. The aim of the current study was to examine the effect of smoking cessation on clinical and patient-reported parameters in AS.
Materials and Methods. SIRAS collects data on clinically diagnosed AS patients in Scotland. Clinical data, including BASDAI and BASFI, is obtained from medical records, and postal questionnaires provide patient-reported data, including smoking status and quality of life (QoL) using the ASQoL (scored 0-18 with a higher score indicating poorer quality of life). Current and ex-smokers were compared using linear regression, adjusting for age, sex, education, socio-economic status, and alcohol consumption. Results are given as regression coefficients with 95% confidence intervals.
Results. SIRAS includes clinical and patient-reported information on 959 patients: 73% male; mean age 52yrs; 22% current smokers and 38% ex-smokers. Compared to smokers, ex-smokers reported significantly lower disease activity (BASDAI) (-0.7; -1.2 to -0.2), although after adjusting for potential confounders this was greatly attenuated (-0.4; -1.0 to 0.1). Ex-smokers also reported significantly better QoL (-1.4; -2.5 to -0.4), and there was some evidence of increased function (BASFI) (0.4; -1.0 to 0.3). There were no other significant statistically nor sizeable differences between current and ex-smokers with any other clinical or patient-reported outcome.
Discussion/Conclusions. In AS, ex-smokers have lower disease activity and better disease-related QoL compared to smokers. For comparison, the difference in disease activity is around 30% of the effect one might achieve with intensive physiotherapy, and 16% that of biologic therapy. Rather than relying on of generic health advice, clinicians should actively promote smoking cessation as an adjunct to usual therapy.

O10

TARGETING SYNOVIAL MAST CELLS IN SPONDYLOARTHRITIS: A PROOF-OF-CONCEPT STUDY WITH THE TYROSINE KINASE INHIBITOR NILOTINIB

Paramarta J.E.[1], Turina M.C.[1], Heijda T.F.[1], Blijdorp I.C.[1,2], Noordenbos T.[1,2], Yeremenko N.[1,2], Baeten D.[1,2]
[1]Dept. of Clinical Immunology and Rheumatology; [2]Laboratory of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands

Introduction. Immunopathological studies on synovitis recently identified mast cells as potential therapeutic target in spondyloarthritis (SpA).[*Noordenbos et al. Arthritis Rheum 2012*] Mast cells can be targeted by inhibiting c-Kit, which is a target of the tyrosine kinase inhibitor nilotinib. This study aimed to evaluate the immunomodulating and clinical effects of nilotinib in SpA.
Patients and Methods. 28 patients with active peripheral and/or axial SpA were included in a randomized, double-blind, placebo-controlled clinical trial and were treated 1:1 with nilotinib or placebo for 12 weeks, followed by an open label extension for 12 weeks. Paired synovial biopsies, serum sampling and assessment of clinical symptoms were performed serially.
Results. In peripheral SpA (n=13) synovial inflammation was reduced after 12 weeks of nilotinib treatment as evidenced by histopathology (decrease in CD68+ and CD163+ macrophages and mast cells). Also, compared to placebo mRNA expression of c-Kit (p=0.037) and pro-inflammatory cytokines such as IL-6 (p=0.024) were reduced, paralleled by a decrease in serum inflammation biomarkers such as CRP (p=0.024) and calprotectin (p=0.055). Clinical parameters such as patient's global assessment of disease activity (p=0.031) and Ankylosing Spondylitis Disease Activity Score (p=0.031) improved upon 12 weeks of nilotinib but not placebo treatment, which was further augmented at week 24. In contrast, neither serum inflammation biomarkers nor clinical parameters improved upon nilotinib treatment in axial SpA. One serious adverse event occurred, which was considered unrelated to nilotinib. There were no unexpected safety signals in comparison with large scale data on nilotinib in chronic myeloid leukemia.
Conclusions. This study supports the concept that mast cells can contribute to synovial inflammation in SpA and that tyrosine kinase inhibition targeting these cells has a biological and clinical immunomodulatory effect in peripheral but not axial SpA. This supports further evaluation of nilotinib and other drugs targeting mast cells in larger trials in peripheral SpA.

O11

OBJECTIVE EVALUATION OF PHYSICAL FUNCTIONING AFTER TNFi THERAPY IN ANKYLOSING SPONDYLITIS PATIENTS – A SELECTION OF THREE FEASIBLE PERFORMANCE-BASED TESTS

van Weely S.F.E.[1], Dekker J.[1,2], Steultjens M.P.M.[3], van Denderen J.C.[1], Nurmohamed M.T.[1], Dijkmans B.A.C.[4], van der Horst-Bruinsma I.E.[4]
[1]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam; [2]VU University Medical Centre, Dept. of Rehabilitation Medicine, EMGO Institute and Dept. of Psychiatry, Amsterdam, The Netherlands; [3]Glasgow Caledonian University, Institute for Applied Health Research Glasgow, UK; [4]VU University Medical Centre, Dept. of Rheumatology Amsterdam, The Netherlands

Introduction/Aim. Performance-based tests can provide a better estimation of physical functioning in AS patients. However, it is important to eliminate redundant testing. Therefore, this study aimed (i) to select a limited number of performance-based tests that are reliable, show improvement in physical functioning after TNFi therapy and generate the equivalent information as the full set of tests and (ii) are feasible for use in daily clinical practice.
Methods. Eight performance-based tests were evaluated. The tests that showed adequate reliability, highest Standardized Response Means (SRM) and the largest proportion of patients with an improved performance-based physical functioning were selected. The selected tests were combined into a new criterion for improvement in physical functioning (AS Performance-based Improvement, ASPI). The number and percentage improved patients identified with the ASPI and identified with the full set of performance tests were compared.
Results. Reliability for all tests was adequate to excellent (Intraclass Correlation Coefficients 0.73-0.96). The tests for bending, putting on socks and getting up from the floor had the highest SRM's (0.52–0.74) and showed the largest proportion of improved patients after TNFi therapy. The combination of these three tests is feasible in daily clinical practice and showed improved physical functioning after TNFi therapy in 67% of the patients.
Conclusion. The three selected tests are recommended for use in daily practice, because they generate comparable information as the full set, are reliable, feasible and the combination of these tests showed an improved physical functioning after TNFi therapy in 67% of the patients. In future, evaluation of physical functioning might be improved by adding these tests to other outcome measures.

O12

CLINICAL AND IMAGING EFFICACY OF ETANERCEPT IN EARLY NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS: 48-WEEK TREATMENT DATA

Maksymowych W.P.[1], van der Heijde D.[2], Dougados M.[3], Sieper J.[4], Braun J.[5], Citera G.[6], Miceli-Richard C.[7], Wei J.C.C.[8], Pedersen R.[9], Bonin R.[9], Logeart I.[10], Wajdula J.[9], Vlahos B.[9], Bukowski J.F.[9]
[1]Dept. of Medicine, University of Alberta, Edmonton, Canada; [2]Dept. of Rheumatology, Leiden University, Leiden, The Netherlands; [3]Dept. of Rheumatology, Paris-Descartes University, Paris, France; [4]Medical Dept. I Rheumatology, Charité-Universitätsmedizin, Berlin; [5]Dept. of Medicine, Rheumazentrum Ruhrgebiet, Herne, Germany; [6]Dept. of Rheumatology, Consultorios Reumatológicos Pampa, Buenos Aires, Argentina; [7]Dept. of Rheumatology, Hôpital de Bicêtre, Paris-Sud University, Paris, France; [8]Dept. of Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan; [9]Dept of Clinical Research, Pfizer Inc, Collegeville, PA, USA; [10]Pfizer France, Paris, France

Introduction/Aim. Our previous trial 12-week data showed that etanercept (ETN) has superior efficacy to placebo (PBO) in non-radiographic axial spondyloarthritis (nr-axSpA) patients with inadequate response to NSAIDs. This study aimed to examine efficacy of ETN at week 48.
Methods. 215 patients with symptoms 3–60 months, fulfilling ASAS axSpA but not NY modified radiographic criteria, BASDAI ≥4, and inadequate-response with ≥2 NSAIDs were randomized to ETN 50 mg QW or PBO. After 12 weeks all patients received ETN 50 mg open-label. Clinical assessments including ASAS40 and MRI of sacroiliac (SI) joint/spine were performed (SPARCC and ASspiMRI scoring).
Results. At week 12, 33.3% of patients treated with ETN and 14.7% PBO achieved ASAS40, improving to 52.7% by week 48 (combined groups). SPARCC MRI-SI joint and SPARCC 6 DVU scores were reduced from baseline–week12 in ETN (56.7%; 40.1%) and PBO (16.4%; 11.1%) groups and 65.2%, 60.8% (combined groups) by week 48, respectively. ASspiMRI improvements were 40.1% (ETN) and 7.7% (PBO) by week 12, and 40.9% by week 48 (combined groups). Infections (the most frequent AE) occurred in 43/208 (20.7%) patients and TEAE (pyrexia/bronchitis) caused 2 discontinuations between weeks 12–48.
Discussion/Conclusions. During the 36-week open-label period, clinical and imaging outcomes continued to improve in etanercept-treated patients or were comparable to responses observed at the end of the 12-week double-blind period. There were no new safety signals.

Short Oral Presentations

SO1

A NOVEL MONOCYTE-SPECIFIC TRANSCRIPT UNDERLIES THE CHROMOSOME 21Q22 INTERGENIC GENETIC ASSOCIATION IN ANKYLOSING SPONDYLITIS

Haynes K., Kenna T., Glazov E., Brown M.A., Thomas G.P.
The University of Queensland Diamantina Institute, Translational Research Institute, Woolloongabba, Australia

Introduction/Aim. Of the 43 independent genetic associations that have been reported for ankylosing spondylitis, most occur in intergenic, intronic or other untranslated regions of the genome. Two in particular, at chromosomes 2p15 and 21q22, occur in gene desert regions with no annotated transcription.
Materials and Methods. We have used a new technique known as CaptureSeq, which utilises RNAseq on samples enriched for transcripts from a genomic region of interest allowing the detection of transcripts expressed at too low levels for detection by conventional RNAseq. Using this technique, we undertook ultra-deep transcriptional profiling in peripheral blood mononuclear cells from 6 cases carrying the protective allele and 6 carrying the susceptibility allele at the 21q22 gene desert locus.
Results. We identified two completely novel divergently transcribed long non-coding RNAs (lncRNA) expressed from this region, which were upregulated in AS cases compared with healthy controls, as well as those subjects carrying the susceptibility allele. This overexpression in PBMCs was confirmed in two independent data sets, using both RNAseq and qPCR.
To further elucidate the potential function of this novel transcript we mined the Fantom5 Atlas of human gene expression which showed expression of the 21q22 transcripts in $CD14^+$ monocytes. We confirmed this in purified $CD14^+$ cells from our PBMC samples with no expression seen in any other cell type. Expression was also significantly enhanced by stimulation of the monocytes with microbial components.
Discussion. This is the first example of a role for a lncRNA in AS and strongly supports a role for monocytes in AS aetiology possibly through responses to microbes. Monocyte antigen presentation has previously been implicated in AS strengthened by the identification of the HLA-B27-ERAP1 genetic interaction. Aberrant microbial-induced $CD14^+$ monocyte expression of the 21q22 transcript presents a novel potential mechanism by which AS might be influenced by microbes.

SO2

IL-23 EXPRESSION AND ACTIVATION OF AUTOPHAGY IN SYNOVIUM AND PBMCS OF HLA-B27 POSITIVE PATIENTS WITH ANKYLOSING SPONDYLITIS

Neerinckx B., Carter S.L, Lories R.J.
Laboratory of Tissue Homeostasis and Disease, KU Leuven, Belgium

Introduction. IL-23 may play a key role in ankylosing spondylitis (AS). Enhanced IL-23 production in the gut of AS patients has been demonstrated and linked to autophagy.
Objectives. To investigate IL-23 expression and autophagy in the synovium and peripheral blood mononuclear cells (PBMCs) of HLA-B27 positive AS patients compared to patients with other forms of spondyloarthritis (SpA), other inflammatory joint diseases and healthy controls.
Methods. Synovial tissues were obtained by arthroscopy from inflamed knees from patients with AS (HLA-B27+; n=11), other forms of SpA (HLA-B27+; n=9 or HLA-B27-; n=10), rheumatoid arthritis (RA) (n=10) or other inflammatory joint diseases (n=10) and from multiple organ donors as non-inflammatory controls (n=10). PBMCs were isolated from whole blood from patients with AS (HLA-B27+; n=17), RA (n=19) and healthy controls (n=12). Np patients were treated with TNF inhibitors. Expression of IL-23 and autophagy genes was analyzed using quantitative RT-PCR (SYBR green) with primers for IL23p19, ATG16L1, IRGM, MAP1LC3A, ATG5, HSPA8 and HSP90AA1.
Results. In synovial tissues, IL-23p19 expression was increased in the inflammatory samples compared to the non-inflammatory samples. There was no difference in IL-23p19 expression in AS patients compared to non-AS SpA and other inflammatory diseases. In PBMCs expression of IL-23p19 was significantly lower in AS patients than in healthy controls with expression levels in RA patients extending over the whole range between AS patients and controls. No difference in expression of autophagy-associated genes was found in synovial tissues between groups. In PBMCs, there was lower expression of ATG16L1, IRGM and HSP90AA1 in AS patients compared to healthy controls. The expression of MAP1LC3A, ATG5 and HSPA8 was not different between the groups.
Conclusions. Notwithstanding recent evidence in gut samples of AS patients, our data do not support higher IL-23 expression and activation of autophagy in synovium or PBMCs of HLA-B27+ AS patients. The production of IL-23, possibly driven by autophagy, in AS patients seems to be tissue specific for the gut.

SO3

STROMAL OVEREXPRESSION OF TRANSMEMBRANE TNF INDUCES EXPERIMENTAL SPONDYLOARTHRITIS IN MICE

Van Duivenvoorde L.M., Van Tok M.N., Baeten D.L.
Dept. of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Background. The failure of TNF blockers to prevent osteoproliferation in SpA patients raised the concept that inflammation and osteoproliferation are uncoupled in SpA. However, inflammation and osteoproliferation are linked in HLA-B27 rats, high CRP is associated with radiographic progression in axial SpA, and NSAID treatment can retard osteoproliferation.
We propose that inflammatory mediators, distinct from soluble TNF, drive pathologic osteoproliferation in SpA. Based on our observations on soluble versus transmembrane TNF (tmTNF) expression in SpA synovitis, we explored if and how tmTNF drives experimental SpA.
Methods. tmTNF mice[1] were studied over time for SpA development. Joints were collected and analyzed for inflammation and osteoproliferation.
To assess the contribution of stromal versus hematopoietic tmTNF overexpression, tmTNF mice and WT mice were lethally irradiated and received bone marrow cells (BM) from either WT or tmTNF mice. Mice were evaluated for 16 weeks until sacrificed for histologic and radiographic analysis.
Results. tmTNF mice (100%; n>50) spontaneously developed arthritis and spondylitis, starting at 4 weeks of age and progressing over time. Arthritis was characterized by inflammation of synovium and enthesis. Hypertrophic chondrocytes were observed outside the bone in the connective tissue next to the inflammation. In spondylitis, inflammation was found in connective tissue located at the junction of the annulus fibrosus with the vertebral bone. Hypertrophic chondrocytes were observed at the edge of the vertebral body, in conjunction with ongoing inflammation.
In the functional experiments, irradiated tmTNF mice receiving tmTNF BM developed arthritis and spondylitis with 100% incidence 3 weeks after transplantation. tmTNF mice receiving WT BM also developed disease with the same incidence, onset and severity as the control group. In sharp contrast, WT mice that received tmTNF BM did not develop any arthritis, and spondylitis occurred less frequently (66%) and later (10 weeks after BMT) compared to the control group.
Conclusions. tmTNF overexpression induces experimental SpA with osteoproliferation, indicating that inflammatory mediators can indeed drive osteoproliferation. These data indicate the relevance of transmembrane TNF and the role of the stromal compartment in the pathophysiology of SpA.

Reference

1. ALEXOPOULOU L et al.: *Eur J Immunol* 1997; 27(10): 2588-92.

SO4

GUT DERIVED IL-23R+CD3+/CD3-CD4-CD8-CD56+RORC-T-BET+ NKP44+ INNATE LYMPHOID CELLS ARE EXPANDED IN THE PERIPHERAL BLOOD, SYNOVIAL FLUID AND BONE MARROW OF ANKYLOSING SPONDYLITIS PATIENTS

Ciccia F., Guggino G., Rizzo A., Saieva L., Giardina A.R., Alessandro R., Triolo G.
University of Palermo, Italy

Introduction. Aim of the study was to better characterize the immunologic origin and the behavior of IL-23-responsive ILCs in the gut, synovial fluid and bone marrow of AS patients.
Methods. Ileal and bone marrow biopsies, peripheral blood (PBMC) and synovial fluid (SFMC) mononuclear cells were obtained from AS patients and controls. ILC1, ILC2 and ILC3 cells were determined and characterized by confocal microscopy and flow cytometry on isolated lamina propria (LPMC), PBMC, BM and SFMC. MADCAM-1, IL-7, and IL-15 were evaluated by immunohistochemistry (IHC). Tissue distribution of lymphoid tissue inducer cells (LTi) was also assessed by confocal microscopy. The in vitro ability of epithelial cells in driving the differentiation of ILC3 was also assessed.
Results. A slight expansion of ILC1 but not ILC2 was observed in the gut of AS patients. CD3-/CD3+CD4-CD8-RORc-Tbet+CD56+NKp44+ (type III ILCs) cells were significantly expanded in the gut, synovial fluid, and bone marrow of AS patients compared to controls, produced high levels of IL-17 and IL-22 and

over-expressed a4b7. MADcAM1 increased expression was also demonstrated in both BM and ileal samples. Strong expression of IL-17 and IL-22 was confirmed by IHC in AS BM. IL-7 was significantly increased in AS gut, especially in the context of Paneth cells (PC) and surrounded by aggregates of c-kit/IL-7R+ cells (LTi) that have been demonstrated to be precursors of gut type III ILC. Epithelial cells from AS patients actively induced differentiation of ILC3 from LTi.
Conclusions. Gut-derived ILC3 are differentiated and expanded in the synovial fluid and inflamed BM of AS patients and produce IL-17 and IL-22. The increased intestinal and BM expression of MADCAM-1 occurring in AS also suggests the presence of an active homing axis between the gut and the inflamed SI joints.

SO5

CALGRANULIN LEVELS ARE ELEVATED IN SPONDYLOARTHRITIS AND REFLECT THE PRESENCE OF ACUTE MICROSCOPIC GUT INFLAMMATION

Cypers H.[1], Varkas G.[1], Van Praet L.[1], Cuvelier C.[2], Roth J.[3], Vogl T.[3], Foell D.[4], Lavric M.[4], Van den Bosch F.[1], Elewaut D.[1]
[1]Dept. of Rheumatology, Ghent University Hospital, Ghent; [2]Dept. of Pathology, Ghent University Hospital, Ghent, Belgium; [3]Institut für Immunologie Westfälische Wilhelms-Universität Münster, Münster; [4]Klinik für Pädiatrische Rheumatologie und Immunologie, Westfälische Wilhelms-Universität Münster, Münster, Germany

Introduction. Microscopic gut inflammation is present in about 50% of spondyloarthritis (SpA) patients. Two types can be distinguished: an acute type resembling infectious enterocolitis, and a chronic type similar to early Crohn's disease. Although subclinical, microscopic gut inflammation appears to be a prognostic factor in SpA, linked with more extensive disease and a less favorable outcome. At this moment, however, reliable biomarkers are missing. The calgranulins S100A8/S100A9 and S100A12 are very sensitive markers of innate immune activation. They are released from monocytes and granulocytes in the early phase of the immune response and exert important pro-inflammatory effects via Toll-like receptor 4 dependent mechanisms. Calgranulins can be measured in serum and stool. Moreover, the S100A8/S100A9 heterodimer, also called calprotectin, has been established for a long time as a fecal marker of disease activity in inflammatory bowel disease.
Aim. To assess whether calgranulins can be used as biomarkers for microscopic gut inflammation in SpA.
Methods. Serum levels of calgranulins were measured in 103 newly diagnosed SpA patients and 24 healthy controls. Ninety-seven SpA patients underwent an ileocolonoscopy to assess the presence of microscopic gut inflammation. Ileal and colonic biopsies were histologically scored and subsequently immuno-stained for S100A8 and S100A9.
Results. Serum levels of S100A8/S100A9 and S100A12 were significantly higher in SpA patients versus healthy controls (p=0,035 and p=0,024). Levels correlated moderately with CRP, but not with ASDAS, BASDAI or swollen joint count. SpA patients with the acute type of microscopic gut inflammation (N=17) had significantly higher calgranulin levels compared to those with normal gut histology (N= 56) (p=0,021 and p=0,05). Furthermore, immunohistology showed high staining of S100A8 and S100A9 on acutely inflamed gut biopsies, compared to absent/minimal staining on normal biopsies. Chronically inflamed biopsies (N=24) stained positive only when they had high inflammatory activity (in ~ 50% of cases). Importantly, NSAID intake had neither influence on immunohistology stainings nor on serum levels of calgranulins.
Conclusion. Calgranulin levels, both systemically and locally, marked the presence of acute microscopic gut inflammation in SpA. These results illustrate their high sensitivity as they reflected inflammation present only on a microscopic level. Therefore we anticipate that they may be of particular value in detecting (or excluding) latent (systemic) disease.
Acknowledgements. The research leading to these results has received funding from the European Union's 7th Framework Program under EC-GA No. 305266 "MIAMI".

Poster Presentations

P1

INCIDENCE AND PREDICTORS OF MORPHOMETRIC VERTEBRAL FRACTURES IN PATIENTS WITH ANKYLOSING SPONDYLITIS

Kang K.Y.[1], Kim I.J.[2]
[1]Division of Rheumatology, Dept. of Internal Medicine, Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon; [2]Division of Rheumatology, Dept. of Internal Medicine, College of Medicine, Ewha Womans University, South Korea

Objectives. Ankylosing spondylitis (AS) is associated with an increased incidence of vertebral fractures (VFs); however, the actual incidence and predictors of morphometric VFs are unknown. The present study examined the incidence and predictors of new VFs in a large AS cohort.
Methods. Two hundred and ninety-eight AS patients who fulfilled the modified New York criteria were enrolled and spinal radiographs were evaluated biennially. Clinical and laboratory data and radiographic progression were assessed according to the BASDAI, ESR, CRP, and the Stoke AS spine score (SASSS). VF was defined according to the Genant criteria. The incidence of VFs at 2 years and 4 years was evaluated using the Kaplan-Meier method. The age-specific standardized prevalence ratio (SPR) for AS patients in comparison with the general population was calculated.
Results. Of 298 patients, 31 (10.8%) had previous VFs at baseline. Thirty new VFs occurred in 26 patients over 4 years. The incidence of morphometric VFs was 4.7% at 2 years and 13.6% at 4 years. Multivariate logistic regression analysis showed that previous VFs at baseline and increased CRP levels at 2 years were predictors of new VFs (OR =12.8, 95% CI = 3.6–45.3 and OR=5.4, 95% CI = 1.4–15.9). The age-specific SPR of morphometric VFs in AS was 3.3 (95% CI 2.1–4.5).
Conclusions. The incidence of morphometric VFs increased in AS. Previous VFs and increased CRP levels predicted future VFs. An appropriate anti-inflammatory therapy may prevent the incidence of new VFs in AS patients with and without previous VFs.

P2

THE PREDICTORS OF DEVELOPMENT OF NEW SYNDESMOPHYTES IN FEMALE PATIENTS WITH ANKYLOSING SPONDYLITIS

Kang K.Y.[1], Lim M.J.[2]
[1]Division of Rheumatology, Dept. of Internal Medicine, Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon; [2]Division of Rheumatology, Dept. of Internal Medicine, Inha University Hospital, Incheon, South Korea

Objectives. Formation of spinal syndesmophytes is an important outcome measure in ankylosing spondylitis (AS), but the predictors of new syndesmophyte development in female AS patients are unknown. This longitudinal study aimed to assess the rate and predictors of development of new syndesmophytes over a two-year period in female AS patients.
Methods. Clinical and radiographic data were collected at baseline and after 2 years in 67 female AS patients. Spinal radiographs were scored using the Stoke AS Spinal Score (SASSS). Univariate and multivariate logistic regression analyses were performed to identify predictors associated with new syndesmophyte development.
Results. Eleven (16%) patients had syndesmophytes at baseline. Nine (13.4%) patients had developed new syndesmophytes in their lumbar spines after 2 years. In the univariate analysis, older age, longer disease duration, severe sacroiliitis, elevated CRP (C-reactive protein) levels at baseline, and one or more pre-existing syndesmophytes were associated with the occurrence of new syndesmophytes. In the multivariate analysis, the presence of syndesmophytes at baseline (OR 20.4, p=0.022) and elevated CRP at baseline (≥1.0 mg/L; OR 14.1, p=0.041) were significant risk factors for the development of new syndesmophytes. After adjustment for baseline SASSS, increases in SASSS were statistically significantly higher in patients with elevated baseline CRP levels (p=0.002) than in patients with normal CRP at baseline.
Conclusion. The baseline presence of syndesmophytes and elevated levels of CRP are independent predictors of development of new syndesmophytes in female AS patients. Tight control of systemic inflammation could therefore decrease the rate of radiographic progression in these patients.

P3

POSITIVE CORRELATION OF URIC ACID AND BONE MINERAL DENSITY IN ANKYLOSING SPONDYLITIS

Kang K.Y.[1], Kim H.A.[2], Ju J.H.[1]
[1]Division of Rheumatology, Dept. of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul; [2]Division of Rheumatology, Dept. of Internal Medicine, Ajou University, Suwon, South Korea

Introduction. Uric acid (UA) has anti-osteoporotic effects in postmenopausal women. This study investigated the association between serum UA levels and bone mineral density (BMD) in young male patients with ankylosing spondylitis (AS).
Methods. One hundred fifty patients who fulfilled the modified New York criteria for the classification of AS were analyzed. All patients were male and under 50 years of age. BMD, serum UA concentrations, clinical parameters, and radiographic progression were assessed. The associations between UA and BMD at the lumbar spine and hip were evaluated using multiple linear regression analysis. Multivariate logistic regression analyses were performed to identify risk factors associated with low BMD.
Results: Mean serum UA concentration in the 150 patients with AS was 5.5±1.3 mg/dl. BMD at the lumbar spine, but not at the total hip and femoral neck, increased with increasing serum UA tertiles (p=0.033). The significant positive association between serum UA and BMD at the lumbar spine remained after adjustment for confounding factors (β=0.185, p=0.014, adjusted R^2=0.310). Multiple logistic regression analyses showed that lower UA concentrations (odds ratio: 4.02, 95% confidence interval: 1.34-12.3) and body mass index and increased erythrocyte sedimentation rate were independently associated with the risk of low BMD.
Conclusion. Lower serum UA levels are associated with lower BMD in young male patients with AS. UA may be a novel predictive marker or therapeutic target in patients with AS.

P4

EVALUATION OF EXTREME ENTHESITIS AND/OR PATIENT-RELATED OUTCOME SCORE AS POTENTIAL SURROGATES FOR FIBROMYALGIA AND AS POTENTIAL CONFOUNDING FACTORS OF ANTI-TNF RESPONSE

Dougados M.[1], Jones H.[2], Szumski A.[2], Logeart I.[3], Coindreau J.[4]
[1]Paris-Descartes University, Paris, France; [2]Pfizer, Collegeville, PA, USA; [3]Pfizer France, Paris, France; [4]Pfizer, New York, NY, USA

Introduction. Differentiating between pain related to spondyloarthritis (in particular polyenthesitis) and pain related to fibromyalgia can be challenging, both in daily practice and in clinical trials.
Some rheumatologists believe an "extreme" enthesitis and/or pain/BASDAI score may reflect a "fibromyalgia" disease. Additionally, depression is frequently observed in fibromyalgia patients, thus, an "extreme" enthesitis and/or pain/BASDAI score may correlate with an elevated depression score.
Aim. To conduct a post-hoc analysis of spondyloarthritis patients in order to: 1) estimate the percentage of patients with such "extreme" scores; 2) evaluate the relationship between "extreme" scores and depression; 3) evaluate the effect of baseline "extreme" scores on treatment outcome for etanercept and placebo.
Methods. *Patients:* participants in a randomized nr-axSpA clinical trial who received double-blind etanercept 50 mg or placebo weekly. Patients were divided into those who did vs. did not have extreme scores at baseline. *Definition of extreme baseline scores*: the highest quintile for enthesitis score (≥6), and/or scores ≥8 on 3 of 5 BASDAI items (morning stiffness duration was excluded).
Evaluation of depression: Hospital Anxiety and Depression Scale, depression subscale (HADS-D).
Treatment outcome: ASAS40 response rate at week 12.
Results. Of 213 patients at baseline, 35 (16%) met only enthesitis criteria, 31 (15%) met only BASDAI criteria, 12 (6%) met both, and 135 (63%) met neither. Patients with extreme enthesitis and/or BASDAI scores vs. those without were more likely to have moderate-severe depression at baseline: 20/68 (29%) vs. 10/118 (9%) of patients had HADS-D score >11 (p<0.001). For patients with vs. without extreme scores, no significant difference existed in week 12 ASAS40: etanercept 13/41 (32%) vs. 21/60 (35%); placebo 5/36 (14%) vs. 12/68 (18%).
Conclusion. Extreme enthesitis and/or BASDAI scores correlated with depression at baseline, but did not have an effect on week 12 ASAS40 in either the etanercept or placebo treatment group.

P5

QUALITY OF LIFE WITH ETANERCEPT IN EARLY NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

Sieper J.[1], Drescher E.[2], Rosa J.[3], Pedersen R.[4], Bonin R.[4], Vlahos B.[4], Bukowski J.F.[4], Kotak S.[5]
[1]Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Csolnoky Ferenc Hospital, Veszprem, Hungary; [3]Mediscan Group, Prague, Czech Republic; [4]Pfizer Inc, Collegeville, PA; [5]Pfizer Inc, New York, NY, USA

Introduction/Aim. Anti-TNF agents are recommended treatment for NSAID-resistant axial spondyloarthritis (axSpA). Long-term quality of life (QoL) data available in axSpA, prior to visible radiographic evidence (*i.e.*, non-radiographic [nr-axSpA]) are limited. To investigate long-term effects of etanercept (ETN) treatment on QoL in patients with nr-axSpA (who had an insufficient response to NSAID treatment).
Methods. Enrolled patients fulfilling ASAS axSpA criteria, not meeting the modified New York criteria for AS, who were symptomatic for 3 months–5 years, with BASDAI ≥4, and failed ≥2 NSAIDs, were randomized to ETN 50mg weekly or PBO (double blind) for 12 weeks followed by open-label ETN 50 mg. QoLs were recorded over a total of 48 weeks. Patients were allowed stable NSAID therapy throughout the study. Analyses used an ANCOVA model with baseline scores, treatment, and MRI sacroiliitis positive/negative status as variables.
Results. Of 208 participants who entered the open-label period (safety population; ETN=102; PBO=106) baseline mean age was 31.9 years; 60.6% were male, and mean disease duration was 2.5 years. By week 12, QoL improvements favoured ETN versus PBO in disease-specific, functional, and productivity domains such as BASDAI, BASFI, BAS-G, WPAI-AS, SF-36 physical component summary, and pain measures (p<0.05) (1). During the open label phase, substantial improvements from baseline at weeks 24 and 48 were observed regardless of original 12-week treatment arm (table).

Table. Improvement from baseline in QoL measures

	Baseline	Week 12[a]		Week 24[b]	Week 48[b]
Endpoint		ETN50/ETN50	PBO/ETN50	ETN50	ETN50
BASDAI (0-10)	6.0 (1.8)	3.5 (2.4) [–2.4 (0.2)]	4.3 (2.3) [–1.7 (0.2)]	2.9 (2.2) [–3.1 (0.2)]	2.5 (2.0) [–3.4 (0.2)]
BASFI (0-10 VAS)	4.0 (2.5)	2.6 (2.2) [–1.7 (0.2)]	3.0 (2.4) [–0.9 (0.2)]	2.2 (2.1) [–1.9 (0.2)]	1.8 (1.8) [–2.2 (0.2)]
EQ-5D (0-100 VAS)	56.4 (20.7)	67.4 (21.2) [10.3 (2.5)]	60.9 (22.3) [4.6 (2.2)]	71.4 (19.6) [15.0 (1.6)]	74.5 (16.0) [17.6 (1.7)]
EQ-5D utility score (0-1)	0.54 (0.32)	0.70 (0.26) [0.19 (0.04)]	0.67 (0.27) [0.08 (0.03)]	0.76 (0.21) [0.21 (0.02)]	0.78 (0.19) [0.23 (0.02)]
EQ-5D improvement ≥0.05 from baseline, n/N (%)	—	51/85 (60.0)	40/93 (43.0)	108/172 (62.8)	106/161 (65.8)
SF-36 (0-100) mental component physical component	42.9 (11.5) 37.5 (8.5)	45.8 (10.7) [3.6 (1.2)] 43.7 (8.9) [6.0 (0.8)]	45.7 (11.2) [2.2 (0.9)] 41.0 (7.8) [3.7 (0.7)]	47.2 (10.7) [4.0 (0.8) 44.5 (9.0) [7.0 (0.6)]	47.0 (10.9) [3.5 (0.8)] 45.8 (8.6) [8.3 (0.6)]
Nocturnal back pain (0-10 VAS)	5.5 (2.5)	3.0 (2.7) [–2.5 (3.2)]	4.1 (2.8) [–1.3 (0.3)]	2.4 (2.4) [–3.0 (0.2)]	2.1 (2.2) [–3.4 (0.2)]
Total back pain (0-10 VAS)	5.5 (2.4)	3.1 (2.6) [–2.4 (0.3)]	4.1 (2.6) [–1.4 (0.2)]	2.6 (2.5) [–2.8 (0.2)]	2.2 (2.2) [–3.2 (0.2)]
SGA (0-10 VAS)	5.8 (2.2)	3.3 (2.5) [–2.5 (0.3)]	4.3 (2.3) [–1.5 (0.2)]	2.7 (2.4) [–3.1 (0.2)]	2.3 (2.2) [–3.4 (0.2)]
WPAI-AS (0-100%) Absenteeism[c] (% work time missed) Presenteeism[c] (% impairment while working	10.4 (26.3) 43.6 (26.4)	9.6 (24.6) [1.2 (3.7)] 25.2 (24.2) [–18.1 (4.1)]	5.9 (17.4) [–6.3 (4.3)] 33.2 (26.0) [–7.0 (3.5)]	6.3 (20.2) [–4.1 (2.9)] 24.5 (24.6) [–17.6 (2.9)]	3.0 (13.9) [–5.6 (2.1)] 21.6 (20.8) [–19.4 (2.6)]

[a]Randomized treatment period (weeks 0-12). [b]All patients received ETN 50 mg weekly during the open-label period (weeks 12-48). [c]Employed patients only. All data observed case represented as: mean (SD) [Δ from baseline (SE)] unless otherwise indicated. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; ETN=etanercept, EQ-5D=EuroQoL 5 Dimensions; SF-36=36-item Short Form Health Survey; SGA=subject global assessment of disease; PBO=placebo; WPAI-AS=Work Productivity and Activity Index in ankylosing spondylitis; VAS=visual analog scale

Improvements with ETN treatment were sustained with little distinction between the groups receiving ETN for 12, 24 and 48 weeks.
Conclusions. In patients with early, active nr-axSpA and an inadequate response to ≥2 NSAIDs, ETN demonstrated improvement in QoL measures for disease specific and functional domains compared to PBO during the first 12 weeks.[1] Improvements in PROs were rapid and sustained after all patients were treated with ETN (weeks 12-48) and similar between original 12-week treatment groups.

Reference

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P6

SIRT-1 ACTIVITY IN PBMC FROM PATIENTS WITH SPONDYLOARTHRITIS - PRELIMINARY RESULT

Wendling D.[1,2], Delattre E.[1], Abbas W.[2], Guillot X.[1], Godfrin-Valnet M.[1], Khan K.A.[2], Toussirot E.[1,2], Baud L.[3], Prati C.[1], Herbein G.[2,3]
[1]Dept. of Rheumatology, University Teaching Hospital, CHRU, Besançon; [2]EA 4266, Université de Franche-Comté, Besançon; [3]Dept. of Virology, University Teaching Hospital, CHRU, Besançon, France

Sirtuin 1 (Sirt1) is a nuclear enzyme from the class III histone deacetylases (HDACs) modulating the expression of genes involved in the regulation of various biological processes.
The main objective of the study was to evaluate Sirt1 activity in peripheral blood mononuclear cells (PBMC) by venous blood aspiration in spondyloarthritis (SpA) patients, compared to control patients.
Methods. A prospective and comparative monocentric study was performed to compare the activity of Sirt1 in patients with SpA (according to ASAS criteria) and controls. Disease activity was assessed by BASDAI, ASDAS, ESR and CRP. PBMC were isolated from venous blood. Sirt1 activity was evaluated, using a fluorometric assay (SIRT1 fluorimetric kit, BML-AK-555, Enzo Life Sciences, Villeurbanne, France) at the 15 minutes point. Culture supernatant levels of TNF alpha, IL-6, IL-8 were quantified before and after resveratrol (1 µmol and 5 µmol) *ex vivo* treatment.
Results. Fourteen patients with SpA, and 18 age-matched controls were included. No differences were found in cytoplasmic or nuclear Sirt1 activity between patients and controls, as whole groups. Cytoplasmic and nuclear Sirt1 activities were correlated each other in patients and controls. Sirt1 activity (nuclear and cytoplasmic) was not correlated with disease activity. Sirt1 activity (cytoplasmic and nuclear) was higher in SpA patients treated with NSAIDs compared to patients without NSAIDs (p=0.005). Comparing patients and controls without NSAIDs, Sirt1 activity was significantly lower in SpA compared to controls, as well for cytoplasmic activity (p=0.01), as for nuclear activity (p=0.04). IL-6 levels at Baseline and after ex vivo treatment by resveratrol were higher in patients under NSAIDs (p=0.03).
Conclusion. Finally, our preliminary results may argue for a decrease in Sirt1 activity in non treated SpA patients compared to age-matched control subjects; NSAID treatment seems to erase this difference, and the impact of treatment upon epigenetics needs further investigation.

P7

COMPARISON OF THE DIFFERENT PAIN ASSESSMENT SCALES USED IN ADULT PATIENTS SEEN AT THE PHILIPPINE GENERAL HOSPITAL RHEUMATOLOGY OUT-PATIENT DEPARTMENT

Limgenco-Hipe J.R., Magbitang A.T., Salido E.O.
Section of Rheumatology, Dept. of Internal Medicine, Philippine General Hospital, Manila, Philippines

Introduction/Aim. Valid and reliable assessment of pain is essential in the management of rheumatologic conditions. Standardized pain assessment scales have been developed and used in clinical trials, but remain underutilized in clinical practice. We aim to evaluate the use of the different pain assessment scales: Numeric Rating Scale (NRS), Verbal Descriptive Scale (VDS), Visual Analog Scale (VAS) and Wong Baker Face Scale (FACES) among adult patients with musculoskeletal pain seen in a Rheumatology Out-patient Clinic in a tertiary government hospital in Metro Manila, Philippines.
Methods. This is a cross sectional study of adult patients with symptoms of musculoskeletal pain seen in a rheumatology out-patient clinic. We collected data on demographics and disease characteristics. The patients answered the different pain assessment scales and ranked them based on ease of use and preference. We checked for correlation of results of the different pain assessment scales using Spearman correlation.
Results. Ninety- four patients are included in this study. Eighty- one percent are females, with mean age of 52 (± SD 14.12) years old. Majority (73%) have low level of education. Forty-one percent have rheumatoid arthritis, 21% have osteoarthritis and 12% have gout. NRS is preferred and ranks easiest to use by 41.5% of patients. FACES is a close second; preferred by 39.4% and considered easy to use by 36.2% VAS ranks last on over-all preference and ease of use. On subgroup analysis, most male patients preferred the VDS while those with low education preferred FACES. The pain score obtained using NRS was significantly correlated with VDS, VAS, and FACES (p=<0.005).
Conclusion. The Numeric Rating Scale is a validated tool that is easy to use and preferred by patients. The Wong Baker Face Scale is a good alternative tool if the patient has difficulty with the NRS. We recommend the use of these pain scales in clinical practice in the Philippines to standardize the assessment and monitoring of pain among patients with rheumatic conditions.

P8

QUALITY OF LIFE OF PATIENTS WITH PSORIATIC ARTHRITIS MUTILANS - THE NORDIC PAM STUDY

Lindqvist U.[1], Gudbjornsson B.[2], Iversen L.[3], Paimela L.[4], Laasonen L.[5], Ejstrup L.[6], Ternowitz T.[7], Ståhle M.[8]
[1]Dept. of Medical Sciences, Uppsala University, Sweden; [2]Center for Rheumatology Research, University Hospital, Reykjavik, Iceland; [3]Dept. of Dermatology, Aarhus University Hospital, Denmark; [4]Helsinki University Central Hospital; [5]Helsinki Medical Imaging Center, Helsinki University Central Hospital, Helsinki, Finland; [6]Dept. of Rheumatology, Odense University Hospital, Denmark; [7]Dept. of Dermatology, Stavanger University Hospital, Norway; [8]Dermatology Unit, Dept. of Medicine, Karolinska Institute, Sweden

Introduction. Psoriatic arthritis mutilans (PAM) has an estimated low prevalence of three to five cases per million inhabitants in the Nordic countries as determined by the recent Nordic PAM study (1). Guidelines for assessment and needs are lacking and the total burden of disease is not known.
Objectives. To describe the social status and to assess the health related quality of life in patients with PAM in the Nordic countries.
Methods. Patients, with at least one verified mutilated joint on radiology, living in Denmark, Iceland, Norway and Sweden were included in the study. Patient´s education and work status was recorded. Short form 36 health survey questionnaire (SF-36), dermatology Life Quality Index (DLQI) questionnaire were obtained with disease duration, pain and general well-being (VAS) used as explanatory variables.
Results. Sixty-four patients were included, 30 from Sweden, 19 from Denmark, 12 from Norway and three patients from Island. Patients had a mean disease history of 33 years. Forty-two percent of the patients were retired or on sick leave. Reduced functional capacity with almost no ability to perform self-care or daily duties was reported by 21% of the participants.
Conclusion. PAM often has a substantial impact on social functions. Whether novel therapies will improve the disease outcome and its consequences on quality of life remains to be seen.

Reference

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P9

SLEEP QUALITY IN PATIENTS WITH PSORIATIC ARTHRITIS

Gezer O.[1], Batmaz İ.[1], Sariyildiz M.A.[1], Sula B.[2], Ucmak D.[2], Bozkurt M.[1], Nas K.[1]
[1]Division of Rheumatology, Dept. of Physical Medicine and Rehabilitation, Medical School, Dicle University, Diyarbakir; [2]Dept. of Dermatology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey

Aim. The purpose of this study was to determine the effects of Psoriatic arthritis (PsA) on sleep quality and investigate the association between sleep quality and clinical parameters of PsA, quality of life and psychological state in patients with PsA.
Patients and Methods. Forty-one patients with PsA and 38 healthy volunteers were included in this study. In both patients and healthy controls, sleep quality was assessed by means of Pittsburgh Sleep Quality Index (PSQI) and anxiety and depression were assessed by means of Hospital Anxiety and Depression Scale (HADS). In addition, PsA Quality of Life (PsAQoL) Index and Psoriasis Area and Severity Index (PASI) were used in patients. Generalised pain was assessed by means of Visual Analogue Scale (VAS).
Results. Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, daytime dysfunction and total PSQI scores were significantly higher in patients with PsA compared to healthy controls. Total PSQI scores significantly correlated with anxiety, generalised pain, PsAQoL scores, enthesitis and levels of CRP and ESR (p<0.05).
Conclusion. Sleep quality is diminished in patients with PsA. Sleep disturbance is particularly associated with generalised pain, anxiety, enthesitis and levels of CRP and ESR in patients carrying the diagnosis of PsA.

P10

SURVEY ON RECOGNITION AND MANAGEMENT OF INFLAMMATORY BACK PAIN AND SPONDYLOARTHRITIS, AND THEIR PROBLEMS AMONG THAI PHYSICIANS

Tangrungruengkit M., Chiowchanwisawakit P.
Dept. of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Introduction/Aim. To assess the diagnosis of inflammatory back pain (IBP) and spondyloarthritis (SpA), and their problems among Thai non-rheumatologist.
Materials and Methods. 2 versions questionnaire was developed, paper and online, using the same content. Paper questionnaires were sent to 330 doctors working at Siriraj Hospital (SH) and 400 doctors at non-SH workplace at a conference where SpA was not a lecture topic. Online questionnaires were emailed to 606 doctors working outside SH.
Results. Three hundred and twenty one (24%) respondents, divided into 3 groups: 48% were clinician1 included internal medicine doctors; 22% were clinician2 included orthopedists and physiatrists; 31% were clinician3 included other specialty. Regarding IBP according to the Assessment of SpondyloArthritis International Society criteria, 27.5%, 15.7%, and 14.3% of clinician1, 2, and 3, respectively recognized all characters with $p<0.001$. Giving a case with features of ankylosing spondylitis (AS), 64%, 59%, and 48% of clinician 1, 2, and 3, respectively made the right diagnosis with p 0.04. Regarding problems of SpA diagnosis, 60%, 25%, and 63%, and 40%, 22%, and 43% of clinician1, 2, and 3, respectively lacked confidence in musculoskeletal examination and radiography interpretation, respectively, with $p<0.05$. Moreover, 38%, 25%, and 65% of clinician1, 2, and 3, respectively lacked confidences to distinguish IBP from mechanical back pain.
Discussion. The proportion of clinician1 had the highest number in diagnosing IBP according ASAS criteria and AS than the others. It might be having rheumatologic education in the internal medicine program; however, there were still plenty of problems related SpA diagnosis.
Conclusions. There were some problems of diagnosis of patients with SpA in Thailand. The main problems were lack of knowledge of IBP and SpA, and confidence in physical examination and radiographic interpretation. Education may improve early detection of SpA.

P11

A PSYCHOMETRIC ANALYSIS OF OUTCOME MEASURES IN TRIALS OF PERIPHERAL SPONDYLOARTHRITIS

Turina M.[1], Ramiro S.[1], Baeten D.[1], Mease P.[2], Paramarta J.[1], Song I.H.[3], Pangan A.[4], Landewé R.[1]
[1]AMC/University of Amsterdam, Amsterdam, The Netherlands; [2]Swedish Medical Center & University of Washington, Seattle, USA; [3]AbbVie Germany; [4]AbbVie, North Chicago, USA

Aim. To assess discriminatory aspects of disease activity measures and response criteria between adalimumab (ADA) and placebo (PBO) in patients with peripheral spondyloarthritis (pSpA).
Methods. Data originated from 2 randomized trials of ADA vs PBO in patients with pSpA, ABILITY-2 and AMC. In ABILITY-2, the primary endpoint was PSpARC40 at wk12, defined as ≥40% improvement from baseline (≥20 mm absolute improvement on a VAS) in PGA-Disease Activity and Pain (PGA-pain) and ≥40% improvement in ≥1 of the following: SJC) and TJC; enthesitis count; dactylitis count. In AMC, the primary endpoint was change in PGA at wk12. Analyses included standardized mean difference (SMD) of mean change from baseline and Guyatt's effect size (ES) for continuous measures and Pearson's χ^2 (for categorical variables).
Results. ABILITY-2 and AMC enrolled 165 (ADA 84, PBO 81) and 40 (ADA 20, PBO 20) pts, respectively. Among continuous variables, ASDAS discriminates better than BASDAI or individual measures such as CRP (Table). PSpARC40, PSpARC50, ASDAS inactive disease and BASDAI50 performed well differentiating between treatment groups.
Conclusions: Composite indices (ASDAS and BASDAI) outperformed individual measures (TJC, SJC, CRP) in sensitivity to change and discriminatory properties. The PSpARC response criteria developed for pSpA, as well as ACR20 and ACR50, have good discriminatory ability in patients with pSpA.

Discrimination between adalimumab vs. placebo:

	ABILITY-2		AMC	
	SMD	Guyatt's ES	SMD	Guyatt's ES
ASDAS	-0.63	-1.18	-0.89	-1.90
BASDAI	-0.50	-0.976	-0.73	-1.26
PGA (0–100 mm VAS)	-0.47	-1.14	-1.12	-1.45
PhGA (0–100 mm VAS)	-0.64	-1.43	-0.87	-1.21
CRP (mg/L)	-0.18	-0.52	-0.53	-0.25
n (%)	Pearson's $\chi2$	p-value	Pearson's $\chi2$	p-value
PSpARC40	8.18	0.004	8.58	0.008
PSpARC50	13.46	<0.001	7.13	0.020
PSpARC70	13.49	<0.001	3.26	0.230
ASDAS Major Improvement	8.04	0.005	1.58	0.405
ASDAS Inactive Disease	7.2	0.007	10.13	0.003
BASDAI50	10.9	0.001	7.13	0.019

SMD: Standardized Mean Difference

P12

CHRONIC BACK PAIN (CBP) CHARACTERISTICS ASSOCIATED WITH THE PRESENCE OF SACROILIITIS ON MAGNETIC RESONANCE IMAGING (MRI) IN PATIENTS WITH SUSPECTED AXIAL SPONDYLOARTHRITIS (AXSPA): RESULTS FROM THE ESPERANZA COHORT

Navarro-Compán V.[1], Almodóvar R.[2], Hernández A.[3], Beltrán E.[4], de Miguel E.[1], Zarco P.[2], on behalf of EsPeranza Group
[1]Dept. Rheumatology, University Hospital La Paz, Madrid; [2]Dept. Rheumatology, Foundation University Hospital Alcorcón, Madrid; [3]Dept. Rheumatology, Hospital Virgen de la Salud, Toledo; [4]Dept. Rheumatology, University General Hospital of Valencia, Spain

Introduction. CBP is nowadays the starting point for the ASAS classification criteria for axSpA. Later, two possible entry criteria based on complementary examinations (imaging and HLA-B27) are considered. CBP is a very common, so it is necessary to identify those characteristics more likely resulting in a positive complementary test.
Aim. To evaluate which inflammatory characteristics of CBP are associated with the presence of sacroiliitis on MRI in patients with suspected axSpA.
Patients and Methods. Baseline dataset from EsPeranza cohort (<45 years, symptoms duration 3-24 months and inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was used. Data from 326 patients with axial symptoms who underwent sacroiliac joint (SIJ) MRI were analysed. Odds ratio were estimated for the association between IBP characteristics (morning stiffness, improve with exercise-not with rest, alternating buttock pain, insidious onset, awakening at 2nd half of night and good response to NSAID) and their different combinations with a positive SIJ MRI (ASAS definition).
Results. A total of 130 (40%) patients had sacroiliitis. Table shows the results for the association between the individual and combined IBP characteristics with a positive MRI. Alternating buttock pain (OR=3.43; $p<0.001$), insidious onset

Table. Association between each of CBP characteristic and the possible IBP definition with a positive SIJ MRI; $p<0.05$;**$p<0.001$

	Sacroiliitis positive (N=130)	Sacroiliitis negative (N=196)	Univariable analysis	Multivariable analysis	Diagnostic utility measures					
	N (%)	N (%)	OR	OR	Sen	Spe	PPV	NPV	LR+	LR-
Table 1A: Individual Characteristic of IBP										
Morn. Stiff > 30 min	89 (68.5)	106 (54.1)	1.84*	1.30	68.5	45.9	45.6	68.7	1.27	0.69
Improve with exercise, not with rest	41 (31.5)	56 (28.6)	1.15		31.5	71.4	42.3	61.1	1.10	0.04
Alter. buttock pain	62 (47.7)	36 (18.4)	4.05**	3.43**	47.7	81.6	63.3	70.2	2.59	0.64
Insidious onset	114 (87.7)	142 (72.4)	2.71**	2.15*	87.7	27.6	44.5	77.1	1.21	0.44
Awake 2nd half night	84 (64.6)	85 (43.4)	2.39**	1.71*	64.6	56.6	49.7	70.7	1.49	0.63
Response to NSAIDs	90 (69.2)	110 (56.1)	1.76*	1.32	69.2	43.9	45.0	68.3	1.23	0.70
Table 1B: Combination of IBP characteristics										
Calin criteria	67 (51.5)	57 (29.1)	2.59**	-	51.5	70.9	54.0	68.8	1.77	0.68
Berlin criteria	94 (72.3)	97 (49.5)	2.67**	-	72.3	50.5	49.2	73.3	1.46	0.55
ASAS criteria	62 (47.7)	45 (23.0)	3.06**	-	47.7	77.0	57.9	68.9	1.45	0.67
Night + Insidious + Buttock (2/3)	52 (40.0)	41 (20.9)	2.52**	-	71.5	59.2	53.8	75.8	1.75	0.48
Night + Insidious + Buttock (3/3)	89 (68.5)	81 (41.3)	3.08**	-	33.8	92.3	74.6	67.8	4.39	0.72

(OR=2.15; $p<0.05$) and awakening at 2nd half of the night (OR=1.71; $p<0.05$) were associated with sacroiliitis. The combination of these characteristics or the addition of alternating buttock pain to the ASAS definition of IBP were the most specific (OR=3.08; $p<0.001$;Spe 92% and OR=6.17; $p<0.001$;Spe 94%, respectively).
Conclusions. Alternating buttock pain is the IBP characteristic most strongly associated with a positive SIJ MRI in patients with suspected axSpA. The inclusion of this characteristic in the current definition of IBP could improve the efficiency of SIJ MRI.
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P13

DIKKOPF-1 (DKK-1) SERUM LEVELS IN AXIAL SPNDYLOARTHRITIS (AXSPA) ARE RELATED TO DISEASE DURATION

Navarro-Compán V.[1], Melguizo-Madrid E.[2], González-Rodríguez C.[2], Navarro-Sarabia F.[3], Ariza-Ariza R.[3]
[1]Dept. of Rheumatology, University Hospital La Paz, Madrid; [2]Dept. of Biochemistry, University Hospital Virgen Macarena, Sevilla; [3]Dept. of Rheumatology, University Hospital Virgen Macarena, Sevilla, Spain

Introduction. Tumor necrosis factor (TNF) alpha is responsible for induction of dkk-1 which down-regulates bone formation. Therefore, it was expected that TNF-blocker therapy would inhibit radiographic progression in patients with axSpA but this effect has not been observed yet. Nevertheless, most of the studies have included patients with long disease duration and it is unknown whether or not this effect would be the same in patients with an early stage of the disease.
Aim. To investigate if disease duration influences on the serum levels of dkk-1 in patients with axSpA.
Patients and Methods. Observational study including consecutive patients with axSpA according to ASAS criteria visiting a tertiary hospital between January 2011 and June 2013. All patients were receiving NSAIDs and none of them was under biologic therapy. The following characteristics were recorded at one visit: Demographic (age, gender), symptoms duration, HLA-B27, disease activity indices (BASDAI, CRP, ESR) and function (BASFI). Blood samples to determine dkk-1 serum levels by enzyme immunoassay were collected at the same visit too. Patients were classified as early axSpA (symptoms duration ≤5 years) and established axSpA (>5 years) and the characteristics enumerated above were compared between both groups. Univariate and multivariate linear regression models were employed to identify the characteristics related to dkk-1 serum levels.
Results. Thirty-one patients with early axSpA and 21 patients with established disease were included. Patients with early axSpA were younger (32.6±9.3 vs 41.0±10.2 years; $p<0.01$), had lower degree of disease activity (BASDAI: 4.6±2.7 vs 6.6±1.9; $p<0.01$ and ESR: 7.7±9.2 vs 18.1±15 mmHg; $p<0.05$) and worst function (3.2±2.9 vs 5.8±2.5; $p<0.01$) compared with patients with established disease. Serum levels of dkk-1 were significantly higher in patients with early disease (25.9±11.5 vs 13.9±13.5; $p<0.001$ ng/dl). No statistically significant differences were found between both groups for the rest of characteristics. In the univariable analysis, symptoms duration and BASDAI were inversely related to dkk-1 levels (std β: -0.435; $p<0.01$ and Std β: -0.283; $p<0.05$, respectively). However, only the relationship with symptoms duration remained statistically significant in the multivariable analysis (std β: -0.415; $p<0.01$).
Conclusions. Serum Dkk-1 levels in patients with axSpA depend on disease duration, being higher in patients with recent onset of the disease. The effect of TNF-blocker therapy on radiographic progression may be different in patients with an early stage of the disease compared with patients with established disease.
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P14

AXIAL DISEASE IN PSORIATIC ARTHRITIS (ADIPSA) STUDY: PREVALENCE AND CHARACTERISTICS OF INFLAMMATORY AXIAL DISEASE IN PSORIATIC ARTHRITIS

Jadon D.R.[1], Sengupta R.[1], Nightingale A.[2], Korendowych E.[1], Lindsay M.[2], McHugh N.J.[1,2]
[1]Rheumatology, Royal National Hospital For Rheumatic Diseases, Bath; [2]Pharmacy & Pharmacology, University of Bath, Bath, UK

Introduction/Aim. To determine the prevalence and characteristics of inflammatory axial disease in psoriatic arthritis (PsA) compared with ankylosing spondylitis (AS).
Materials/Methods. A prospective cross-sectional study was conducted of unselected consecutive patients attending dedicated PsA and AS outpatient clinics in a teaching hospital. All cases completed patient-reported outcome measure questionnaires, clinical examination, and interview regarding inflammatory musculoskeletal and extra-articular manifestations. Univariate analyses were performed using Chi^2 and Mann-Whitney-U tests as appropriate.
Results. 201 PsA and 201 AS patients completed the study. Median age at assessment was 59.4 for PsA and 55.1 years for AS cases ($p=0.001$). A history of psoriasis was present in 96.5% PsA compared with 22.4% AS cases ($p<0.0001$). A history of inflammatory axial symptoms was present in 60.7% PsA cases, especially in the neck (43.8%; compared with 84.1% of AS cases; $p<0.001$) and lumbar (44.3%) spine. Current inflammatory axial symptoms were present in 44.3% PsA compared with 75.6% AS cases (OR 0.256; $p<0.0001$).
The following were poorer in AS compared with PsA: BASFI (median 3.9 *vs*. 3.0, respectively; $p=0.027$); BASMI (median 3.0 *vs*. 2.0, respectively; $p<0.0001$); back pain at night score (median 3.0 *vs*. 2.0, respectively; $p<0.003$); tragus-to-wall distance (median 14.7 *vs*. 11.2cm, respectively; $p<0.0001$); lumbar side-flexion (median 10.3 *vs*. 12.3cm; p=0.005); modified Schober (median 4.5 *vs*. 6.0cm; $p<0.0001$); cervical rotation (median 52.5 *vs*. 62.5degrees; $p=0.009$); chest expansion (median 4.2cm *vs*. 5.5cm; $p<0.0001$). AS and PsA cases were statistically no different in terms of BASDAI, back pain at anytime score, patient global assessment of disease activity and inter-malleolar distance.
Discussion. Inflammatory axial symptoms were common in this unselected PsA cohort, especially in the cervical and lumbar spine. Whilst less than in AS, PsA cases had significant impairment of BASFI, BASMI and metrology.
Conclusions. Inflammatory axial disease in PsA may be more prevalent than previously reported.

P15

EVALUATION OF THE NONSTEROIDAL ANTI-INFLAMMATORY DRUG-SPARING EFFECT OF ETANERCEPT IN AXIAL SPONDYLOARTHRITIS: RESULTS OF THE MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SPARSE TRIAL

Dougados M.[1], Wood E.[2], Combe B.[3], Miceli-Richard C.[4], Berenbaum F.[5], Koppiker N.[6], Dubanchet A.[7], Logeart I.[7]
[1]Rheumatology, Paris-Descartes University, Hôpital Cochin, Paris, France; [2]Statistical Consultancy, Quanticate, UK; [3]Rheumatology, Lapeyronie Hospital, Montpellier I University, Montpellier; [4]Rheumatology, Hôpital de Bicêtre, Paris-Sud University, Paris; [5]Rheumatology, University of Paris, Saint-Antoine Hospital, Paris, France; [6]Pfizer PGRD, Sandwich, UK; [7]Pfizer, Paris, France

Introduction/Aim. NSAIDs are first-line pharmacotherapy in axial spondyloarthritis (axSpA) but are recommended for use at the lowest effective dose for the shortest possible time due to safety concerns. The SPARSE trial was conducted to assess the effects of etanercept (ETN) on NSAID intake as measured by the ASAS-NSAID score and conventional clinical outcomes in axSpA.
Patients and Methods. In the initial 8-week, double-blind (DB), placebo (PBO)-controlled period, patients with active (mini BASDAI ≥4) axSpA despite optimal NSAID intake were randomised to ETN 50 mg or PBO once weekly for 8 weeks. All patients were advised to taper/stop their NSAID intake during the study treatment period. Completers were eligible for ETN 50 mg in the subsequent 8-week open-label (OL) period.
Results. In 90 randomised patients at BL, mean age (±SD) was 38.9±11.8 years; disease duration, 5.7±8.1 years; 62% were male; 66% were HLA-B27 positive; and 50% were MRI sacroiliitis positive. A between-group difference in changes in ASAS-NSAID scores of -27.3 ($p=0.002$) favouring ETN was observed at week 8 (ANCOVA). Significantly more patients in the ETN vs PBO group were NSAID-free (48% vs 20%; $p<0.01$) and achieved BASDAI50 (39% vs 18%; $p<0.05$) and ASAS40 (44% vs 21%; $p<0.05$) at week 8 (logistic regression). Significant reductions in ASAS-NSAID scores were seen in the ETN/ETN group

from BL to week 16 (–65.9; $p<0.0001$) and in the PBO/ETN group from week 8 to 16 (–39.2; $p<0.0001$); response rates increased in the ETN/ETN and PBO/ETN groups for most clinical endpoints in the OL period.
Conclusions. In this population of patients with axSpA, etanercept was associated with clinically relevant NSAID-sparing effects and significant improvements in conventional clinical outcomes.

P16

CHANGE OVER TIME IN THE PROFILE OF ANKYLOSING SPONDYLITIS PATIENTS TREATED WITH INFLIXIMAB IN CANADIAN ROUTINE CARE

Choquette D.[1], Starr M.[2], Khraishi M.[3], Bensen W.G.[4], Shaikh S.[4], Rodrigues J.[5], Sholter D.[6], Sheriff M.[7], Vaillancourt J.[8], Sampalis J.S.[8], Lehman A.J.[9], Otawa S.[9], Nantel F.[9], Shawi M.[9]
[1]Institut de Rhumatologie de Montréal, Montreal, QC; [2]Montreal General Hospital, Montreal, QC; [3]Memorial University of Newfoundland, St. John's, NL; [4]McMaster University, Hamilton, ON; [5]Windsor, ON; [6]University of Alberta, Edmonton, Alberta; [7]Nanaimo Regional General Hospital, Nanaimo, BC; [8]JSS Medical Research, Montreal, QC; [9]Janssen, Toronto, ON, Canada

Introduction/Aim. The objective of this study was to describe and compare over time the demographics and disease parameters at infliximab (IFX) treatment initiation and to assess the effectiveness of treatment at 6 months in Canadian ankylosing spondylitis (AS) patients.
Methods. AS patients treated with infliximab who were enrolled in the BioTRAC registry between 2002 and 2013 were included in this analysis (N=303) and stratified to two groups (2005-2007: n=135; 2008-2013: n=168) based on the year of enrolment in the registry.
Results. Patient demographics were comparable with a mean (SD) age of 45.72 (11.74) years and the majority being males (62.4%). A significant change in the geographic distribution was observed (p=0.001) and more patients with provincial coverage were enrolled in 2008-2013 (p=0.012). A trend towards earlier initiation was observed in more recent years as indicated by the shorter disease duration (11.12 vs. 8.24 years; p=0.013) and lower disease activity: ESR (29.96 vs. 19.91 mm/hr; $p<0.001$), MDGA (6.99 vs. 6.26; p=0.001) were significantly lower in the 2008-2013 cohort while a statistical trend was observed in morning stiffness (78.96 vs. 70.11 minutes; p=0.064) and ASDAS (3.90 vs. 3.70; p=0.103). Treatment for 6 months resulted in a greater proportion of patients in the 2008-2013 cohort achieving inactive disease (ASDAS<1.3) without reaching statistical significance (20.7% vs. 34.9%; p=0.140).
Conclusions. The profile of the AS patient population in the BioTRAC registry changed over time towards lower disease activity and earlier initiation of IFX. 6-month treatment with IFX was effective in reducing disease activity.

P17

ASSESSING TREATMENT DURABILITY OF INFLIXIMAB IN THE MANAGEMENT OF PSORIATIC ARTHRITIS PATIENTS IN A CANADIAN SETTING

Kelsall J.[1], Jovaisas A.[2], Rahman P.[3], Sholter D.[4], Starr M.[5], Bensen W.[6], Sheriff M.[7], Olszynski W.[8], Zummer M.[9], Faraawi R.[6], Chow A.[10], Kapur S.[11], Rampakakis E.[12], Sampalis J.S.[12], Nantel F.[13], Otawa S.[13], Shawi M.[13], Lehman A.J.[13]
[1]Mary Pack Arthritis Centre, Vancouver, BC; [2]University of Ottawa, Ottawa, ON; [3]Memorial University of Newfoundland, St. John's, NL; [4]University of Alberta, Edmonton, AB; [5]Montreal General Hospital, Montreal, QC; [6]McMaster University, Hamilton, ON; [7]Nanaimo Regional General Hospital, Nanaimo, BC; [8]University of Saskatchewan, Saskatoon, SK; [9]Université de Montréal Montreal, QC; [10]Credit Valley Rheumatology, Mississauga, ON; [11]University of Ottawa, ON; [12]JSS Medical Research, Montreal, QC; [13]Janssen Inc. Toronto, ON, Canada

Introduction. The objective of this analysis was to assess in routine clinical practice the durability of treatment with infliximab (IFX) in PsA and the determinants associated with sustainability of IFX.
Method. BioTRAC is an ongoing, prospective registry of rheumatology patients initiating treatment with IFX or golimumab as first biologics or after having been treated for <6 months. A total of 92 PsA Patients who were enrolled between 2005 and 2012 were included. Dose optimization was defined as an increase in the frequency and/or dosing of IFX. Kaplan Meier estimates and Cox proportional models were used.
Results. Mean (SD) age was 48.7 (9.9) years and mean (SD) duration was 6.8 (9.1) years. Twenty seven (29.3%) patients discontinued treatment. Overall mean (SE) duration of treatment was 41.4 (3.6) months. Longer treatment duration was associated with significantly greater improvements in pain (-0.21, p=0.020), PtGA (-0.35, $p<0.001$) and HAQ (-0.01, $p<0.001$). Significant associations with duration of treatment were observed for disease duration (HR=1.04), previous biologic (HR=2.10), baseline TJC28 (HR=1.10), baseline PASI (HR=0.86) and concomitant use of DMARD(s) (HR=0.16) or NSAID(s) (HR=0.38).
Conclusions. The results of this observational study have shown a high durability of treatment with IFX for patients with PsA in a real-world setting. Concomitant medication use significantly impacts treatment durability. Longer disease duration, higher TJC, less severe skin disease at initiation and previous biologic use may be associated with reduced treatment durability.

P18

HOW SHOULD WE CALCULATE THE ASDAS IF THE CONVENTIONAL C-REACTIVE PROTEIN IS BELOW THE LIMIT OF DETECTION? AN ANALYSIS IN THE DESIR COHORT

Machado P.[1,2], Navarro-Compán V.[1,3], Landewé R.[4,5], van Gaalen F.A.[1], van der Heijde D.[1]
[1]Leiden University Medical Center, Leiden, The Netherlands; [2]Coimbra University Hospital, Coimbra, Portugal; [3]University Hospital La Paz, Madrid, Spain; [4]Amsterdam; [5]Heerlen, The Netherlands

Introduction. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritis. It was suggested that when the conventional CRP (cCRP) is below the limit of detection, and high sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate ASDAS-CRP. However, this recommendation was not data driven and requires further testing and validation.
Aims. Our aims were to investigate the most appropriate ASDAS-CRP calculation method when the cCRP is below the limit of detection, to study the arithmetic influence of low hsCRP values in ASDAS results and to test agreement between different ASDAS formulae.
Methods. Baseline data from the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort was used. Patients with axial spondyloarthritis and cCRP below the limit of detection (5mg/L, n=257) were selected. ASDAS-cCRP was calculated using eleven imputation strategies for the cCRP (range 0-5, at 0.5 intervals). Agreement between ASDAS formulae was tested.
Results. ASDAS-CRP(1.5), ASDAS-CRP(2) and ASDAS-erythrocyte sedimentation rate (ESR) had better agreement with ASDAS-hsCRP than other imputed formulae (table). Disagreement was mainly in lower disease activity states (inactive/moderate disease activity). When the hsCRP value is <2mg/L, the CRP component of the ASDAS-CRP formula can take very low values that may result in inappropriately low ASDAS-CRP values.

Table. Agreement between ASDAS-hsCRP and other ASDAS formulae (ASDAS-cCRP with multiple imputation strategies and ASDAS-ESR).

ASDAS formulae	ASDAS-hsCRP			
	ASDAS values		ASDAS disease activity states	
	ICC (95% CI)	Mean difference (95%CI)	Weighted kappa (95%CI)	Disagreement (%)
ASDAS-CRP(0)	0.78 (-0.06 to 0.94)	-0.52 (-1.02 to -0.03)	0.51 (0.44 to 0.57)	46.7%
ASDAS-CRP(0.5)	0.89 (0.33 to 0.96)	-0.29 (-0.79 to 0.21)	0.73 (0.67 to 0.79)	25.0%
ASDAS-CRP(1)	0.94 (0.89 to 0.96)	-0.12 (-0.62 to 0.38)	0.73 (0.67 to 0.79)	24.4%
ASDAS-CRP(1.5)	0.95 (0.93 to 0.96)	0.01 (-0.49 to 0.51)	0.75 (0.69 to 0.81)	21.9%
ASDAS-CRP(2)	0.94 (0.90 to 0.96)	0.11 (-0.38 to 0.61)	0.76 (0.70 to 0.81)	21.8%
ASDAS-CRP(2.5)	0.92 (0.70 to 0.96)	0.20 (-0.29 to 0.70)	0.71 (0.65 to 0.77)	25.3%
ASDAS-CRP(3)	0.89 (0.37 to 0.96)	0.28 (-0.22 to 0.78)	0.66 (0.60 to 0.73)	29.1%
ASDAS-CRP(3.5)	0.86 (0.11 to 0.96)	0.35 (-0.15 to 0.85)	0.64 (0.58 to 0.70)	31.6%
ASDAS-CRP(4)	0.83 (0.00 to 0.95)	0.41 (-0.09 to 0.91)	0.61 (0.54 to 0.67)	4.3%
ASDAS-CRP(4.5)	0.81 (-0.04 to 0.94)	0.47 (-0.03 to 0.96)	0.59 (0.53 to 0.65)	35.8%
ASDAS-CRP(5)	0.78 (-0.06 to 0.94)	0.52 (0.02 to 1.01)	0.50 (0.44 to 0.57)	43.6%
ASDAS-ESR	0.91 (0.85 to 0.94)	0.13 (-0.52 to 0.79)	0.69 (0.63 to 0.76)	8.1%

Conclusion: When the cCRP is below the limit of detection, the value of 2mg/L should be used to calculate ASDAS-CRP. When hsCRP values are below 2mg/L, the value of 2mg/L should be used to calculate ASDAS-CRP. There is good agreement between ASDAS-hsCRP and ASDAS-ESR; however, formulae are not interchangeable.

P19

DO NOT UNDERESTMINATE PROBLEMS IN WORK PARTICIPATION IN RECENTLY DIAGNOSED SPONDYLOARTHRITIS PATIENTS

Van der Weijden M.A.C.[1,2], Boonen A.[3], Van der Horst-Bruinsma I.E.[1,2]
[1]VU University Medical Center, Dept. of Rheumatology, Amsterdam; [2]Reade, Dept. of Rheumatology, Amsterdam; [3]Maastricht University Medical Center, Dept. of Internal Medicine, Division of Rheumatology and Caphri research institute, Maastricht, The Netherlands

Aim. To explore the impact of early SpA on worker participation and to investigate variables associated with work outcomes as well as the impact on resource utilisation.
Methods. Patients included in an Early SpA cohort completed a questionnaire comprising questions on employment status, sick leave, presenteeism and resource utilisation. Logistic regressions were used to investigate the associations between work status and clinical characteristics, and between productivity loss and clinical characteristics. Resource utilisation across patient groups with different employment status was investigated with univariate analyses.
Results. 140 patients participated in this study of which 96% was male, mean age of 41 years and disease duration of 4.8 years. Twenty-six patients (19%) were not employed due to SpA. Among 114 employed patients, sick leave was reported in 28% in the previous year (Table). Forty-one percent of the patients reported reduced productivity at work. Multivariable regression analyses showed that high BASMI and ASQoL were associated with work loss, ASQoL was associated with reduced productivity. Annual costs of productivity loss due to sick leave and presenteeism mounted to €2000 per patient. Patients who report sick leave, are work disabled or experience problems at work, report more visits to health professionals, need more help in daily activities and adjustments at home.
Conclusion. After only 5 years of diagnosis, a considerable proportion of SpA patients is not employed and those working have substantial sick leave and productivity loss. Among patients reporting sick leave, problems at work or work disability, resource utilisation is higher. Alertness to work participation even in patients with a short disease duration is urgently needed.

Table. Sick leave and presenteeism in working early SpA patients

Sick leave	N=114
Sick leave[a]	32 (28)
Number of days of sick leave[c], (per year)	4.0 (3.0-12.8)
Cost of sick leave[c*], (€/patient/year)	0.0 (0.0-263.0)
Quantity and Quality method	
Quantity*Quality[b], (0-100%)	84.7 (23.7)
At-work productivity loss[c], (hours/year)	30.4 (0.0-347.8)
Costs of at-work productivity loss[c*], (€/patient/year)	991.0 (0.0 - 10,591.0)
Costs of productivity loss and sick leave[c*], (€/patient/year)	1,983.0 (0.0 - 10,591.0)

[a]number (%), [b]mean (SD), [c]median (IQR), *measured over N=140.

P20

COMPARISON OF THE TWO SUBTYPES OF AXIAL SPONDYLOARTHRITIS PATIENTS FULFILLING THE IMAGING ARM BASED ON RADIOGRAPHIC AND MRI FINDINGS

Solmaz D., Cetin P., Sari I., Birlik M., Onen F., Akkoç N.
Dokuz Eylul University School of Medicine, Dept. of Internal Medicine, Division of Rheumatology, Izmir, Turkey

Introduction. New AxialSpondyloarthritis Classification Criteria include an imaging arm and a clinical arm. The imaging arm includes radiographic ax-SpA patients who have radiographic sacroilitis according to modified New York criteria and non-radiographic (nr) ax-SpA patients who have sacroiliitis only by MRI. Although there is no doubt that radiographic and non-radiographic axSpA have many overlapping features, it is one of the hot topics of discussion whether they are different entities.
Objectives. To compare the demographics and clinical characteristics between the radiographic and nr-axSpA patients fulfilling the criteria of the imaging arm.
Patients and Methods. A local database has been used since December 2008 to register patients fulfilling the imaging arm of AxSpA classification criteria. Data related to demographics, clinical features, disease activity, functional status, treatment were recorded.
Results. 720 patients who met the study criteria were identified. Radiographic sacroiliitis according to modified New York criteria was present in 533 patients. The remaining 187 patients were classified as nr-axSpA based on MRI findings. Demographics and clinical characteristics are summarized in Table 1. Patients with nr-axSpA had an earlier onset of symptoms and were more often females. Prevalence of extra spinal manifestations was similar in both groups, except for anterior uveitis, which was more frequently reported by the patients with radiographic axSpA. C-reactive protein levels were significantly higher in patients with radiographic sacroiliitis as compared to those with nr-AxSpA. HLA-B27 prevalence was numerically greater among patients with radiographic axSpA, but was not statistically significant. Disease activity measured by BASDAI, but not by ASDAS, was higher in the nr-axSpA group; BASFI scores were similar in both groups. BASMI score was higher in radiographic ax-SpA patients.
Conclusion. Although manydemographic and clinical features are similar between the ax-SpA patients with and without radiographic sacroiliitis classified with the imaging arm, differences such as higher prevalence of females and numerically lower prevalence of HLA-B27 among with patients with nr-axSpA are of interest.

Table I. Demographics and clinical characteristics of the radiographic and non-radiographic axSpA patients.

Demographic and clinical features	Radiographic sacroiliitis (n:533)	Non-radiographic sacroiliitis (n:187)	*p*
Age, mean ± SD	43 ± 12.0	42 ± 13.2	0.232
Male sex n,%	395, 74.1	72, 38.5	<0.001
Age at beginning of the symptoms, mean ± SD	25 ± 9.1	28 ± 10.3	0.010
Diagnostic delay, mean ± SD	8 ± 8.5	7 ± 8.0	0.023
Arthritis n,(%)	195, (36.6)	42, (22.5)	0.491
Hip replacement n,(%)	23, (4.3)	0	0.023
Anterior uveitis n,%	97, (18.2)	10, (5.3)	0.007
Psoriasis n,%	16, (3.0)	4, (2.1)	0.399
IBD n,%	16, (3.0)	2, (1.0)	0.082
HLA B27 positivity n1/n2(%)	166/243 (68.3)	46.3 % (36/78)	0.146
CRP mg/dl, mean ± SD	19.0 ± 25.6	9.5 ±17.1	<0.001
BASDAI, mean ± SD	3.5 ± 2.2	4.3 ± 2.5	<0.001
ASDAS-CRP, mean ± SD	2.9 ±1.1	2.1 ±1.1	0.223
BASFI, mean ± SD	2.9 ±2.6	2.7 ±2.5	0.346
BASMI, mean ± SD	3.9 ±1.9	2.3 ±1.0	<0.001
SSZ, n, (%)	132, (24.2)	21, (11.2)	0.316
MTX, n, (%)	34, (6.3)	4, (2.1)	0.317
Anti TNF, n,(%)	103, (19.3)	8, (4.2)	<0.001

P21

WHICH CHRONIC BACK PAIN (CBP) CHARACTERISTICS ARE ASSOCIATED WITH A POSITIVE HLA-B27 IN PATIENTS WITH SUSPECTED AXIAL SPONDYLOARTHRITIS (AXSPA)? RESULTS FROM THE ESPERANZA COHORT

Navarro-Compán V.[1], Aznar J.J.[2], Linares L.F.[3], Collantes-Estevez E.[4], Zarco P.[5], on behalf of EsPeranza Group
[1]Dept. Rheumatology, University Hospital La Paz, Madrid; [2]Mérida Hospital, Mérida; [3]University Hospital Virgen de la Arrixaca, Murcia; [4]IMIBIC/University Hospital Reina Sofía, Córdoba; [5]Foundation University Hospital Alcorcón, Madrid, Spain

Introduction. CBP is nowadays the starting point for the ASAS classification criteria for axSpA. Later, two possible entry criteria based on complementary examinations (imaging and HLA-B27) are considered. CBP is a very common, so it is necessary to identify those characteristics more likely resulting in a positive complementary test.
Aim. To evaluate which inflammatory characteristics of CBP are associated with the presence of HLA-B27 in patients with suspected axSpA.
Patients and Methods. Baseline dataset from EsPeranza cohort (<45 yrs, symptoms duration 3-24 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was used. Data from 653 patients with axial symptoms and HLA-B27 assessed were analysed. Odds ratio were estimated for the association between IBP characteristics (morning stiffness, improve with exercise and not with rest, alternating buttock pain, insidious onset, awakening at 2nd half of night and good response to NSAIDs) and their different combinations with a positive HLA-B27.
Results. A total of 270 (41%) patients were HLA-B27+. Table shows results for the association between individual and combined IBP characteristics with HLA-B27+. Awakening at 2nd half of night (OR=1.53; $p<0.05$) and response to NSAID (OR=1.46; $p<0.05$) were the only characteristics independently associated with HLA-B27+ but had lower specificity than the existing IBP criteria. The

addition of these two characteristics to these criteria just improved their specificity slightly. The ASAS criteria were the most strongly associated with HLA-B27 and the most specific.

Conclusions. Awakening at second half of night and good response to NSAIDs are both related to positive HLA-B27 in patients with suspected axSpA although they are less specific than the existing criteria to define IBP. The most specific criteria for a positive HLA-B27 are the ASAS criteria.

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Table. Association between each of CBP characteristic and the possible IBP definition with a positive HLA-B27; *p<0.1;**p<0.05;***p<0.01.

	HLA-B27 + N=270	HLA-B27 - N=383	Univariable analysis	Multivariable analysis	Diagnostic utility measures					
	N (%)	N (%)	OR	OR	Sen	Spe	PPV	NPV	LR+	LR-
Table 1A: Individual Characteristic of IBP										
Morn. Stiff > 30 min	171 (63.3)	216 (56.4)	1.34*	1.10	63.3	43.6	44.2	62.8	1.12	0.84
Improve with exercise, not with rest	91 (33.7)	114 (29.8)	1.20		33.7	70.2	44.4	60.0	1.13	0.94
Alter. buttock pain	86 (31.9)	110 (28.7)	1.16		31.9	71.3	43.9	59.7	1.11	0.96
Insidious onset	184 (68.1)	241 (62.9)	1.26		68.1	37.1	43.3	62.3	1.08	0.86
Awakening 2nd half night	149 (55.2)	163 (42.6)	1.66***	1.53**	55.2	57.4	47.8	64.5	1.30	0.78
Response to NSAIDs	182 (67.4)	217 (56.7)	1.58***	1.46**	67.4	43.3	45.6	65.4	1.19	0.75
Table 1B: Combination of IBP characteristics										
Calin criteria	98 (36.1)	99 (25.8)	1.63**	-	36.3	74.2	49.7	62.3	1.41	0.86
Berlin criteria	173 (64.1)	194 (50.7)	1.74**	-	64.1	49.3	47.1	66.1	1.26	0.73
ASAS criteria	85 (31.5)	74 (19.3)	1.92***	-	31.5	80.7	53.5	62.3	1.63	0.85
Night + NSAID response (2/2)	108 (40)	109 (28.5)	1.68**	-	40.0	71.5	49.8	62.8	1.40	0.84
Calin + Night + NSAID response (6/7)	58 (21.5)	45 (11.7)	2.06**	-	21.5	88.3	56.3	61.5	1.84	0.89

P22

PREVALENCE OF SELF-REPORTED DEPRESSION IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

Meirinhos T., Aguiar R., Ambrósio C., Barcelos A.
Rheumatology Unit, Centro Hospitalar do Baixo Vouga E.P.E., Aveiro, Portugal

Introduction. Axial Spondyloarthritis (aSpA) are chronic inflammatory rheumatic diseases often conditioning a negative impact on quality of life and social relationships and leading to depressive symptoms. Depression is associated with worse disease control, poor adherence, and increases the risk of death and suicide. Thus, assessment and early identification of depression is essential for the control and treatment of these patients.
The Beck Depression Inventory II (BDI-II) allows the evaluation of depressive symptoms as well as physical symptoms.

Objectives. To assess the rates of depression in a group of patients with aSpA as well as possible correlations with disease activity and function.

Methods. Cross-sectional case-control study. A convenient sample of patients diagnosed with aSpA according to the ASAS criteria attending a Rheumatology department as outpatients, was recruited. The control group consisted of 40 healthy individuals recruited from the group of friends of the researchers.
Collected data included age, sex, education, disease activity and function. Depression status were assessed in both groups by BDI-II questionnaire. Statistical analysis was performed using SPSS version 17.0® and significance was set at 0.05.

Results. 38 patients were enrolled (25 men and 13 women), mean age was 45.3±14.9 years. Mean BASDAI was 3.81±2.42 and BASFI 3.57±2.8. The mean BDI-II was 12.05±8.2, which corresponds to mild to moderate depression. In our sample, both higher BASDAI and BASFI values, correlate to higher values of BDI-II (p<0.001). There were no statistically significant differences in depression rates regarding gender and education. The BDI-II values were higher in patients compared to controls (p<0.001).

Conclusion. The results from this study show that a significant proportion of our patients have values of "mild to moderate" depression, directly related to disease activity and function, and higher than the control group of healthy individuals. This suggests that an optimal care of aSpA patients should include the detection and management of depression.

P23

UTILITY OF ENTHESITIS ASSESSMENTS IN PERIPHERAL SPONDYLOARTHRITIS – DATA FROM THE ABILITY-2 TRIAL

Mease P.[1], Van den Bosch F.[2], Baeten D.[3], Sieper J.[4], Song I.H.[5], Karunaratne P.[6], Pangan A.[6]
[1]Swedish Medical Center and University of Washington, Seattle, USA; [2]Ghent University Hospital, Ghent, Belgium; [3]AMC/University of Amsterdam, Amsterdam, The Netherlands; [4]Charité Universitätsmedizin Berlin, Berlin; [5]AbbVie Deutschland, Ludwigshafen, Germany; [6]AbbVie, North Chicago, USA

Aim. To evaluate enthesitis tools in peripheral spondyloarthritis (pSpA).

Methods. ABILITY-2 is a multicenter phase 3 study. Eligible patients were age ≥18 years, fulfilled ASAS pSpA criteria, and had active disease. Patients were randomized to adalimumab (ADA) or placebo (PBO) every other week for 12 weeks followed by a 144-week open-label extension. 29 enthesitis sites based on Leeds, SPARCC and MASES scores were assessed through week104.
Remission was defined as enthesitis score = 0 during follow-up among patients having baseline score ≥1.

Results. 165 pts (ADA 84/PBO 81) were randomized. At baseline (BL) 143 (87%) had ≥1 enthesitis site. Of those with ≥1 positive enthesitis site, Leeds score was ≥1 in 72.0%, SPARCC in 90.2%, and MASES in 86.0%. Mean BL scores for patients receiving ADA vs. PBO were 2.4 vs. 2.3 for Leeds, 5.0 vs. 5.1 for SPARCC, and 4.5 vs. 4.5 for MASES among those with a BL score ≥1 for the respective indices. Question 4 of BASDAI showed mean values (±SD) of 6.2 (±2.3) in pts with ≥1 enthesitis sites at BL (n=143) vs. 5.3 (±2.3) for those without (n=22) and thus was unable to discriminate between these sub-groups. Leeds did better than SPARCC or MASES in discriminating ADA-treated pts from PBO-treated at week12.

Enthesitis Indices at Week 12*	ADA	PBO
Leeds		
Mean % change	-68.4%	-20.7%
% in enthesitis remission	60.8%	27.5%
SPARCC		
Mean % change	-50.0%	-15.1%
% in enthesitis remission	33.3%	20.0%
MASES		
Mean % change	-32.1%	-27.5%
% in enthesitis remission	31.6%	30.8%

Observed data analysis; *Among patients with BL score ≥1 for the respective enthesitis indices.

Conclusions. In ABILITY-2, Leeds and SPARCC enthesitis tools had better discriminatory capacity than MASES for the effect of adalimumab in pSpA patients.

P24

HIGH DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS PATIENTS REDUCES WORK PRODUCTIVITY

van Hoeven L.[1,2], Boonen A.[3], Hazes J.M.W.[1], Weel A.E.A.M.[1,2]
[1]Rheumatology, Erasmus MC, Rotterdam; [2]Rheumatology, Maasstad Hospital, Rotterdam; [3]Rheumatology, Maastricht UMC, Maastricht, The Netherlands

Introduction/Aim. Axial spondyloarthritis (axSpA) affects patients in various ways, including work participation. Little is known about the relationship between work participation and disease activity. The disease activity of axSpA can be measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or Ankylosing Spondylitis Disease Activity Score (ASDAS). Our aim is to examine the relationship between work participation and disease activity in axSpA patients.

Material and Methods. Patients (18-45 years) fulfilling the ASAS axSpA criteria (n=95) of the CaFaSpA 2 study (a cohort of primary care patients identified with axSpA) are used in this analysis. Disease activity was measured by BASDAI and ASDAS. BASDAI score >4 was scored as high disease activity. ASDAS was divided in four subgroups: inactive (<1.3), moderate (1.3-2.1), high (2.1-3.5) and very high disease activity (>3.5). Work participation in the past 7 days was measured using the Work Productivity and Activity Impairment (WPAI) questionnaire. Four sub scores (all percentages) can be derived; absenteeism (health related inability to work), presenteeism (health related reduction in work productivity), work impairment (combines absenteeism and presenteeism) and impairment in activities performed outside of work. Higher percentages indicates worse outcomes.

To evaluate the relationship between the BASDAI and work productivity, Mann-Whitney test was used.
For ASDAS and work productivity Kruskal-Wallis test was used.
Results. In total 95 axSpA patients participated, (38% male, mean age 37 years). Mean BASDAI was 4.2, mean ASDAS 2.4. Mean activity impairment in all patients was 34.5%. Most patients (n=70; 74%) were employed. In the working population absenteeism was 5.5%, presenteeism was 23.9% and work impairment was 27.4%. There was a difference in all work sub scores between low and high BASDAI score, but only the difference in work impairment (19.2 vs 39.5, $p<0.03$) was significant. By an increasing ASDAS score, presenteeism ($p<0.02$), work impairment ($p<0.02$) and activity impairment ($p<0.02$) significantly increases.
Conclusions. Increased disease activity is associated with reduced work productivity in axSpA patients. The ASDAS score discriminates better in work productivity than the BASDAI.

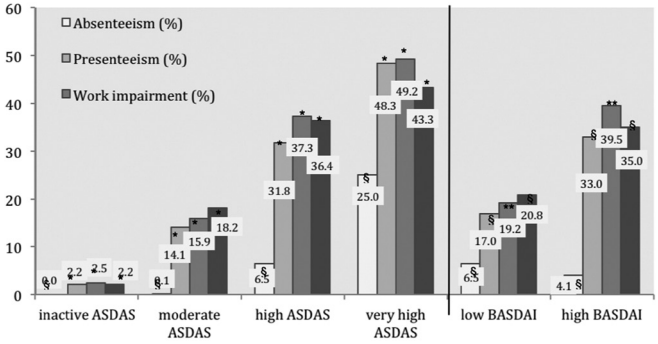

Fig. 1. Relationship between disease activity and work productivity in axSpA patients (n=95).
*$p<0.02$, **$p<0.03$, §$p>0.05$

Table I. Characteristics in employed axSpA patients (n=70).

	ASDAS inactive n=9	ASDAS moderate n=22	ASDAS high n=33	ASDAS very high n=6	BASDAI low n=40	BASDAI high n=30
Sex (male), n (%)	3 (33.3)	11 (50.0)	13 (39.4)	1 (16.7)	18 (45.0)	10 (33.3)
Age, years (sd)	35.4 (7.1)	38.2 (6.0)	36.1 (7.6)	36.2 (4.5)	36.0 (7.5)	37.6 (5.8)
Low back pain duration, years (sd)	6.7 (3.9)	10.9 (9.2)	9.6 (7.6)	8.5 (8.3)	9.2 (7.8)	10.0 (7.9)

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P25

WHAT IS THE OPTIMAL STRATEGY TO REFER POSSIBLE AXIAL SPONDYLOARTHRITIS PATIENTS FROM PRIMARY CARE TO THE RHEUMATOLOGIST?

van Hoeven L.[1,2], Vergouwe Y.[3], Hazes J.M.W.[1], Weel A.E.A.M.[1,2]
[1]Rheumatology, Erasmus MC, Rotterdam; [2]Rheumatology, Maasstadziekenhuis, Rotterdam; [3]Public Health, Erasmus MC, Rotterdam, The Netherlands

Introduction/Aim. Recognizing axial spondyloarthritis (axSpA) in primary care is difficult. To support general practitioners several referral models for axSpA are proposed. However, most of them are tested in preselected patients, resulting in too optimistic results. Furthermore, most models include diagnostic tools that are unfeasible and costly to use in primary care. Our aim is to test in an unselected chronic low back pain (CLBP) population which axSpA features are most valuable and to assess how many features should be present for referring.
Methods. All CLBP (>3 months) primary care patients (18-45 years) of the two CaFaSpA studies were analysed. AxSpA features were inflammatory back pain (IBP), arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to NSAIDs, family history for SpA, elevated CRP and HLA-B27. Classification as axSpA by the ASAS criteria was used as reference standard. Features were associated with axSpA as outcome variable by logistic regression. Performance of the referral was measured by sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (LR+).
Results. 941 patients participated, (42% male, mean age 36 years). 181 (19%) patients were diagnosed as axSpA. HLA-B27 had the highest odds ratio, followed by IBP, good response to NSAIDs, elevated CRP and family history (Table I). Table II shows performance by number of present features.
Conclusions. In this large, unselected CLBP population HLA-B27, IBP, response to NSAIDs, CRP and family history are the most valuable features, however it is questionable if the costly HLA-B27 test is always accessible in primary care. By referring patients on the presence of only one present feature, 71% of those referred patients will undergo unnecessary diagnostic work up. Therefore, we recommend to use in primary care a referral strategy consisting of features that are easy to use and without additional costs. Such as a combination of IBP, good response to NSAIDs and family history for SpA.

Table I. Logistic regression of axSpA features (n=941).

AxSpA feature	Odds ratio	*p*-value	95% confidence interval
IBP	*2.9*	*<0.001*	*2.0-4.1*
Arthritis	1.0	0.9	0.5-1.7
Enthesitis	0.6	0.1	0.3-1.2
Dactylitis	1.9	0.2	0.8-4.6
Psoriasis	0.6	0.3	0.3-1.5
Crohn's/colitis	1.0	1.0	0.3-3.4
Uveitis	1.3	0.6	0.5-3.4
Good response to NSAIDs	*2.7*	*<0.001*	*1.8-3.9*
Family history for SpA	*2.3*	*<0.001*	*1.4-3.9*
Elevated CRP	*2.4*	*0.009*	*1.2-4.7*
HLA-B27	*13.2*	*<0.001*	*6.9-25.2*

Table II. Performance of referral of CLBP patient based on the number of axSpA features present.

Number of axSpA features	Sensitivity	Specificity	PPV	LR+
≥1	1.0	0.29	0.34	1.4
≥2	0.64	0.66	0.31	1.9
≥3	0.27	0.89	0.36	2.5
≥4	0.12	0.97	0.46	4.0
≥5	0.04	0.99	0.42	4.0

Acknowledgement. This study was supported by an unrestricted research grant from AbbVie.

P26

THREE-YEAR COURSE AND PREDICTION OF PHYSICAL FUNCTIONING AND SPINAL MOBILITY IN ANKYLOSING SPONDYLITIS PATIENTS TREATED WITH TNF-INHIBITORS

van Weely S.F.E.[1], Kneepkens E.L.[1], Nurmohamed M.T.[1], Dekker J.[1,2], van der Horst-Bruinsma I.E.[3]
[1]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam; [2]VU University Medical Centre, Dept. of Rehabilitation Medicine, EMGO Institute and Dept. of Psychiatry, Amsterdam; [3]VU University Medical Centre, Dept. of Rheumatology Amsterdam, The Netherlands

Introduction/Aim. Currently, only limited information is available on the long-term course of limitations in physical functioning and spinal mobility in Ankylosing Spondylitis (AS) patients receiving TNF inhibiting (TNFi) therapy in daily clinical care. Therefore this study aimed (i) to examine the 3-years course of physical functioning and spinal mobility impairments in patients routinely treated with TNFi; (ii) to predict the 3-years level and (iii) to predict the 3-years course of physical functioning and spinal mobility.
Methods. AS patients eligible for TNFi were followed in a prospective observational cohort for 3 years. Prediction models were developed with linear mixed modelling using 18 baseline variables. BASFI and BASMI were used as outcome measures for physical functioning and spinal mobility, respectively.
Results. At baseline 257 patients were included and treated with etanercept (n=174) or adalimumab (n=83). Physical functioning improved significantly during the first 24 weeks after the start of TNFi. The BASFI score decreased from 5.4±2.4 to 3.3±2.6 in week 24, and stabilised thereafter (BASFI 3-years 3.6±2.5; see figure-1). The BASMI showed a stable course over time. Lower baseline BASFI and BASMI-scores predicted a better physical functioning and spinal mobility after 3-years of TNFi therapy.
Other predictors for a higher 3-years level and better 3-years course of physical functioning included absence of comorbidity, physical activity, younger age and lower BMI at baseline. However, large between-patient variations were observed.
Conclusions. Improvement of physical functioning in TNFi treated AS patients continues up to 24-weeks and stabilises thereafter. Therefore, the efficacy of treatment should be determined at 6 months. Predictors for the level and course of physical functioning and spinal mobility after 3-years of TNFi treatment include baseline BASFI, BASMI, absence of comorbidity, physical activity and BMI.

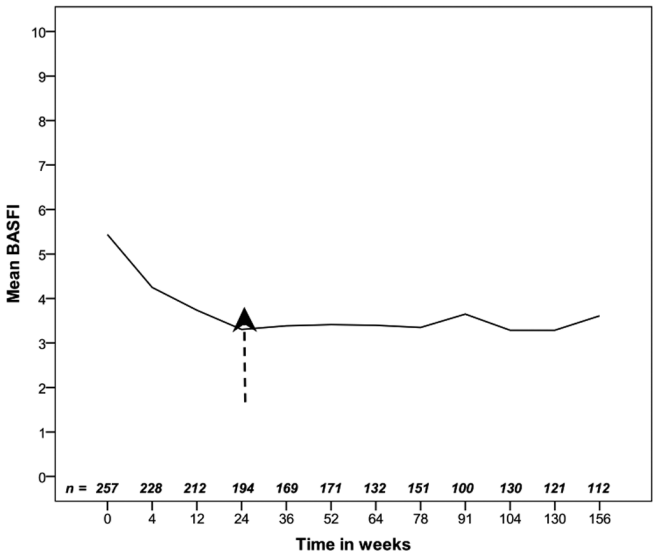

Fig. 1. Course of physical function (BASFI) during 3-years follow-up in TNFi treated AS patients.

P27

RAPID3 IN 90 KOREAN PATIENTS WITH ANKYLOSING SPONDYLITIS YIELDS SIMILAR INFORMATION TO BASDAI AND ASDAS, WITH GREATER FEASIBILITY FOR BUSY CLINICAL SETTINGS

Choe J.Y., Kim S.K., Lee H.
Catholic University of Daegu School of Medicine, Daegu, Korea

Background. The BASDAI is a self-report index to assess disease activity in patients with AS. The ASDAS is recorded by the rheumatologist, based on the ASAS core data set of 11 measures in 7 domains. These quantitative measures are invaluable in clinical trials and clinical research, but are difficult to administer in busy clinical care settings. An MDHAQ/RAPID3 is easily completed by all patients prior to seeing a rheumatologist, and has been found an informative in patients with rheumatic diseases.
Objectives. To compare scores on 3 indices, BASDAI, ASDAS and RAPID3 in 90 Korean patients with AS seen in a usual care setting.
Methods. All patients complete an MDHAQ/RAPID3 in this setting. Patients with AS complete a BASDAI, and have ASDAS assessed by a rheumatologist. Indices and individual measures were compared using Spearman correlation coefficients, cross-tabulations, and kappa statistics.
Results. Ninety AS patients were studied; median age was 39.1 years, median duration of disease 7.0 years, and 76.7% were male. RAPID3 scores were correlated significantly with BASDAI (rho=0.751) and ASDAS (rho=0.690), as well as with individual BASDAI and ASDAS scores for spinal pain, spinal stiffness, fatigue, Bath AS Functional Index (BASFI) physical function (rho >0.66) (all p <0.001).

Cross-tabulations of numbers of 90 patients in different disease activity/severity categories according to 3 indices: RAPID3, BASDAI and ASDAS.

RAPID3 (0-30 scale)		BASDAI		ASDAS	
Severity category	N	Inactive (<4)	Active (≥4)	Inactive (<1.3)	Active (≥1.3)
Remission (0-3)	20	20	0	17	3
Low (3.1-6)	17	17	0	8	9
Moderate (6.1-12)	14	14	0	6	8
High (>12)	39	18	21	3	36
Total	90	69	21	34	56

Conclusions. RAPID3 provides similar information to BASDAI and ASDAS. BASDAI and ASDAS are more specific for clinical trials and clinical research, but the feasibility of MDHAQ/RAPID3 in busy clinical settings suggests possible value in usual clinical care of patients with AS.

P28

WORK PRODUCTIVITY IN EMPLOYED PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH ETANERCEPT

Boonen A.[1], Boone C.[2], Boon T.[2], Albert A.[3], Mielants H.[4]
[1]Dept. of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, Netherlands and Caphri Research Institute Maastricht University, The Netherlands; [2]Medical Dept., Pfizer, Brussels; [3]Dept. of Public Health, University of Liège; [4]Dept. of Rheumatology, Ghent University, Belgium

Aim. The primary outcome was to determine the evolution of presenteeism and absenteeism in patients with ankylosing spondylitis (AS) receiving etanercept (ETN) over 24 months.
Materials and Methods. This was a prospective, open-label, observational study undertaken in clinical practices in Belgium. In order to be eligible, patients had to be diagnosed with AS, in paid employment, and prescribed ETN by their physician. Patients completed the Work Productivity and Impairment for AS (WPAI-AS) questionnaire and the scores were used to measure presenteeism (% impairment while working due to AS) and absenteeism (% work time missed due to AS). Absenteeism and presenteeism time-related data were analyzed by a generalized linear mixed model in those completing the study.
Results. 80 patients were included in the study and 75 (93.8%) started ETN treatment and had ≥1 follow-up visit. At entry into the cohort, the distribution between males and females was equal, the mean age was 38.1 years (SD 9.1), and the mean disease duration (symptoms) was 10.8 years (SD 8.8). A total of 57 (76.0%) patients were seen after 24 months: 52 (89.5%) of these continued to receive ETN therapy and 47 (83.9%) of these patients were still employed. Presenteeism decreased significantly (p<0.0001) from 49.1% (95% CI 42.9, 55.3) at baseline (n=55) to 24.9% (95% CI 18.4, 31.3) at 24 months (n=41). Absenteeism also decreased significantly (p<0.0001) from 30.2% (95% CI 20.3, 40.1) at baseline (n=67) to 6.3% (95% CI –0.7, 13.4) at 24 months (n=41).
Conclusions. In Belgian clinical practice, the majority of patients with AS remained on ETN treatment and in employment over 24 months and both their presenteeism and absenteeism were dramatically reduced during this period.

P29

LONG-TERM SAFETY AND EFFICACY OF CERTOLIZUMAB PEGOL IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS: 96-WEEK OUTCOMES OF THE RAPID-AXSPA TRIAL

Sieper J.[1], Rudwaleit M.[2], van der Heijde D.[3], Maksymowych W.P.[4], Dougados M.[5], Mease P.J.[6], Reveille J.[7], Braun J.[8], Deodhar A.[9], Arledge T.[10], Nurminen T.[11], Landewé R.[12]
[1]Rheumatology Dept., University Hospital Charité, Berlin; [2]Endokrinologikum, Berlin, Germany; [3]Dept. of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands; [4]Dept. of Medicine, University of Alberta, Edmonton, Canada; [5]Dept. of Rheumatology, Cochin Hospital, Paris, France; [6]Swedish Medical Center and University of Washington, Seattle; [7]Division of Rheumatology, University of Texas Health Science Center at Houston, Houston, USA; [8]Rheumazentrum Ruhrgebiet, Herne, Germany; [9]Oregon Health & Science University, Portland; [10]UCB Pharma, Raleigh, USA; [11]UCB Pharma, Monheim, Germany; [12]Academic Medical Center, Amsterdam and Atrium Medical Center, Heerlen, The Netherlands

Introduction. Previous reports of RAPID-axSpA (NCT01087762) demonstrated efficacy and safety of certolizumab pegol (CZP) to Week (Wk) 48 in patients with axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA.
Aim. To report efficacy and safety of CZP from a 96-wk interim data-cut of RAPID-axSpA.
Patients and Methods. RAPID-axSpA was double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label to Wk204. Patients fulfilled ASAS criteria and had active axSpA. We present efficacy data for patients originally randomized to CZP (combined doses [200mg Q2W/400mg Q4W]), and enriched subpopulations (baseline enthesitis [MASES], SJC, TJC). Observed and imputed data are shown (categorical measures: NRI; continuous measures: LOCF). Safety set consists of patients treated with ≥1 CZP-dose.
Results. 218 patients were randomized to CZP at Wk0, 93% completed Wk24, 88% Wk48 and 80% Wk96. Improvements in ASAS and ASDAS responses, BASDAI, BASFI, BASMI-linear, enthesitis, SJC and TJC were maintained from Wk24 through Wk96 (Table). Similar improvements were seen with both dosing regimens and both AS and nr-axSpA subpopulations. In the safety set (N=315) adverse events occurred in 279 patients (88.6%) and serious adverse events in 41 (13.0%). No deaths or malignancies were reported.
Conclusion. Rapid improvements in both CZP dosing regimens, and AS and nr-axSpA patients, were sustained to Wk96. The safety profile was in line with previous reports from RAPID-axSpA.

Table: Maintenance of CZP efficacy to Week 96 of the RAPID-axSpA trial

Outcome	Combined CZP 200mg Q2W + 400mg Q4W								
	axSpA (n=218)			AS (n=121)			nr-axSpA (n=97)		
	Wk24 (NRI)	Wk96 (NRI)	Wk96[a] (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96[b] (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96[c] (OC)
ASAS20 (%)	67.4	62.8	82.0	66.9	64.5	83.9	68.0	60.8	79.7
ASAS40 (%)	50.9	50.5	65.9	51.2	50.4	65.6	50.5	50.5	66.2
ASAS PR (%)	30.3	28.4	37.1	28.1	24.8	32.3	33.0	33.0	43.2
BASDAI50 (%)	52.3	47.7	60.8	48.8	46.3	57.7	56.7	49.5	64.9
	Baseline (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)	Baseline (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)	Baseline (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)
ASDAS (mean)	3.8	2.1	2.0	3.9	2.1	2.0	3.8	2.0	1.9
ASDAS MI (%)	-	42.2	49.5	-	42.1	51.2	-	42.3	47.4
ASDAS ID (%)	-	30.3	33.9	-	27.3	30.6	-	34.0	38.1
BASDAI (mean)	6.4	3.3	3.0	6.4	3.4	3.1	6.6	3.3	3.0
BASFI (mean)	5.3	3.0	2.7	5.6	3.3	3.0	5.0	2.6	2.4
BASMI-lin (mean)	3.8	3.2	3.1	4.2	3.6	3.6	3.2	2.6	2.5
MASES[d] (mean)	5.1	2.3	1.8	4.7	1.7	1.1	5.6	2.9	2.4
SJC[e] (mean)	4.2	1.5	0.9	4.0	1.7	1.2	4.5	1.2	0.5
TJC[f] (mean)	6.3	3.6	2.5	5.9	3.0	2.7	6.8	4.3	2.3

[a]n=167; [b]n=93; [c]n=74;[d]patients with baseline enthesitis in ≥1 enthesial site (axSpA: n=148; AS: n=78; nr-axSpA: n=70); [e]patients with baseline SJC ≥1 (axSpA: n=76; AS: n=42; nr-axSpA: n=34); [f]patients with baseline TJC ≥1 (axSpA: n=138; AS: n=74; nr-axSpA N=64). LOCF: Last Observation Carried Forward; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; NRI: Non-Responder Imputation; OC: Observed Case

P30

DISEASE ACTIVITY AND CLINICAL RESPONSE EARLY IN THE COURSE OF TREATMENT PREDICTS LONG-TERM OUTCOMES IN AXIAL SPONDYLOARTHRITIS AND PSORIATIC ARTHRITIS PATIENTS TREATED WITH CERTOLIZUMAB PEGOL

van der Heijde D.[1], Deodhar A.[2], Fleischmann R.[3], Rudwaleit M.[4], Davies O.[5], Nurminen T.[6], Mease P.J.[7]
[1]Leiden University Medical Centre, Leiden, The Netherlands; [2]Oregon Health & Science University, Portland; [3]University of Texas SW Medical Center, Texas, USA; [4]Endokrinologikum, Berlin, Germany; [5]UCB Pharma, Slough, UK; [6]UCB Pharma, Monheim, Germany; [7]Swedish Medical Center and University of Washington, Seattle, USA

Introduction. Early identification of patients unlikely to achieve good long-term disease control by anti-TNF therapy in axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) has not been thoroughly investigated.
Aim. To assess the association between disease activity (DA) or clinical response (CR) during the first 12 weeks (wks) of treatment, and attainment of treatment targets at Wk48 in axSpA and PsA patients receiving certolizumab pegol (CZP).
Patients and Methods. The relationship between DA and CR during the first 12 wks of treatment, and ASDAS inactive disease (ID) [axSpA], or Minimal Disease Activity (minDA) [PsA] at Wk48, was assessed post hoc using data from the RAPID-axSpA (NCT01087762) and RAPID-PsA (NCT01087788) trials. DA was defined using ASDAS-ID, moderate (MD), high (HD) or very high (vHD) DA [axSpA] and DAS28(CRP)<2.6, 2.6–3.2, 3.2–5.1, and >5.1 [PsA]. Analyses were based on patients randomized to CZP. LOCF was applied for missing Wk48 evaluations.
Results. A clear relationship between DA from Wk2 to Wk12 and Wk48 treatment target was observed in both axSpA and PsA populations. 68% (34/50) of axSpA patients with ID at Wk12 achieved Wk48 ID, and 0% (0/21) of patients with vHD at Wk12 achieved ID at Wk48 (Table A). 73% (57/78) of PsA patients with DAS28(CRP)<2.6 at Wk12 achieved minDA at Wk48, and 0% (0/26) of patients with DAS28(CRP)>5.1 at Wk12 achieved minDA at Wk48 (Table B). CR also predicted Wk48 outcomes, but to a lesser extent than DA.

Table A: axSpA: Likelihood of achieving ASDAS ID at Week 48 based on ASDAS classification of disease activity at Baseline, Week 2, Week 8 and Week 12

Visit	ASDAS ID n/N (%)	ASDAS MD n/N (%)	ASDAS HD n/N (%)	ASDAS vHD n/N (%)
Baseline	0/0	1/3 (33.3%)	32/70 (45.7%)	34/145 (23.4%)
Week 2	22/31 (71.0%)	30/59 (50.8%)	15/100 (15.0%)	0/27
Week 8	35/49 (71.4%)	22/57 (38.6%)	10/89 (11.2%)	0/20
Week 12	34/50 (68.0%)	20/54 (37.0%)	13/86 (15.1%)	0/21

Table B: PsA: Likelihood of achieving minDA at Week 48 based on DAS28 classification of disease activity at Baseline, Week 2, Week 8 and Week 12

Visit	DAS28(CRP) <2.6 n/N (%)	DAS28(CRP) 2.6–3.2 n/N (%)	DAS28(CRP) 3.2–5.1 n/N (%)	DAS28(CRP) >5.1 n/N (%)
Baseline	1/1 (100.0%)	2/6 (33.3%)	64/145 (44.1%)	32/120 (26.7%)
Week 2	17/25 (68.0%)	22/34 (64.7%)	55/159 (34.6%)	5/52 (9.6%)
Week 8	50/71 (70.4%)	23/38 (60.5%)	25/114 (21.9%)	1/39 (2.6%)
Week 12	57/78 (73.1%)	23/47 (48.9%)	19/105 (18.1%)	0/26

Colors represent probability:	White: >20%	Light grey: 10–20%	Dark grey: 0–10%

Conclusions. Using DA and CR state during the first 12 wks of CZP treatment, it was possible to identify subsets of axSpA and PsA patients unlikely to achieve long-term treatment goals.

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LONG-TERM SAFETY AND EFFICACY OF CERTOLIZUMAB PEGOL IN PATIENTS WITH PSORIATIC ARTHRITIS WITH AND WITHOUT PRIOR ANTI-TUMOR NECROSIS FACTOR EXPOSURE: 96-WEEK OUTCOMES OF THE RAPID-PSA TRIAL

Mease P.J.[1], Fleischmann R.[2], Wollenhaupt J.[3], Deodhar A.[4], Gladman D.[5], Arledge T.[6], Peterson L.[6], van der Heijde D.[7]
[1]Swedish Medical Center and University of Washington, Seattle; [2]University of Texas SW Medical Center, Dallas, USA; [3]Schön Klinik, Hamburg, Germany; [4]Oregon Health & Science University, Portland, USA; [5]Toronto Western Research Institute, Toronto, Canada; [6]UCB Pharma, Raleigh, USA; [7]Leiden University Medical Centre, Leiden, The Netherlands

Introduction. Previous reports of RAPID-PsA (NCT01087788) demonstrated efficacy and safety of certolizumab pegol (CZP) over 48 weeks (wks) in psoriatic arthritis (PsA) patients, including patients with prior anti-TNF therapy.
Aims. To report the efficacy and safety of CZP from a 96-wk interim data cut of RAPID-PsA.
Patients and Methods. RAPID-PsA is double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label to Wk216. Patients had active PsA and had failed ≥1 DMARD. We present efficacy data for patients originally randomized to CZP (combined dose regimens [200mg Q2W/400mg Q4W]) and in patients with/without prior anti-TNF exposure. Observed and imputed data are shown (categorical measures: NRI; continuous measures: LOCF). Safety set consists of all patients treated with ≥1 dose of CZP.
Results. 273 patients were randomized to CZP at Wk0, of these, 91% completed Wk24, 87% Wk48 and 80% Wk96. Improvements observed to Wk24 were maintained to Wk96, including ACR20/50/70 and Minimal Disease Activity (MDA) responses, PASI75/90 responses (in patients with ≥3% skin involvement at baseline [60.8%]), HAQ-DI and pain (Table). In the safety set (N=393) adverse events occurred in 345 patients (87.8%) and serious adverse events in 67 (17.0%). 6 deaths were reported to Wk96 (2 cardiac disorders, 1 sudden death, 1 infection, 1 breast cancer and 1 lymphoma).
Conclusions. The efficacy of CZP was maintained through both the dose-blind and open-label phases of RAPID-PsA. Efficacy was maintained in both dosing regimens and in both TNF-naïve and TNF-experienced patients. The safety profile was in line with that previously reported from the RAPID-PsA trial, with no new safety signals observed with increased exposure.

Figure: Maintenance of CZP efficacy to Week 96 of the RAPID-PsA trial

	CZP 200mg Q2W (n=138)			CZP 400mg Q4W (n=135)			CZP Combined (n=273)		
Outcome (%)	Wk24 (NRI)	Wk96 (NRI)	Wk96 (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96 (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96 (OC)
ACR20	63.8	68.8	84.8	56.3	59.3	76.2	60.1	64.1	80.6
TNF-naïve[a]	64.5	68.2	83.0	56.3	60.7	75.6	60.3	64.4	79.2
TNF-experienced[b]	61.3	71.0	91.7	56.5	52.2	80.0	59.3	63.0	87.2
ACR50	44.2	50.7	62.5	40.0	48.9	62.9	42.1	49.8	62.7
TNF-naïve[a]	44.9	50.5	61.4	38.4	49.1	61.1	41.6	49.8	61.2
TNF-experienced[b]	41.9	51.6	66.7	47.8	47.8	73.3	44.4	50.0	69.2
ACR70	28.3	34.1	42.0	23.7	35.6	45.7	26.0	34.8	43.8
TNF-naïve[a]	29.0	32.7	39.8	23.2	37.5	46.7	26.0	35.2	43.3
TNF-experienced[b]	25.8	38.7	50.0	26.1	26.1	40.0	25.9	33.3	46.2
MDA	34.8	39.9	49.1	34.8	42.2	54.3	34.8	41.0	51.6
PASI75[c]	62.2	58.9	77.9	60.5	46.1	66.0	61.4	53.0	72.7
PASI90[c]	46.7	48.9	64.7	35.5	38.2	54.7	41.6	44.0	60.3
PROs	Wk0 (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)	Wk0 (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)	Wk0 (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)
HAQ-DI	1.33	0.81	0.79	1.29	0.86	0.79	1.31	0.83	0.79
Pain (100 mm VAS)	59.7	31.1	28.7	61.1	32.7	29.4	60.4	31.9	29.1

[a]TNF-naive pts: CZP 200mg Q2W, N=107; CZP 400mg Q4W, N=112. [b]TNF experienced pts: CZP 200mg Q2W, N=31; CZP 400mg Q4W, N=23. [c]PASI response rates reported in pts with ≥3% body surface area skin involvement at baseline (CZP 200mg Q2W, N=90; CZP 400mg Q4W, N=76). LOCF: Last Observation Carried Forward; MDA: Minimal Disease Activity; NRI: Non-Responder Imputation; OC: Observed Case; VAS: Visual Analogue Scale

P32

OBSERVED INCIDENCE RATES OF UVEITIS FOLLOWING CERTOLIZUMAB PEGOL TREATMENT IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

Rudwaleit M.[1], Landewé R.[2], Marzo-Ortega H.[3], Sieper J.[4], van der Heijde D.[5], Rosenbaum J.[6,7], Davies O.[8], Stach C.[9], Nurminen T.[9], Deodhar A.[7]
[1]Endokrinologikum, Berlin, Germany; [2]Academic Medical Center, Amsterdam and Atrium Medical Center, Heerlen, The Netherlands; [3]Leeds Teaching Hospitals NHS Trust and NIHR Musculoskeletal Biomedical Research Unit, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK; [4]Rheumatology Dept., University Hospital Charité, Berlin, Germany; [5]Leiden University Medical Centre, Leiden, The Netherlands; [6]Devers Eye Institute, Legacy Health System, Portland; [7]Oregon Health & Science University, Portland, USA; [8]UCB Pharma, Slough, UK; [9]UCB Pharma, Monheim, Germany

Introduction. Axial spondyloarthritis (axSpA) is characterized by inflammation in the spine and sacroiliac joints, but also manifests as inflammation at extra-spinal sites, most commonly the uvea (uveitis).[1]
Aims. To estimate the incidence of uveitis flares in RAPID-axSpA patients undergoing certolizumab pegol (CZP) treatment.
Patients and Methods. RAPID-axSpA was double-blind and placebo-controlled to Week (Wk) 24, dose-blind to Wk48 and open-label to Wk204. Patients fulfilled ASAS criteria and had active axSpA, including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA. Patients were randomized to CZP (200mg Q2W/400mg Q4W) or placebo. Uveitis events were recorded on extra-articular manifestation forms or adverse event forms (preferred term "Uveitis"). Events were analyzed in patients with/without history of uveitis, (defined using standard medical history, ASAS classification criteria screening assessment and baseline extra-articular assessment). Wk24 analyses compared combined CZP doses with placebo. At Wk96, all patients exposed to CZP were considered. Incidence rates (IR) are reported per 100 patient-years.
Results. At baseline, 38/218 (17.4%) CZP-randomized patients had history of uveitis, as did 31/107 (29.0%) placebo-randomized patients. During the 24-wk double-blind phase, the IR of uveitis flares was lower in CZP than placebo patients (Table A). Overall IR of uveitis remained low to Wk96 in CZP-treated patients (Table B). IRs were similar in AS and nr-axSpA patients and were comparable to rates reported in AS patients for other anti-TNFs.
Conclusions. During the double-blind phase, uveitis IR was lower for CZP-treated patients than placebo-treated patients, and remained low to Wk96.

Table A: Incidence of uveitis flares in axSpA patients treated with CZP or placebo to Week 24

	CZP			Placebo		
	All Patients (n=218)	History of Uveitis (n=38)	No History of Uveitis (n=180)	All Patients (n=107)	History of Uveitis (n=31)	No History of Uveitis (n=76)
IR per 100 pt-yrs	2.0	11.9	0.0	10.6	42.1	0.0
Pts (Exposure, pt-yrs)	2 (97.6)	2 (16.8)	0 (80.7)	4 (37.7)	4 (9.5)	0 (28.2)

Table B: Incidence of uveitis flares in axSpA patients treated with CZP to Week 96

	All Patients (n=315)	History of Uveitis (n=63)	No History of Uveitis (n=252)
IR per 100 pt-yrs	4.0	16.3	1.3
Pts (Exposure, pt-yrs)	19 (469.4)	14 (86.0)	5 (383.4)

P33

IMPACT OF REPEATING IMAGING OF THE SACROILIAC JOINTS OVER ONE YEAR ON THE CLASSIFICATION ACCORDING THE ASAS AXIAL SPA CRITERIA OF PATIENTS

Bakker P.A.C., de Hooge M.S.M., van den Berg R., van Gaalen F.A., Reijnierse M., Huizinga T., van der Heijde D.M.F.M.
Rheumatology, LUMC, Leiden, The Netherlands

Background. It is known that in axial spondyloarthritis (axSpA) inflammatory lesions on MRI of the SI joints (MRI-SI) can change over time. The usefulness of repeating imaging in the diagnostic process is unclear.
Objectives. To investigate how patients with short-term chronic back pain are classified by the ASAS axSpA- criteria at baseline and after 1-year follow-up, focussing on the role of imaging.
Methods. Patients in the SPACE-cohort (back pain: ≥ 3 months, ≤ 2 years, onset < 45 years) with (suspicion of) axSpA underwent MRI and X-rays of the SI-joints at baseline and 1-year follow-up. MRI-SI and X-SI were scored independently by 3 well-calibrated readers according to the ASAS-definition for a positive MRI and the mNY-criteria blinded for patient characteristics and time sequence. Fulfillment of ASAS or mNY criteria was considered positive if 2/3 readers agreed. At each timepoint, patients were classified according the ASAS axSpA-criteria and grouped in the different arms.
Results. At baseline, 41/80 patients (32.8%) fulfilled the ASAS criteria (clinical arm: 22; imaging arm: 12, both arms: 7) (table). After 1 year, in 5 patients MRI-SI became positive and 1 patient fulfilled the mNY criteria. MRI-SI became negative after 1 year in 4 patients. Of these patients, 3 still fulfilled the ASAS criteria (imaging arm (mNY+, n=1) or clinical arm (n=2)). Only 1 patient (classified as axSpA at baseline) would be missed if imaging would have been performed at 1 year only.
Conclusions. With 1 year longer symptom duration, 3/39 (8%) of the possible SpA patients could be classified additionally as axSpA because of additional SpA features (5%) or positive MRI (3%), while 1/41 (2%) of the axSpA patients would not be classified due to a normal MRI. Therefore, our data show the robustness of the axSpA criteria and does not support repeating imaging after one year.

			1 year							
			Both arms			Imaging arm			Clinical arm	Possible SpA
			mNY+ MRI+	mNY+ MRI-	mNY- MRI+	mNY+ MRI+	mNY+ MRI-	mNY- MRI+		
Baseline	Both arms	mNY+ MRI+	2	1						
		mNY+ MRI-								
		mNY- MRI+			2				2	
	Imaging arm	mNY+ MRI+	1			2				
		mNY+ MRI-		1			4			
		mNY- MRI+			2	1				1
	Clinical arm				3				19	
	Possible SpA							1	2	36

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C-REACTIVE PROTEIN AS A PREDICTOR OF TREATMENT RESPONSE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

Baraliakos X.[1], Szumski A.[2], Koenig A.[2], Jones H.[2]
[1]Ruhr-University Bochum, Herne, Germany; [2]Pfizer Inc, Collegeville, PA, USA

Introduction/Aim. The aim of this post hoc analysis was to determine if baseline C-reactive protein (CRP) levels correlate with ankylosing spondylitis (AS) demographics and disease characteristics and to compare CRP to other AS-specific measures as predictors of treatment response in patients with active AS.
Materials and Methods. Responses to etanercept (ETN), sulfasalazine (SSZ), or placebo (PBO) were analyzed from four pooled large randomized controlled AS studies. Baseline CRP ≤upper limit of normal (ULN) versus CRP >ULN was compared across a number of AS-specific baseline measures. Baseline predictors, including CRP (≤ULN versus >ULN), were analyzed using odds ratios (ORs) in logistic models with treatment response defined as ASAS20 at Week 12 (Assessment of SpondyloArthritis International Society 20 criteria).
Results. In total, data from 1283 patients were used for this analysis: ETN n=867, SSZ n=187, and PBO n=229. Across all treatment groups, baseline CRP >ULN was significantly associated with lower age at diagnosis, higher Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) score, more males, and a higher proportion with positive Human Leukocyte Antigen B27 (HLA-B27) status ($p<0.05$ for all). With ETN treatment, the following baseline parameters were significantly predictive of ASAS20 response after 12 weeks (OR, 95% CI): CRP >ULN (1.7, 1.3–2.3), ASDAS-CRP >3.5 (1.7, 1.3–2.3), age of diagnosis ≤40 (1.8, 1.3–2.5), positive HLA-B27 (2.0, 1.4–3.0), and higher nocturnal back pain based on quartiles (1.2, 1.1–1.4), with all predictors appearing to have similar effects on ASAS20 based on similar odds ratios. A Bath Ankylosing Spondylitis Disease Activity Index score of ≤40 was significantly predictive of response to SSZ (OR 3.0, 95% CI 1.1–8.0), as was ASDAS-CRP >3.5 (OR 0.51, 95% CI 0.28–0.92) for PBO.
Conclusions. Baseline CRP was significantly associated with typical parameters of the disease (age of diagnosis, ASDAS-CRP, gender, HLA-B27) and significantly predictive of short-term treatment response only in patients receiving ETN, along with other AS-specific measures, including ASDAS-CRP.

P35

AORTIC REGURGITATION IS COMMON IN ANKYLOSING SPONDYLITIS AND JUSTIFIES ROUTINE ECHOCARDIOGRAPHIC SCREENING

Klingberg E.[1], Grüner-Sveälv B.[2], Scharin-Täng M.[2], Bech-Hanssen O.[2], Bergfeldt L.[2], Forsblad-d'Elia H.[1]
[1]Dept. of Rheumatology and Inflammation Research; [2]Dept. of Molecular and Clinical Medicine/Cardiology, Sahlgrenska Academy at University of Gothenburg, Sweden

Introduction/Aim. Ankylosing spondylitis (AS) can be complicated by cardiac involvement, typically aortic regurgitation (AR) and conduction system abnormalities. The aims of this study were to assess the prevalence of AR in a cohort of AS patients and to explore associations with demographics and parameters related to disease activity.
Methods. All registered AS patients (modified NY-criteria) at the study centres were invited to participate. Exclusion criteria were psoriasis and inflammatory bowel disease. Transthoracic echocardiography and electrocardiography were performed. The patients answered questionnaires concerning medical history, cardiovascular risk factors and disease activity (BASDAI, ASDAS, BASFI). Spinal mobility was assessed with BASMI and syndesmophyte formation with mSASSS.
Results. 187 patients (56%men), with mean age±SD 50±13 years, symptom duration 24±13 years and BASDAI 3.5±2.1 were included. An AR was found in 34 patients (18%), and was mild in 24, moderate in 9, and severe in one. Conduction system abnormalities were documented in 10 (29%) of the patients with AR. The proximal ascending aorta was wider in the patients with an AR, but no differences were found in left ventricular ejection fraction or end-diastolic volume in patients with vs. without AR. AR was related to increasing age and longstanding disease and increased from ~20% in the 50's to 55% in the 70's. The patients with an AR had significantly higher BASFI, BASMI, mSASSS, ESR and more often a history of anterior uveitis. In logistic regression the presence of an AR was independently associated with long symptom duration, high mSASSS and having had an anterior uveitis.
Conclusion. An AR was found in 18% of the included AS patients and associated with longstanding disease, high mSASSS and anterior uveitis. Most cases of AR were undiagnosed prior to the study. We suggest that both electrocardiographic and echocardiographic evaluation should be part of the routine management in AS, especially in patients older than 50 years.

P36

COMPARISON OF THE RISK OF DEVELOPING ADVERSE EVENTS BETWEEN PSA AND AS: RESULTS FROM THE LORHEN REGISTRY

Atzeni F.[1], Ricci C.[2], Caporali R.[3], Marchesoni A.[4], Bongiovanni S.[1], Favalli E.[4], Gorla R.[5], Pellerito R.[6], Filippini M.[5], Todoerti M.[3], Paolazzi G.[7], Bortolotti R.[7], Fusaro E.[8], Sarzi-Puttini P.[1], on behalf of LORHEN Registry
[1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy; [2]Dept. of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany, [3]Chair of Rheumatology, IRCCS Policlinico S. Matteo, Pavia; [4]G. Pini Orthopedic Institute, Chair of Rheumatology in Milan, Milan; [5]Spedali Civili di Brescia, Brescia; [6]Rheumatoloy Unit, Mariziano Hospital, Turin; [7]Rheumatology Unit, Santa Chiara Hospital, Trento; [8]Rheumatology Unit, Le Molinette Hospital, Health City of Turin, Turin, Italy

Objectives. The primary aim of this multicenter study was to identify the most frequent comorbidities and adverse events (AEs) in PsA and AS patients on the basis of the data in the LORHEN register.
The secondary aim was to identify the effect of biological anti-TNF on adverse events development.
Methods. The study involved 372 with long-standing PsA (mean age 41.2±13.5 years; mean disease duration 11.6±7.6 years; F(%) = 38.3%), and 410 with AS (mean age 36.8±13.3 years; mean disease duration 11.6±8.9 years; F(%) = 47.7%), all of whom had been treated with biological drugs for at least six months or had discontinued therapy due to serious adverse events. The majority of PsA and AS patients had been treated with only one DMARD (respectively 40.22% and 39.85%). Many patients were treated with low-dose corticosteroids (<7.5 mg/day): 75.41% of the PsA patients, and 55.92% of the AS patients. All of the patients were treated with the anti-TNF agents ADA, IFN, ETN, GOL and CTZ. Logistic regression analysis corrected by age, gender, disease duration, smoking habit, study centre and therapy or diagnosis if appropriate were used.
Results. Many of the patients suffered from comorbidities, particularly hypertension (10.36% of PsA patients, and 7.28% of AS patients), cardiovascular diseases (CVD; respectively 0.35% and 1.53%), dyslipidemia (3.93% and 1.92%), osteoporosis (3.21% and 5.75%). The most frequent adverse events were infections (34.15% and 30.32%), neoplasias (5.28% and 4.07%), and CVD (2.85% and 1.81%).
The odds ratios (ORs) for the risk of a comorbidity between PsA *vs* AS was: 0.81 (95% CI 0.53-1.23).
The ORs of developing an adverse event was PsA *vs* AS: 0.96 (95% CI 0.66-1.41). The ORs of the effect of anti-TNF *vs* no anti-TNF therapy on adverse events were 5.49 (95% CI 1.12-26.92) in the PsA group; and 3.38 (95% CI 0.42-27.11) in the AS group.
Conclusions. Our results suggest that patients with PsA are at greater risk of having comorbidities and developing adverse events than those with AS. The effect of anti-TNF therapy on the development of adverse events is greater in PsA than in AS patients.

P37

VALIDITY OF ASDAS AND BASDAI AS A MEASURE OF DISEASE ACTIVITY IN AXIAL PSORIATIC ARTHRITIS

Kilic G.[1], Kilic E.[1], Nas K.[2], Karkucak M.[3], Capkin E.[3], Dagli A.Z.[2], Cevik R.[2], Ozgocmen S.[1]
[1]Division of Rheumatology, Dept. PMR, Erciyes University, Kayseri; [2]Dept. PMR, Dicle University, Diyarbakir; [3] Dept. PMR, Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkey

Aim. To assess the discriminative ability of Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Activity Disease Activity Index (BASDAI) as the measures of disease activity in patients with axial psoriatic arthritis (axPsA).
Materials and Methods. Patients were recruited from Erciyes Spondyloarthritis Cohort (ESPAC) and Anatolian Group for the Assessment in Rheumatic Disease (ANGARD) cohort. The BASDAI, ASDAS, BASFI, Ankylosing Spondylitis Quality of Life (ASQoL), VAS-pain were assessed. The discriminative ability was assessed in patient who were grouped for high and low disease activity according to the physician global (>6 vs <4), patient global (>6 vs <4) and ASAS partial remission criteria. The standardized mean differences were used to compare discriminant ability of ASDAS-C-reactive protein (-CRP) and ASDAS-erythrocyte sedimentation rate (-ESR). Receiver operating characteristic (ROC) curves were used to compare the discriminative ability of ASDAS and BASDAI. Cut-off values were calculated.
Results. Both ASDAS scores (ASDAS-CRP and ASDAS-ESR) showed good discriminative ability between high and low disease activity states in patients with axPsA (n=54). Both ASDAS versions and BASDAI had relatively high area under the curve (AUC) according to ASAS partial remission, patient and physician global assessments. There was no significant difference between AUC scores for the models that compared ASDAS-CRP and ASDAS-ESR with BASDAI for each individual definition of disease activity states. The cut-off values for discriminating inactive disease to high disease activity were relatively similar to the cut-off values estimated for ankylosing spondylitis.
Conclusions. ASDAS versions and BASDAI scores had similarly good discriminative ability in patients with axPsA in terms of high and low disease activity states. ESR and CRP had a limited role in detecting the disease activity. Further prospective validation is now required to identify the appropriate assessment tools and cut off values in axPsA.

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VALIDITY OF THE ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE (ASDAS) IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

Kilic G.[1], Kilic E.[1], Akgul O.[2], Ozgocmen S.[1]
[1]Division of Rheumatology, Dept. PMR, Erciyes University, Faculty of Medicine, Kayseri; [2]Division of Rheumatology, Dept. PMR, Celal Bayar University, Faculty of Medicine, Manisa, Turkey

Introduction. Axial spondyloarthritis (SpA) consisted patients with advanced axial SpA or ankylosing spondylitis (AS) and non-radiographic axial SpA (nr-axSpA). Evaluation of disease activity in axSpA is complex due to the phenotypic heterogeneity of the disease.
Aim. To assess the validity of AS Disease Activity Score (ASDAS)-CRP and ASDAS-ESR as clinical tools for assessing disease activity in patients with nr-axSpA and to compare their correlation with other disease activity measures. The predefined cut-off values for ASDAS-CRP in nr-axSpA and AS is also revisited.
Materials and Methods. Patients with axSpA were recruited from Erciyes Spondyloarthritis Cohort (ESPAC) and assessed for BASDAI, ASDAS, BASFI, BASMI, Ankylosing Spondylitis Quality of Life (ASQoL), and VAS-pain. Patients were grouped into low and high disease activity according to the physician's and patient's global assessment score (>6/10 vs <4/10), ASAS partial remission criteria, treatments and presence of peripheral arthritis. The discriminant ability of ASDAS-CRP and ASDAS-ESR was assessed using standardized mean differences. Receiver operating characteristic (ROC) curves were used for comparisons. Optimal cut-off values for disease activity scores were calculated.
Results. Two hundred eighty-seven patients with axSpA (nr-axSpA:132, AS:155) were included in this study. Two ASDAS versions and BASDAI had good correlations with patient's and physician's global in both groups. Discriminant ability of ASDAS-CRP, ASDAS-ESR and BASDAI were similar in nr-axSpA and AS when patients were assigned into low and high disease activity based on the ASAS partial remission, patient's and physician's global scores (assessed by comparing AUC of ROC curves). ASDAS cut-off values are quite similar in all groups indicating that ASDAS-CRP works similarly well in nr-axSpA and AS. The calculated cut-offs in both groups were very similar to predefined values by ASAS.
Conclusion. The construct validity of ASDAS to discriminate low and high disease activity and cut off values are quite similar in patients with AS and nr-axSpA.

P39

ATTITUDE OF DOCTOR AND PATIENT TO ANKYLOSING SPONDYLITIS: QUESTIONS OF UNDERSTANDING

Myasoutova L., Lapshina S.
Kazan State Medical University, Russia

Relevance. Effective control of ankylosing spondylitis (AS) activity involves prolonged drug therapy primarily NSAIDs and active participation of the patient in treatment, performing of recommendations on non-pharmacological treatment. Is it always effective physician-patient interaction in relation to treatment.
Purpose. To identify the most significant problems for AS patient about the disease in order to create a system of effective interaction: physician – AS patient.
Materials and Methods. 30 patients with confirmed AS diagnosis, the average disease duration 5,7±3,2 years, mean age 34,4±12. 8 years responded to 10 survey questions regarding their understanding of the disease and treatment issues and the impact on daily life with the need to evaluate the importance of each question on a scale from 1 to 10. Doctors rheumatologists (n = 10) and physicians (n = 20) answered the same questions from the position what they think is important for patients. Responses were ranked and compared.
Results. Considering the young age of patients, priority for patients and doctors was the outlook for the future (1). Important for doctors and patients were issues related restrictions on daily life (patients - 4 place, doctors - 2nd place) and earning capacity (patients – 3rd place, doctors - 5th place). At the same time, doctors underestimate (10th place) the complexity of the patient (2nd place) associated with the need to exercise constantly. Physicians overestimated the importance of persistent pain for patients (4th place) and side effects of drugs (2nd place), patients put on the importance of these issues at 7 and 5th place respectively.
Conclusion. In communicating with the patient doctor needs to pay more attention to the importance of non-pharmacological treatment, in particular right physical exercises. Understanding the patients view to their condition will improve the efficiency of AS control.

P40

AXIAL ANKYLOSING SPONDYLITIS AND RADIOLOGICAL: NOT THE SAME SYNDROME OR DIFFERENT DISEASES? ANALYSIS OF "ESPERANZA" COHORT

Hernández-Sanz A.[1], Navarro-Compán V.[2], Fernández-Carballido C.[3], Montilla-Morales C.[4], Mulero-Mendoza J.[5], de Miguel E.[2], on behalf of EsPeranza Group
[1]Rheumatology, Hospital Virgen de la Salud, Toledo; [2]Rheumatology, University Hospital La Paz, Madrid; [3]University General Hospital of Elda, Alicante; [4]Rheumatology, University Hospital of Salamanca, Salamanca; [5]Rheumatology, Hospital Puerta de Hierro of Majadahonda, Madrid, Spain

Background. New ASAS criteria for axial spondyloarthritis (axSpA) have two entrances: the imaging and clinical arm (HLA B27+). The imaging arm allows classifying patients as non-radiological axial spondyloarthritis (axSpA-nr) and ankylosing spondylitis (AS). The importance of the concept of axSpA-nr or the clinic arm is questioned currently, so it is interesting to investigate how homogeneous or different populations are compared to the classical AS.
Objectives. To compare the characteristics of AS and axSpA-nr of recent onset. Secondary, characteristics between groups axial SpA diagnosed by clinical and imaging arm were compared.
Methods. A descriptive study of the baseline data of the patients included in the "Esperanza" proyect that met criteria ASAS axSpA was performed. Demographic, clinical, activity indices (BASDAI and CRP), mobility (BASMI) and physical function (BASFI) were compared.
Results. Of the 775 patients included in the "Esperanza" program we included 291: 194 imaging arm (43.8% axSpA-nr and 56.2 %EA), and 97 clinical arm. 65% of patients were male with a mean age of 32±7 years and mean disease duration of 13±6.7 months. Males were more frequently observed in patients with AS compared to group axSpA-nr and only diarrhea and genito-urinary disease were more frequent in the group of axSpA-nr (Table I). Instead mobility was lower in the AS group. No significant differences in the activity or other baseline characteristics were observed. Peripheral and genito-urinary disease and arthritis, enthesitis, uveitis, diarrhea, and family history were significantly more frequent in patients in the clinical arm, while physical function was more impaired in patients on image arm.

	Clinical arm n 97 (33%)	Imaging arm n 194 (67%)				*p*** value
		Global	nr-axSpA (n=85)	AS (n=109)	*p** value	
Age (years)	31.9±7.5	32.1±6.8	31.3±6.7	32.7±6.8	0.2	0.8
Male	64 (66.0)	127 (65.5)	46 (54.1)	81 (74.3)	<0.01	0.9
Symptoms duration (m)	12.0±6.9	13.5±6.6	13.0±6.8	13.9±6.4	0.3	0.08
Morning stiffness	60 (61.9)	138 (71.1)	57 (67.1)	81 (74.3)	0.3	0.1
IBP (AS.AS definition)	35 (36.1)	77 (39.7)	35 (41.2)	42 (38.5)	0.7	0.6
Peripheral arthritis	25 (25.8)	28 (14,4)	9 (10.6)	19 (17.4)	0.2	0.02
Enthesitis	36 (37.1)	21 (10.8)	11 (12.9)	10 (9.2)	0.4	<0.001
Psoriasis	14 (14.4)	19 (9.8)	11 (12.9)	8 (7.3)	0.2	0.2
Dactylitis	10 (10.3)	6 (3.1)	2 (2.4)	4 (3.7)	0.6	0.01
IBD	1 (1.0)	8 (4.1)	2 (2.4)	6 (5.5)	0.3	0.2
Uveitis	12 (12.4)	11 (5.7)	4 (4.7)	7 (6.4)	0.6	0.046
Diarrhea, cervicitis, urethritis	8 (8.2)	3 (1.5)	3 (3.5)	0	0.048	<0.01
Family history	45 (46.4)	56 (28.9)	25 (29.4)	31 (28.4)	0.8	<0.01
HLA-B27	97 (100)	122 (62.9)	49 (58.3)	73 (67,6)	0.2	<0.001
CRP (mg/L)	10.9±16.4	10.8±14.6	9.8±13.8	11.5±15.3	0.4	0.9
VAS (0-10) night pain	3.4±2.9	4.0±2.9	3.9±2.9	4.1±3.0	0.7	0.9
VAS (0-10) physician	2.5±2.1	3.1±2.2	2.7±2.1	3.4±2.2	0.047	0.5
VAS (0-10) patient	4.1±2.6	4.2±2.7	4.3±2.9	4.1±2.6	0.7	0.5
BASDAI	3.8±2.2	3.8±2.3	3.7±2.1	4.0±2.4	0.4	0.8
BASFI	2.0±2.0	2.5±2.4	2.3±2.4	2.7±2.5	0.3	0.02
BASMI	1.2±1.0	1.6±1.3	1.2±1.2	1.8±1.4	<0.01	0.1

P41

IS 25MG ETANERCEPT EFFECTIVE IN MAINTAINING A CLINICAL RESPONSE IN PATIENTS WITH ANKYLOSING SPONDYLITIS WHO HAVE RESPONDED TO 50MG ONCE WEEKLY: A MULTICENTRE RANDOMISED CONTROLLED TRIAL

Elender F.[1], Hamilton L.[1], Yates M.[1], Dean L.[1], Doll H.[2], Thomas H.[3], Gaffney K.[1]
[1]Rheumatology, Norfolk & Norwich University Hospital NHS Foundation Trust, Norwich; [2]ICON, Commercialisation and Outcomes, Oxford; [3]James Paget University Hospital, Gorleston, UK

Aim. To investigate, in a pilot randomised controlled trial, whether etanercept 25mg once weekly is effective in maintaining a clinical response in patients with Ankylosing Spondylitis (AS) who have responded to the standard 50mg dose.
Patients and Methods. Adults with AS not responding to conventional therapies were prescribed 50mg etanercept once weekly for six months. Those with sufficient clinical response, as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), were randomly assigned to step-down to 25mg or continue on 50mg and followed up for a further six months. The primary outcome measure was maintenance of a 50% reduction in the BASDAI or fall in BASDAI by ≥2 units.
Results. Of 59 enrolled patients; 47 (80%) were eligible for randomisation, with 24 assigned to continue on 50mg etanercept and 23 to step-down to 25mg. After six months, 22 (92%) of the 50mg arm maintained clinical response compared with 12 (52%) of the 25mg arm (a difference of -39%, p=0.003, 95% CI -64% to -15%). Non-inferiority was not demonstrated in the step-down arm (lower 95% CI = 70% of the observed effect). Adjusted BASMI (p<0.001), ASDAS (p=0.019), ASAS pain (p=0.003) and global assessment scores (p=0.002) were also significantly higher in the 25mg arm after step-down, with individuals less likely to reach ASAS 40 (adjusted Odds Ratio [OR] 0.21, p=0.049) or achieve partial remission (adjusted OR 0.08, p=0.061).
Discussion. This pilot study finds that treatment effect is not sustained overall for patients with AS when the standard dose of etanercept is reduced by 50%. However of those that stepped down 52% maintained response.
Conclusion. Further studies are required to determine whether suitable patients can be identified for step-down prior to initiation of treatment.

P42

EFFICACY AND SAFETY OF KUNXIAN CAPSULE FOR TREATMENT OF SPONDYLOARTHROPATHY (SPA) AND ANKYLOSING SPONDYLITIS (AS): RESULTS OF A MULTI-CENTER RANDOMIZED PLACEBO-CONTROLLED TRIAL

Li Q.[1], Li L.[1], He D.[2], Bi L.[3], Lin Z.[1], Cao S.[1], Liu H.[4], Liao Z.[1], Xiao C.[5], Wang G.[6], Zhou H.[6], Wu H.[7], Gu J.[1]
[1]Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou; [2]Rheumatology, Shanghai Guanghua Hospital, Shanghai; [3]Rheumatology, China-Japan Union Hospital of Jilin University, Changchun; [4]Rheumatology, Affiliated Hospital of Guangdong Medical College, Zhangjiang; [5]Rheumatology, Integrated Traditional and Western Medicine Hospital of Southern Medical University, Guangzhou; [6]Rheumatology, Beijing China-Japan Friendship Hospital, Beijing; [7]Rheumatology, Dongguan People's Hospital, Dongguan, China

Introduction/Aim. To study the efficacy and safety of the Kunxian capsule (the main extract is Tripterygium hypoglaucum (levl.) Hutch, Original name: Fengshi Ping, Brand Name: Kunxian Capsule) for treatment of Spondyloarthropathy (SpA) and ankylosing spondylitis (AS).
Methods. A randomized double-blind, parallel control trial involving 126 SpA patients (ESSG-standard and in the active disease phase, accompanied with inflammatory back pain, VAS ≥ 40 mm) were assigned to Kunxian, sulfasalazine (SSZ) and placebo group, for 12 weeks of therapy. In addition, 80 AS patients (modified New York criteria (1984) and in the active disease phase, VAS ≥40 mm) were assigned to Kunxian and placebo group, for 12 weeks of therapy. At 2, 6 and 12 weeks (W2, W6 and W12), the change in clinical symptoms was observed (measured by ASAS 20, 40, 70, BASDAI 20, 50, 70, BASFI, BASMI, ASDAS-3, MASES, AS-QoL, and CRP), and the occurrence of adverse reactions were recorded.
Results. The SpA-Kunxian group had a higher proportion of patients who achieved ASAS20 at W2 and W6 compared to the AS-Kunxian group (W2, 40.6% vs 8.1% and W6, 56.3% vs 31.4%, respectively, p<0.05). At W12, the SpA-Kunxian group achieved higher BASDAI 20, 50 and 70 scores than AS-Kunxian group (p<0.05). Kunxian Capsule has better improvements on ASDAS3, AS-QoL and CRP than SSZ (compared with W0). It is worth mentioning, Kun Xian Capsule can significantly improve the CRP on SpA and AS patients.
Conclusion: Kunxian capsule can significantly improve some clinical symptoms for SpA and AS patients, especially for SpA patients. It is a potential worthy medicine for AS patient in China.

P43

A RETROSPECTIVE STUDY ON CLINICAL FEATURES OF IgA NEPHROPATHY IN ANKYLOSING SPONDYLITIS

Qi J., Lv Q., Gu J.
Dept. of Rheumatology, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Aim. To investigate the clinical features of IgA (immunoglobulin A) nephropathy and its prognosis in ankylosing spondylitis (AS).
Methods. We retrospectively analyzed the clinical data of IgA nephropathy in AS patients. A morphologic study of renal biopsy specimens from IgA nephropathy patients was carried out using conventional light microscopy, immunofluorescence light microscopy and electron microscopy.
Results. Fourteen AS patients were diagnosed as IgA nephropathy, including 7 cases of patients with HLA-B27 (+). All subjects were male, with a mean±SD age of 24.8±4.9 years old. Two out of 14 patients, the initial symptoms were peripheral arthritis, microscopic or gross hematuria, and proteinuria; in another 12 patients, joints involvement were the initial symptoms, including peripheral arthritis in two patients and axial joint involvement in the rest. One of the 14 patients were HBsAg-positive. Microscopic hematuria was found ranging from 2+ to 3+ in all subjects. Nine out of 14 subjects were found to have positive urinary protein, with 5 patients being 1+, two patients 2+, and other two patients were 3+. Pathological examination demonstrated IgA nephropathy. There were segmental hyperplasia with mesangial cells (mild) in 5 cases; mesangial broadening in one case, mesangial cell hyperplasia (moderate), with segmental increased; the rest were mild mesangial cell proliferation. Humoral immunity test showed that the level of complement in all patients was normal, and furthermore, without increased IgA. Patients were treated mainly with prednisone (10mg) and Nonsteroidal Anti-inflammatory Drugs (NSAIDs); after one year follow-up, only one patient still had microscopic hematuria and trace proteinuria, the remaining 13 patients were normal in urine routine examination.
Conclusion. Kidney damage such as hematuria and proteinuria could be the first manifestation in a small number of AS patients, however, the kidney damage is mild. The kidney may recover when the primary disease is treated, and the prognosis may be good for IgA nephropathy in AS.

P44

TGP MAY INTERVENE AS IMMUNE FUNCTION, MAINTAINING CLINICAL REMISSION ON ANKYLOSING SPONDYLITIS PATIENTS

Li Q., Li W., Cao S., Gu J.
Rheumatology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Introduction/Aim. To study the effect and mechanism of the total glucosides of paeony(TGP) remission ankylosing spondylitis (AS) patients after the treatment of TNF-α antagonists.
Methods. 38 AS outpatients (modified New York criteria) were enrolled who achieved ASAS20 remission for more than 6-8weeks and BASDAI<4 after at least 12 weeks treatments of TNF-α antagonist. Group1 taking NSAIDS alone, group 2 taking NSAIDS and TGP, the third group taking TGP only. Meanwhile 15 staff of our hospital were selected as health control. All patients were followed up respectively at baseline and 24 weeks, recorded the BASDAI, VAS, BASFI, ASDAS core and CRP, ESR, ALT, AST, BUN, CREAT concentration. Detected the TLR4, TLR5,TRAF6, Myd88mRNA relative expression value of the patients and the healthy staff by RT-PCR, sampled their serum for TNF-α, IL-17α, TGF-β1 detection. And the patients with disease recurrence should compare these corresponding indicators in recurrence and baseline.
Results. There is no statistically difference during 3 groups in the recurrence rati (BASDAI≥4 as recurrence standard), and also no difference between baseline and after 24 weeks treatments in clinical assessment core and CRP, ESR, BUN, ALT, AST, CREAT concentrations. AS patients have higher expression level of TLR4mRNA and TLR5mRNA and higher concentration of serum TNF-α, IL-17α, TGF-β1 than the healthy control group at the baseline. And after 24 weeks' treatment, the 2nd group has decreased both in TLR4mRNA and TLR5mRNA expression, the 3rd group decreased in TLR5mRNA expression only. TNF-α, IL-17α concentration of all 3 groups were reduced after 24 weeks.
Conclusion. TGP has potential value for treating remission AS patients, and the possible mechanism may be decreasing related inflammatory indicators and blocking TLR4/5 signal pathway.

P45

MEASUREMENT OF LATERAL SPINAL FLEXION AND SCHOBER IS SUFFICIENT TO BE INFORMED ABOUT SPINAL MOBILITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS: 12-YEAR OASIS RESULTS

Ramiro S.[1], Landewé R.[1], van der Heijde D.[2], Stolwijk C.[3], Dougados M.[4], van den Bosch F.[5], van Tubergen A.[3]
[1]ARC, Amsterdam; [2]LUMC, Leiden; [3]MUMC, Maastricht, The Netherlands; [4]Paris-Descartes University, Paris, France; [5]GUH, Ghent, Belgium

Aim. To investigate whether assessing few spinal mobility measures (SMMs) could capture full information on impairment in spinal mobility.
Methods. Patients from the Outcome in AS International Study (OASIS) were followed-up for 12 years with regular mobility measurements. From a previous study in normal subjects (1), percentile curves (2.5th to 97.5th) were obtained for each SMM. We added 4 parallel curves (helplines a' to d') to be able to plot impaired measures. Each of the SMMs was defined as impaired if the measurement fell below helpline a' (first cutoff below normal subjects). The number of observations and of patients (baseline observation) with ≥1 SMM impaired was calculated. Of those, the proportion of observations (of patients) with each of the SMMs impaired was calculated. We investigated how often would impairment in spinal mobility be missed if only a fixed number of SMMs was assessed.
Results. A total of 216 patients were included (70% males, 85% HLA-B27 positive). Impairment in spinal mobility was present in 1111 (78%) of 1422 observations and in 161 (79%) of 203 patients with complete (baseline) assessment. From the observations (patients) with ≥1 SMM impaired, in 83% (86% of patients) lateral spinal flexion (LSF) was impaired, followed by Schober in 63% (58% of patients). If only LSF was measured, 17% of the observations (14% of patients) with impairment in SMM would be missed. If additionally Schober was measured, only 9% of the observations (of patients) would be missed.
Conclusion. Impairment in spinal mobility can be investigated by assessing only 2 SMMs. We recommend that measurement of LSF and Schober is sufficient to be informed about impairment in spinal mobility in patients with AS. Only if these are impaired is it important to assess additional measures.

Reference
1. RAMIRO *et al*.: *ARD* 2014.

P46

SPINAL MOBILITY GETS IMPAIRED IN A FIXED ORDER IN PATIENTS WITH ANKYLOSING SPONDYLITIS: 12-YEAR OASIS RESULTS

Ramiro S.[1], Landewé R.[1], van der Heijde D.[2], Stolwijk C.[3], Dougados M.[4], van den Bosch F.[5], van Tubergen A.[3]
[1]ARC, Amsterdam; [2]LUMC, Leiden; [3]MUMC, Maastricht, The Netherlands; [4]Paris-Descartes University, Paris, France; [5]GUH, Ghent, Belgium

Aim. To investigate which spinal mobility measures (SMM) are most frequently impaired in patients with AS and whether a hierarchy for the impairment of the measures could be established.
Methods. Patients from the Outcome in AS International Study (OASIS) were followed-up for up to 12 years with regular spinal mobility measurements. From a previous study in normal subjects (1), percentile curves (2.5th to 97.5th) were obtained for each of the SMMs. We added 4 parallel curves (helplines a' to d') to be able to plot impaired measures. For every observation, and taking patient's age into account, each of the SMMs was defined as impaired if the measurement fell below each of the cutoffs (2.5th percentile and each of the 4 helplines). The proportion of observations and also of patients (using baseline observation) in which each of the SMMs was impaired was calculated.
Analyses were repeated in strata according to gender, symptom duration (median and tertiles) and baseline number of syndemophytes (0 vs ≥1 and <5 vs≥5).
Results. A total of 216 patients were included (70% males, mean age 44(SD 13) years, mean symptom duration 21(12) years and 85% HLA-B27 positive). Lateral spinal flexion (LSF) was always the most frequently impaired measure, sequentially followed by Schober's, tragus-to-wall, cervical rotation, intermalleolar distance and chest expansion. This order was strikingly similar at both the observation-level and the patient-level (baseline observations only) as well as for all cutoffs. Even with stratifications did this hierarchy in general persists.
Conclusion. LSF and Schober's are the most frequently impaired mobility measures in AS, reflecting an earlier involvement of lumbar spine in spinal mobility impairment, followed by the involvement of the thoracic and cervical spine. This fixed order of involvement of the spine persists across different patient groups.

Reference
1. RAMIRO *et al*.: *ARD* 2014 (epub).

P47

A PHYSICALLY DEMANDING JOB MAY AMPLIFY THE EFFECT OF DISEASE ACTIVITY ON RADIOGRAPHIC PROGRESSION IN PATIENTS WITH AS

Ramiro S.[1], van Tubergen A.[2], Landewé R.[1], Boonen A.[2], Stolwijk C.[2], Dougados M.[3], van den Bosch F.[4], van der Heijde D.[5]
[1]ARC, Amsterdam; [2]MUMC, Maastricht, The Netherlands; [3]Paris-Descartes University, Paris, France; [4]GUH, Ghent, Belgium; [5]LUMC, Leiden, The Netherlands

Aim. To investigate the complex relationship between inflammation, mechanical stress and radiographic progression in patients with AS, using job type as a proxy for continuous mechanical stress.
Methods. Patients from OASIS were followed-up for 12 years, with 2-yearly assessments. Two readers independently scored the x-rays according to the mSASSS. Disease activity was assessed by the ASDAS-CRP. The relationship between ASDAS and spinal radiographic progression was investigated with longitudinal analysis, with job type at baseline (physically demanding ('blue collar') vs sedentary ('white collar') labor) as a potential factor influencing this relationship. The effects of smoking status and socio-economic factors were also investigated.
Results. In total, 184 patients were included in the analyses (70% males, 83% HLA-B27 positive, 39% smokers, 48% blue-collar workers (65/136 patients in whom data on job type were available)). The relationship between disease activity and radiographic progression was significantly and independently modified by job type: In 'blue-collar' workers vs 'white collar' workers every additional unit of ASDAS resulted in an increase of 1.2 vs 0.2 mSASSS-units/2-years (p=0.014 for the difference between blue collar and white collar workers). The relationship ASDAS-mSASSS was also influenced by personal income and by smoking.
Conclusion. Physically demanding jobs may amplify the driving effects of inflammation on radiographic progression, thus supporting the theory that mechanical stress leads to bone formation in AS. Smoking and personal income are likely classic confounders of this relationship but a separate detrimental effect of smoking on radiographic progression could not be excluded. If confirmed, these findings may have implications for our commonly given advice to patients with SpA to strenuously exercise.

P48

INITIAL PRESENTATION AND CLINICAL COURSE BETWEEN LATE-ONSET ANKYLOSING SPONDYLITIS AND ADULT-ONSET AS

Lee S.H.[1], Song R.[1], Lee Y.A.[2], Choi J.Y.[2], Yang H.I.[1], Hong S.J.[2]
[1]Hospital at Gangdong, Kyung Hee University, Seoul; [2]Kyung Hee University Medical Center, Seoul, South Korea

Introduction/Aim. Most ankylosing spondylitis (AS) patients experience their first symptoms prior to age 45. However, symptoms of AS can develop after the age 45 and the initial manifestations may vary according to the different onset-age subsets. This study was performed to investigate whether there are characteristic clinical features in the late-onset AS patients compared to adult-onset AS.
Patients and Methods. We retrospectively studied the clinical and laboratory features of 499 AS patients. These patients fulfilled the modified New York criteria for AS and were classified into 2 groups based on their age at symptom onset: adult-onset AS (>16 but <45 years; AOAS); and late-onset AS (≥45 years; LOAS). The onset of disease was defined by the day of appearance of the first manifestation of AS. In both groups, the following data were compared:(1) epidemiological variables; (2) laboratory results (HLA-B27, ESR and CRP); (3) clinical manifestations, including signs and symptoms at diagnosis and during follow-up; (4) BASDAI and BASMI; (5) radiographic data (BASRI total and BASRI spine); (6) use of anti-TNF-α agent and time to start anti-TNF-α therapy.
Results. There were 29 patients (5.8%) with LOAS. LOAS group had more female patients (44.8% vs. 21.5%, p=0.004), shorter disease duration (6.2±4.9 vs.11.3±6.8 years, p<0.001) and less HLA-B27 positivity (69.0% vs. 82.6%, p=0.037) than AOAS group. As an initial manifestation, the patients with LOAS more often presented cervical pain (40.0% vs. 18.8%, p=0.005), shoulder pain (30.0% vs. 6.6%, p<0.001), lower extremity arthritis (56.7% vs. 36.5%, p=0.027), and the anterior chest wall pain (30.0% vs. 6.6%, p<0.001) than AOAS. Clinical symptoms during follow-up and the radiological scores did not differ between the two groups. The most notable findings of the LOAS group were higher initial ESR (47.8±29.8 vs. 29.6±23.8 mm/hr, p<0.001) and more frequent use of TNF-α inhibitors during the course of the disease (58.6% vs. 38.5%, p<0.001).
Conclusion. Our results suggest that LOAS has distinctive presenting symptoms and a higher inflammatory burden.

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PRELIMINARY STUDY OF PERIPHERAL BLOOD DISORDERS OF ACTIVE ANKYLOSING SPONDYLITIS – A RETROSPECTIVE STUDY

Lv Q., Gu J.
Dept. of Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Introduction and Aim. Ankylosing spondylitis (AS) is a chronic systemic disease known that mainly affects the axial joints (spine and pelvis). AS related peripheral blood disorders still remains to be explored. In this study, we investigated whether AS pathogenesis involve peripheral blood disorders.
Patients and Methods. A total of 50 patients who fulfilled the Modified New York Criteria for Ankylosing Spondylitis (1984) were included. It was demanded that the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of all patients in this study were at least 4. We analyzed the parameters of the blood routine, including blood count and blood cell morphology distribution. Normal population data were taken as reference value. Data were presented as the mean ± standard deviation. Statistical analyses were performed using SPSS 10.0. Differences between AS patients and normal population were analyzed with t-test.
Results. The average age of these 50 patients was 27.5 years, and the male to female ratio was 1:1. The leukocytes (7.94±3.13*10e9/L), platelets (282.31±90.75*10e9/L), erythrocyte count (4.83±0.63*10e12/L), or haemoglobin (131.9±9.9g/L) of AS patients was within normal limits. Patients with AS displayed significantly lower levels of platelet distribution width (10.9±1.53 vs. 13.95±4.15), and mean platelet volume (9.75±0.80 fL vs. 10.95±1.55 fL).
Conclusions. Patients with AS have lower levels of platelet distribution width and mean platelet volume.

P50

HOW TO IMPROVE EARLY DIAGNOSIS OF AXIAL SPONDYLOARTHRITIS (ACCORDING TO RHEUMATOLOGIC CITY CENTER, KAZAN, RUSSIA)

Myasoutova L., Lapshina S.
Kazan State Medical University, Kazan, Russia

Diagnosis of axial spondyloarthritis (SpA) today has a lot of complexity, so the diagnosis of ankylosing spondylitis (AS) is exhibited an average of 7-8 years from the first symptoms of the disease, which leads to later onset of potentially effective therapy.
Purpose. To assess the significance of educational activities for primary contact physicians in the early diagnosis of AS.
Materials and Methods. In Kazan from 2010 to 2013 a cycle of «rheumatologist schools» for physicians of primary contact was held with discussions about inflammatory back pain criteria, variants of the onset and algorithm of the early diagnosis of AS. To assess the effectiveness of schools, medical records of patients directed to a rheumatologist with AS diagnosis were analysed. The study included patients with newly SpA in a given year: 36 people in 2009 (base year), 42 – in 2010, 54 - in 2011, 58 patients in 2012, 64 cases in 2013. All participants underwent clinical examination with determination of HLA B27, radiographs of the pelvis, if necessary - MRI of sacroiliac joints (1,5 Tl, T2 mode with fat sat).
Results. The result was improving of AS detection in Kazan population: from 2009 to 2013 significantly (p<0,05) decreased the time from onset of symptoms to the time of diagnosis: 8,4±2,5 years in 2009, the base year, to 4,2±1,3 years in 2010, 3,5±1,7 years in 2011, 2,9±1,9 years in 2012, 2,8±1,7 years in 2013. Proportion of women among patients with AS was 16.7% in 2009 to 26.2% in 2010, 29.6% in 2011 and 29.3% in 2012, 31.2% in 2013.
In 2009 non-radiological stage of SpA was not found in any patient. In 2010, according to MRI of sacroiliac joints (the presence of osteitis), non-radiological stage was exhibited in 16.7% of patients, in 2011 - 20.3%, in 2012 - 27.5% and in 2013 -29.7% of patients.
Conclusion. Experience in conducting educational activities in Kazan led to improving of early AS diagnosis.

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EVALUATION OF THE TWO-STEP REFERRAL STRATEGY FOR AXIAL SPONDYLOARTHRITIS IN THE SPONDYLOARTHRITIS CAUGHT EARLY COHORT

Abawi O., van den Berg R., van der Heijde D., de Hooge M., Bakker P., Huizinga T. van Gaalen F.
Rheumatology, LUMC, Leiden, The Netherlands

Introduction. In primary care no referral strategy exists for patients with chronic back pain (CBP) with possible axial spondyloarthritis (axSpA). Recently, a non-invasive, easily applicable two-step referral strategy was developed, based on a computer-generated model (1).
Aim. To validate this strategy in the SPondyloArthritis Caught Early (SPACE)-cohort.
Materials and Methods. In the first step of the strategy, psoriasis, alternating buttock pain (ABP) and improvement of back pain by exercise (IBPE) are registered. If ≥2 are present, the patient is referred. In the second step, if ≤1 is present, HLA-B27 is tested; positive patients are referred. The SPACE cohort includes patients with CBP (≥3 months, ≤2 years, onset <45 years, n=192).
Performance of the model was evaluated (sensitivity, specificity and LR) using ASAS axSpA criteria as external standard (2). For the false positively and false negatively referred patients, post-test probabilities for axSpA were calculated based on LR products for the presence of SpA features (3), with a LR product of ≥78 (probability of ≥80%) defined as cut-off for probable axSpA.
Results. Seventy-four patients had axSpA, 61 of which would have been referred by the strategy (sensitivity 82.4%). The 13 false negatives are obligatory HLA-B27- and have sacroiliitis on imaging, 3/13 (23%) on X-ray. The strategy referred 93/192 patients (specificity 72.9%). Of the false positive patients, 8/32 (25%) were HLA-B27+. Half of these 32 patients (n=16) had ABP and IPBE, which are features of inflammatory back pain, which itself is not specific for axSpA. Although none of these false positives fulfil the ASAS criteria, 6/32 (19%) had probable axSpA (figure).
Conclusions. The two-step referral strategy performed well in SPACE. This shows the potential of referral strategies for early recognition of axSpA. However, all patients in SPACE were already referred to the rheumatologist. Thus, the performance of this model in primary care remains to be addressed in further studies.

Referred to rheumatologist by referral strategy	axSpA by ASAS criteria Yes	No
Yes	61	32
No	13	86

Sensitivity: 82.4%	Specificity. 72.9%	LR+: 3.04	LR–: 0.24

Post-test probability for axSpA

Number of anamnestic features present in false positive patients (n=32)	0-20% n (%)	20-50% n (%)	50-80% n (%)	≥80% probable axSpA) n (%)
3: ABP, IBPE and psoriasis (n=2)	1 (3)	0 (0)	0 (0)	1 (3)
2: ABP andIBPE (n=16)	8 (25)	3 (9)	3 (9)	2 (6)
Psoriasis and IBPE (n=5)	2 (6)	2 (6)	0 (0)	1 (3)
ABP and psoriasis (n=1)	1 (3)	0 (0)	0 (0)	0 (0)
1*: ABP (n=2)	0 (0)	0 (0)	0 (0)	2 (6)
IBPE (n=3)	0 (0)	0 (0)	3 (9)	0 (0)
Psoriasis (n=0)	n/a	n/a	n/a	n/a
0* (n=3)	0 (0)	1 (3)	2 (6)	0 (0)

Post-test probability for axSpA

Number of anamnestic features present in false negative patients (n=13)	0-20% n (%)	20-50% n (%)	50-80% n (%)	≥80% (probable axSpA) n (%)
1: ABP (n=2)	0 (0)	1 (8)	0 (0)	1 (8)
IBPE (n=7)	3 (23)	2 (15)	0 (0)	2 (15)
Psoriasis (n=2)	0 (0)	1 (8)	1 (8)	0 (0)
0 (n=2)	0 (0)	0 (0)	0 (0)	2 (15)

Anamnestic features: ABP: alternating buttock pain; IBPE: Improvement of back pain by exercise, psoriasis.
*: These patients are referred due to HLA-B27 positivity, not anamnestic features.

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P52

IMPACT OF UVEITIS ON CHARACTERISTICS OF PATIENTS WITH ANKYLOSING SPONDYLITIS

Zepa J.[1,2], Bulina I.[1,3], Lavrentjevs V.[1], Zepa L.[4], Priedite I.[5], Nikitina-Zake L.[4], Lejnieks A.[2,6], Andersone D.[1,3]
[1]Dept. of Rheumatology, Pauls Stradins Clinical University Hospital, Riga; [2]Riga Stradins University; [3]University of Latvia; [4]Biomedical Research and Study Centre of Latvia; [5]Institution of Radiology, Pauls Stradins Clinical University Hospital, Riga; [6]Riga East Clinical University Hospital, Latvia

Introduction. Ankylosing spondylitis (AS) is a chronic, systemic, inflammatory disease with varied manifestations. Uveitis is the most common extraarticular location of AS - it occurs approximately in one third of the patients. Does AS with uveitis differ from AS without uveitis? The impact of the presence of uveitis during the course of AS still remains a challenge. The objective of this study was to detect the link between the uveitis ever during the course of the AS and routinely measured parameters in patients with AS.
Materials and Methods. 108 AS patients classified by the modified New York diagnostic criteria were divided into two groups: with and without uveitis. The following parameters were chosen for characteristics of the groups: the age of AS onset (AOO), C-reactive protein (CRP), functional (BASFI) and metrological (BASMI) indices, intermalleolar distance (IMD) for the evaluation of hip involvement.
Results. The mean value of parameters in AS group with uveitis (n=38) was: AOO - 24.5 years (SD 5.92), CRP - 11.7 mg/l (SD 14.99), BASFI - 3.0 (SD 2.43), BASMI - 3.5 (SD 2.42), IMD - 125.3 cm (SD 23.98). The mean value of AOO, CRP, BASFI, BASMI and IMD in AS group without uveitis (n=70) was respectively 26.9 years (SD 7.05), 17.3 mg/l (SD 21.55), 3.8 (SD 2.76), 3.7 (SD 2.71) and 117.6 cm (SD 28.60). The values of the parameters were not statistically different between the groups.
Conclusions. These results suggest that uveitis does not impact the routinely measured spinal/articular and inflammatory signs in patients with AS. Thus it can be proposed that aspects of the pathogenesis, genetics of the uveitis in the patients with AS do not interfere with pathways of articular/spinal damage. Further investigations are needed.

P53

EVALUATION OF REFERRAL MODELS FOR AXIAL SPONDYLOARTHRITIS IN PRIMARY CARE IN THE SPONDYLOARTHRITIS CAUGHT EARLY COHORT

Abawi O., van den Berg R., van der Heijde D., van Gaalen F.
Rheumatology, LUMC, Leiden, The Netherlands

Introduction. Several models have been proposed to refer patients with possible axial spondyloarthritis (axSpA) to the rheumatologist.
Aim. To evaluate the performance of published referral models for axSpA in the SPondyloarthritis Caught Early (SPACE)-cohort.
Methods. Ten referral models were found in literature and tested in the Leiden SPACE cohort, which includes patients with back pain (≥3months–≤2years, onset <45years; n=192). Imaging was omitted from models if used, as it is unfeasible for screening in primary care.

Model	Criteria	Referif
Brandt I	HLA-B27, IBP (based on 3 criteria[1]; positive if 1/3 criteria fulfilled)	≥1 out of 2 positive
Brandt II	HLA-B27, IBP (positive if 2/3 criteria fulfilled)	≥1 out of 2 positive
Brandt III	HLA-B27, IBP (positive if 3/3 criteria fulfilled)	≥1 out of 2 positive
Braun[2]	Psoriasis, buttock pain, improvement of back pain by exercise (if ≤1 positive answer, HLA-B27 is tested)	≥2 positive or ≤1 positive and HLA-B27 positive
Braun alt.	Psoriasis, alternating buttock pain, improvement of back pain by exercise (if ≤1 positive answer, HLA-B27 is tested)	≥2 positive or ≤1 positive and HLA-B27 positive
MASTER[3]	HLA-B27, IBP, family history for ankylosing spondylitis, good response to NSAIDs	≥2 out of 4 positive
RADAR[4]	HLA-B27, IBP, family kistory for SpA, good response to NSAIDs, extra-articular manifestations (uveitis, psoriasis or IBD	≥2 out of 5 positive
RADAR 2/3	IBP, good response to NSAIDs, extra-articular manifestations (uveitis, psoriasis or IBD)	≥2 out of 3 positive
CaFaSpA 1 pt[5]	IBP (ASAS), family history for SpA, good response to NSAIDs	≥1 out of 3 positive
CaFaSpA 2 pt	IBP (ASAS), family history for SpA, good response to NSAIDs	≥2 out of 3 positive

Performance of the models was evaluated (sensitivity, specificity, PPV, LR+) using classification by ASAS axSpA criteria as external standard. For referred patients not fulfilling ASAS criteria, post-test probability for axSpA was calculated based on the LR product for presence of SpA features. A LR product ≥78 (post-test probability ≥80%) was used as cut-off for probable axSpA. Patients who were incorrectly not referred met the ASAS axSpA criteria by fulfilling the clinical arm only or the imaging arm (imaging arm only or both arms).
Results: In total, 74/192 patients fulfilled axSpA criteria; 48 with imaging+ (n=15 radiographic sacroiliitis). Most models performed well regarding sensitivity/specificity. The Braun alt. model has the most balanced sensitivity/specificity and highest LR+. All models that include HLA-B27 miss axSpA patients with imaging+, 14-23% with radiographic sacroiliitis (depending on the model). PPV of the models is low, indicating that many patients are referred erroneously. However, 6-16%(depending on the model) of these patients have a post-test probability ≥80% for axSpA.

In SPACE: 74 patients fulfilling ax SpA criteria 118 patients not fulfilling ax SpA criteria			Referred patients fulfilling ax SpA criteria	Referred patients not fulfilling ax SpA criteria	Referred patients not fulfilling ax SpA criteria	Patients not referred but fulfilling ax SpA criteria	
Model	LR+	PPV	n (sens.)	n (spec.)	with ≥80% ax SpA n	imaging arm	clinical arm only
Brandt I	1.08	0.40	73 (0.99)	108 (0.08)	7	1/1	-
Brandt II	1.27	0.44	71 (0.96)	89 (0.24)	7	3/3	-
Brandt III	1.87	0.54	60 (0.82)	52 (0.56)	6	13/13	-
Braun	1.90	0.54	63 (0.85)	53 (0.55)	7	11/11	-
Braun alt.	3.04	0.66	61 (0.82)	32 (0.73)	6	13/13	-
MASTER	2.67	0.63	52 (0.70)	31 (0.74)	5	21/22	1/22
RADAR	2.27	0.59	64 (0.86)	45 (0.62)	6	10/10	-
RADAR 2/3	1.52	0.49	43 (0.58)	45 (0.62)	4	23/31	8/31
CaFa SpA 1 pt	1.27	0.44	69 (0.93)	87 (0.26)	6	5/5	-
CaFa SpA 2 pt	2.18	0.58	41 (0.56)	30 (0.75)	3	26/33	7/33

Conclusions. Most referral models performed well in the SPACE cohort. However, this cohort includes patients already referred from primary care, probably causing overestimation of performance of all models. All models miss patients fulfilling the ASAS imaging arm, 14-23% of which have radiographic sacroiliitis, which is highly undesirable. Moreover, large numbers of patients referred unnecessarily might lead to a burden for health care systems. Further studies should be conducted in primary care setting to evaluate these models in their target population.

Reference

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P54

VALIDATION OF TOUCH-SCREEN QUESTIONNAIRES IN SPONDYLOARTHROPATHIES

Cunha-Miranda L.[1], Santos H.[1], Miguel C.[1], Barcelos F.[1], Silva C.[1], Fernandes S.[1], Borges J.[1], Trinca R.[2], Vicente V.[3], Aguiar P.[3,4]
[1]Rheumatology; [2]Nursing, Instituto Português De Reumatologia; [3]Statistics, Eurotrials Scientific Consultants; [4]Escola Nacional de Saúde Pública, Universidade Nova de Lisboa, Lisboa, Portugal

Introduction. The use of questionnaires has a key role in the follow-up of patients with spondyloarthropaties in accessing disease activity, disability and quality of life. With the increasing use of new technologies, it is mandatory to access if the merge of questionnaires in computer assisted platforms are clinically the same.
Objectives. To evaluate and validate an electronic based BASDAI, BASFI and AsQol questionnaires in a touch-screen platform.

Table I. Validation of questionnaires.

	Touch-screen	Paper	ICC* (Touch-screen vs Paper)
BASDAI Score (n=55)			
Mean (standard deviation)	3.09 (2.53)	3.29 (2.65)	0.977
Cronbach's Alpha	0.952	0.961	
BASFI Score (n=53)			
Mean (standard deviation)	2.49 (2.19)	2.63 (2.22)	0.958
Cronbach's Alpha	0.938	0.948	
ASQOL Score (n=54)			
Mean (standard deviation)	6.76 (5.87)	6.80 (5.87)	0. 940
Cronbach's Alpha	0.938	0.935	

*ICC: Intraclass Correlation Coefficients.

Methods. Patients followed at our biologic clinic first were evaluated with a paper version BASDAI, BASFI and AsQol questionnaires and after with the electronic version. The touch-screen was specially developed for our patients, integrating software that recognized the patient by disease through a bar code and presented the questionnaires according to the disease. Concordance between paper rand touch-screen questionnaire was done through Intraclass Correlation Coefficients. Internal consistency was evaluated by Cronbach's alpha coefficient.
Results. 55 patients with spondyloarthropathies were included, 32.7% had psoriatic arthritis, 67.3% ankylosing spondylitis. 58.2% were female; mean age was 46.77+11.72 years with the mean disease duration of 10.49 + 8.85 years. 54.9% had less than 12 years of scholarship.
Conclusions. We have validated the use BASDAI, BASFI and AsQol in touch-screen technology to access patients with spondyloarthropathies. There is a very good concordance between the gold standard and the new platform. That will allow us to use a tablet based technology in our biologic clinic.

P55

SPONDYLOARTHRITIS WITH AND WITHOUT CONCOMITTANT PSORIASIS

Hansen I.M.[1], Bakland G.[2], Førre Ø.[3]
[1]Medical dept., Helgelandssykehuset Mo i Rana, Mo i Rana; [2]Rheumatology Dept., University Hospital of Northern Norway, Tromsø; [3]Rheumatology Dept., Oslo University Hospital, Oslo, Norway

Background. Spondyloarthritis is a rheumatic disease with axial and peripheral symptoms. It is divided into 6 groups; Ankylosing spondylitis, Psoriatic arthritis, Entero-associated spondyloarthritis, Reactive arthritis, Unspecified spondyloarthritis and Juvenile spondyloarthritis. There is an ongoing discussion whether it is one disease or separate diseases. The prevalence of spondyolarthritis have been reported ranging from 0,3% to 1,9% in different populations. The proportion with concommitant psoriasis varies from 13% to 60%. Psoriatic arthritis, especially with predominantly peripheral symptoms is often seen as a separate entity, and will often not be included in the spondyloarthritis cohorts. We do not know if spondyloarthritis with concommitant psoriasis is different from spondyloarthritis without psoriasis.
Objectives. To compare spondyolarthritis patients from Rana, Norway with and without psoriasis. Do they differ in age, age at symptom debut, disease duration, gender, body mass index, inflammation, disease activity, physical function, proportion of synovitis, inflammatory back pain, radiological sacroiliitis, sacroiliitis on mri, axial disease only, combined peripheral and axial disease, inflammatory bowel disease, acute uveitis, reactive arthritis and HLAB27 positivity? Do the data support that psoriatic arthritis is a separate entity or is it just spondyloarthritis with psoriasis?

Statistic testing with SPSS Chi square test or Students T-test.

	Spa-patients with psoriasis		Spa-patients without psoriasis		Total		Chi square test
	N	%	N	%	N	%	
Total	162		225		387		
Female	82	52,6	137	59,3	219	56,6	n.s.
Male	74	47,4	94	40,7	168	43,4	n.s.
Synovitis	81	51,9	87	37,7	168	43,4	0,003
Inflammatory backpain	127	81,4	211	91,3	338	87,3	0,005
AS (new York criteria)	20	12,8	55	23,8	75	19,4	0,005
Axial disease only	78	48,1	140	62,2	218	56,3	0,007
Peripheral and axial disease	52	32,1	68	30,2	120	31	n.s.
Inflammatory bowel disease	4	2,6	14	6,1	18	4,7	n.s.
Reactive arthritis	4	2,6	11	4,8	15	3,9	n.s.
HLA B27 positive	50	32,5	107	47,7	157	41.6	0,01
Acute uveitis	11	6,8	24	10,7	35	9	n.s.
Mri of si-joints performed					273		
Mri with sacroileitis according to ASAS-criteria	29	27,9	50	29,6	79	28,9	n.s.
	Mean		Mean				T-test
Age in years	51,5		47,4				0,003
Age at symptomdebut	31,6		28				0,01
Disease duration	19,5		18,7				0.527
Body mass index	28,02		27,72				n.s.
Crp	6,6		6,1				n.s.
BASDAI	4,42		4,36				n.s.
BASFI	2,75		2,52				n.s.

Methods. Patients with spondyloarthritis, including psoriatic arthritis were recruited from hospital registers, family doctors and by advertisement in local newspaper. Clinical data, Crp and HLAB27 were collected, x-ray and mri of SI-joint was performed if the patient had inflammatory back pain. If they fulfilled the ESSG-critera for Spondylarthritis they were included. The first degree relatives of the included patients were contacted and asked for symptoms of synovitis or inflammatory backpain by questionnaire. Symptomatic relatives were investigated, and included if they fulfilled the ESSG-critera. 387 spondylarthrits patients were included.
162 patients with psoriasis were compared to 225 patients without psoriasis. 273 patients had mri of SI-joints.
Results. Spondyolarthritis patients with psoriasis are approximately 4 years older at examination, age at symptom debut 2,6 years older and they are more likely to have peripheral synovitis. They were less likely to have inflammatory back pain, axial disease only, radiological sacroiliitis and HLAB27 positivity. There was no difference in gender, disease duration, body mass index, inflammatory bowel disease, reactive arthritis, acute uveitis, Crp, disease activity and physical function. They were as likely to have sacroiliitis (ASAS-definition).
Conclusions. Spondyloarthritis with and without concomitant psoriasis have many similarities. The age difference can reflect that it takes time to develop more manifestations. There is more peripheral disease with concomitant psoriasis. A possible explanation can be that concomittant psoriasis modifies spondyloarthritis.

P56

52-WEEK RESPONSE TO BRODALUMAB, AN ANTI-IL-17R ANTIBODY, IN SUBJECTS WITH PSORIATIC ARTHRITIS

Mease P.J.[1], Genovese M.C.[2], Greenwald M.W.[3], Ritchlin C.T.[4], Beaulieu A.[5], Deodhar A.[6], Newmark R.[7], Feng J.Y.[7], Erondu N.[7], Nirula A.[7]
[1]Swedish Medical Center and University of Washington, Seattle, WA; [2]Stanford University, Palo Alto, CA; [3]Desert Medical Advances, Palm Desert, CA; [4]University of Rochester Medical Center, Rochester, NY, USA; [5]Laval University, Laval, Quebec, Canada; [6]Oregon Health & Science University, Portland, OR; [7]Amgen Inc, Thousand Oaks, CA, USA

Aim. Assess long-term efficacy and safety of brodalumab in patients with psoriatic arthritis (PsA) in an open-label extension (OLE) of a Phase 2 study (NCT01516957).
Patients and Methods. Adults (n=168) with active PsA for ≥6 months were randomized to brodalumab (n=113) (280 or 140 mg Q2W) or placebo (pbo) (n=55). At week 12, all subjects entering the OLE received 280 mg brodalumab (Q2W). Outcomes at week 52 included American College of Rheumatology 20% response (ACR20), ACR50, changes in Disease Activity Score for 28-joint count (DAS28) and ACR response components. Efficacy was analyzed using as observed data. Safety was assessed by monitoring adverse events (AEs).
Results. Of the 159 subjects completing week 12,156 entered the OLE (51 280 mg, 53 140 mg, 52 pbo). By week 52, 22 subjects had discontinued. The percent of ACR20 and ACR50 responders at week 12 was higher in the brodalumab arms than in pbo (44% 280 mg, 40% 140 mg, 19% pbo for ACR20; 16% 280 mg, 15% 140 mg and 4% pbo for ACR50). Response rates improved through to week 52 (56% prior 280 mg, 71% prior 140 mg, 50% prior pbo for ACR20; 27% prior 280 mg, 47% prior 140 mg and 38% prior pbo for ACR50). DAS 28 and several ACR components improved from baseline to week 52. Most common AEs included nasopharyngitis, upper respiratory tract infection and psoriatic arthropathy. Serious AEs were reported by 10 subjects. No clinically significant neutropenia was reported.
Discussion. Brodalumab was associated with sustained musculoskeletal and skin symptom improvements.
Conclusions. These results support continued evaluation of brodalumab in PsA.

P57

SLEEP AND QUALITY OF LIFE IN PSORIATIC ARTHRITIS

Arancibia L.A., Gonçalves C.R., Sampaio P.B., Goldenstein-Schainberg C.
Disciplina de Reumatologia, Faculdade de Medicina, Universidade de São Paulo, Brazil

Introduction. Psoriatic arthritis (PsA) is a multisystemic disease influenced by co morbidities including depression, sleep disturbances and fatigue, which may affect episodes of disease exacerbation and patients' quality of life. The aim of this study was to assess the quality of sleep, fatigue, anxiety, depression in a cohort of PsA patients and correlate findings with clinical parameters of the disease.
Methods. This was a descriptive, observational, cross-sectional study that included PsA patients diagnosed according to CASPAR criteria from a single rheumatology center during January to April 2014. Sleep involvement was assessed by the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness scales (ESS); poor quality of sleep was considered if PSQI >5 and sleepiness if ESS ≥11. Fatigue was evaluated by the FACIT-F (lower scores = worse), anxiety/depression by the HADS (higher scores = worse).PsA disease activity, functional capacity and quality of life were evaluated by DAS28, HAQ and SF-36 respectively. According to DAS 28, patients were classified in Group I (DAS28<2.6), Group II(DAS28=2.6-3.2)and Group III(DAS28>3.2).PsA patients with known psychiatric disorder were excluded. Student t-tests, Mann-Whitney and Fisher test were used for statistical analysis. $p<0.05$ was considered significant.
Results. A total of 29 PsA patients were evaluated, 14M:15F, with mean age 51.9±11.1yrs old (27-70yrs) and mean disease duration 15.27±12.78yrs (2-52yrs).Sleep evaluation revealed that PSQI was >5 for 12/16(75%), 4/6 (67%) and 7/7(100%) and EES ≥11 was 4/16(25%), 1/6(17%) and 3/7(43%) patients from groups I, II and III respectively($p>0,05$).For Groups III, II and I, FACIT-F was 83, 101 and 117; HAQ was 1.22, 0.69 and 0.4; SF-36 was 89.7, 95.3 and 95.3;HAD-A was 8.4, 8.3 and 5.75; HAD-D was 7.7, 5.17 and 5.4.
Conclusions. We describe for the first time poor quality of sleep, sleepiness, fatigue, anxiety and depression in patients with moderate/high disease activity associated to worse quality of life. These findings reinforce the need of a multidisciplinary approach for the patient with PsA and larger studies in order to clarify the role of these parameters in the induction of disease activity.

P58

HIGH PREVALENCE OF UNDIAGNOSED AXIAL SPA IN PATIENTS BELOW 45 YEARS OF AGE WITH CHRONIC BACK PAIN VISITING PHYSIOTHERAPISTS, ORTHOPEDICS AND OPHTHALMOLOGISTS

Gangji V[1], Tant L.[1], Delmotte N.[2], Van den Enden M.[2], Mielants H.[3]
[1]Rheumatology Dept., Erasme Hospital, Bruxelles; [2]AbbVie, Wavre; [3]Rheumatology Dept., University Hospital, Gent, Belgium

Introduction. Patients with chronic back pain visiting orthopedics and physiotherapists are seldom diagnosed with axial spondyloarthritis (SpA). Patients suffering from uveitis are usually visiting an ophthalmologist. Referring these patients to a rheumatologist may help diagnosing SpA and initiating appropriate treatment. The objective of this observational study was to evaluate whether screening patients with chronic back pain with simple referral recommendations is useful in detecting axial SpA.
Methods. 161 patients >18-<45 years suffering from chronic back pain (>3 months) and back pain at night without known axial SpA were included. Patients were evaluated for presence of inflammatory back pain (IBP) and SpA features specified in the ASAS criteria for axial SpA. If IBP was present in combination with ≥1 SpA feature, it was advised to refer the patient to a rheumatologist.
Results. Out of the 161 included patients, 72 satisfied the referral criteria. Nevertheless, 117 patients were referred to a rheumatologist. For 85 patients feedback from the rheumatologist was available. In 37 (43.5%) diagnosis of axial SpA was confirmed, among which 15 did not fulfil the referral criteria. ASAS criteria were fulfilled in 33 patients (22 in the imaging and 11 in the clinical arm).
Conclusions. There is a high prevalence of undiagnosed axial SpA in patients below 45 years of age with chronic back pain visiting physiotherapists, orthopedics and ophthalmologists. A prevalence of 30% (22/72) of axial SpA was noted amongst patients satisfying the referral criteria used in this study. Among patients not satisfying the referral criteria, but still referred to a rheumatologist, 33% (15/45) were diagnosed with axial SpA. This may lead to conclude that the referral criteria used in this study were too stringent. When applying the ASAS classification criteria for axial SpA, 89% (33/37) of diagnosed patients were classified as axial SpA. The clinical arm seems also important for early diagnosis.

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DEFINING FLARE IN SPONDYLOARTHRITIS: THRESHOLDS OF DISEASE ACTIVITY VARIATIONS

Godfrin-Valnet M.[1], Puyraveau M.[2], Wendling D.[3]
[1]Rheumatology, [2]Investigation Center, [3]University Teaching Hospital, CHRU, Besançon, France

There is no definition of flare in spondyloarthritis (SpA). The aim of this study was to evaluate thresholds of disease activity variations using validated composite indexes.
Methods. SpA patients (ASAS criteria) prospectively followed with at least two visits were evaluated. Patients and physician answered at each visit the question: "do you consider your SpA/ patient in a state of flare?" Variations of BASDAI and ASDAS between visits were assessed and associated to the change of perception of a flare (yes/no). ROC curves were built to assess thresholds of variation in BASDAI and ASDAS associated with the change Flare between visits.
Results. The patients were issued from a prospective series of 250 SpA. 99 situations with at least 2 visits were analyzed. The main characteristics of this cohort were: 67% men, mean age 45±12 years; disease duration: 16±10 y; 84% HLA-B27 positive; purely axial SpA: 81%; PASS at baseline: 56%; mean CRP: 8.6±13.5 mg/l. Mean BASDAI and ASDAS-CRP at baseline were 4.3±2.2 and 2.5±1.1 respectively. The kappa coefficient of agreement between patient and physician for considering a flare was 0.68. The main results of the ROC curves are reported in the table:

Variation of the activity score	Flare considered by Patient and physician	Flare considered by Physician	Flare considered by Patient
BASDAI	**2.1**	**2.1**	**2.1**
Number of 2 visits	67	97	76
AUC	0.715	0.671	0.694
Specificity %	83	82	83
Sensitivity %	59	53	55
ASDAS-CRP	**1.3**	**0.7**	**1.3**
Number of 2 visits	30	45	34
AUC	0.740	0.698	0.682
Specificity %	100	72	100
Sensitivity %	47	59	40
ASDAS-ESR	**0.8**	**0.8**	**0.8**
Number of 2 visits	28	28	31
AUC	0.779	0.779	0.759
Specificity %	91	91	92
Sensitivity %	56	56	50

Conclusion. According to these results, an increase from a non-flare state of at least 2.1 units in BASDAI, 0.8 units in ASDAS-ESR or 1.3 units in ASDA-CRP is associated to (and may define) a flare, as considered by the patient and the physician.

P60

JUVENILE SPONDYLOARTHRITIS (JSpA) IN A COHORT OF BRAZILIAN PATIENTS

Perez M.O., Aikawa N.E., Carrasco S., Sampaio-Barros P.D., Gonçalves C.R., Saad C.G.S., Moraes J.C.B., Goldenstein-Schainberg C.
Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Introduction. JSpA affects children ≤16yrs of age and is characterized by lombar and sacroliliiac involvement, peripheral lower limbs arthritis, enthesitis and association with HLAB27 in 60-90%.
Objectives. To describe clinical profile of Brazilian patients with JSpA from a single tertiary university center and determine HLAB27 prevalence.
Materials and Methods. Descriptive cross-sectional study of JSpA patients according to 2004 ILAR criteria. Demographic, clinical and radiological data were obtained by chart review. HLAB27 was analysed by flow cytometry (Becton Dickinson). Fisher test was performed for statistical analyses and $p < 0.05$ was considered significant.
Results. Fifty patients with JSpA were evaluated, mean age=31.5±11.1yrs(15-60), mean age at initial manifestations=12.2±2.73yrs(7-16), mean age at diagnosis=19.8±9.0yrs(7-44) and mean disease duration=18.9±11.4yrs(3-44). Most were males (44M:6F,88%) and whites (n=42,84%). Eleven (22%) patients had a first-degree relative with SpA. At disease onset, 70% (35/50) presented peripheral manifestations namely asymmetric oligoarthritis in 24/35 (68.5%), polyarthritis in 10/35 (28.5%) and symmetric oligoarthritis in 1/35 (2.8%) while 58% (29/50) had axial involvement characterized by inflammatory back pain

(25/29=86%) and buttocks pain (22/29=75.8%); enthesitis was documented in 21/50 (42%) subjects, all at the Achilles tendon insertion and 12/14 (85.7%) patients with extra-articular involvement had anterior uveitis. Sera ANA were positive in 16% (6/38) and 87% were HLAB27+. At follow, 58% (28/48) developed radiological sacroiliitis<10yrs of onset. HLAB27 was associated to early sacroiliitis<5yrs of symptoms (p=0.02), elevated ESR (p=0.04) and progression to ankylosing spondylitis (AS) (p=0.02). All JSpA patients received NSAIDs, mostly naproxen (n=24,5%), 43 sulfasalazine (93%) and 36 MTX (78%); 17 were on anti-TNF therapy.
Conclusion. Despite different environment and/or genetic, though in accordance to worldwide literature, Brazilian JSpA patients are typically white boys with peripheral joint manifestations and diagnosed late. Peripheral enthesitis, anterior uveitis and late radiological sacroiliitis are common. The high prevalence of HLAB27+ associated to early sacroiliitis and progression to AS reinforces its role as a marker of disease severity in children.

P61

MORTALITY AND CARDIOVASCULAR COMORBIDITY IN PSORIATIC ARTHRITIS

Juneblad K., Alenius G.M.
Dept. of Public Health and Clinical Medicine/Rheumatology, University of Umeå, Sweden

Aim. To analyze Standardized Mortality Rate Ratio (SMR) and Standardized Incidence Ratio (SIR) of cardiovascular events, e.g. stroke and acute myocardial infarction (AMI), in patients with Psoriatic Arthritis (PsA) compared with the general population.
Materials and Methods. 464 individuals (234m, 230f) from the county of Västerbotten with Psoriatic Arthritis were included. Patients included had during the period 1995-2005 been examined and the diagnosis had been set by a specialist in rheumatology. Patients included had a mean PsA disease duration of 20.4±11.1 years. To investigate mortality and courses of death, data was extracted from the National Causes of death Register in Sweden from 2000 to 2011 and compared with the general population of the same county. To investigate the incidence of acute cardiovascular disease, e.g. stroke and AMI, data was collected from the national in-patient care register between 1995-2010 and compared with the general population of the same county. Accumulated disease activity index over time was calculated as a composite index where number of swollen joints, level of ESR and doctors estimated disease activity were extracted from patients charts every 2 years during PsA disease duration.
Results. During follow-up 29 PsA patients had an acute event of AMI/stroke, of these 3 AMI were fatal. SIR (95%CI) was 0,597 (0.40-0.86). 44 patients died (24m, 19f) during the period of the study. SMR (95%CI) was 1.28 (0.89-1.63). Dominant causes of death were diseases of the circulatory system (n=21, 47.7%) (12m, 9f) (stroke n=3, AMI n=5) followed by malignant neoplasm's (n=14, 31.8%). SMR (95%CI) for death in diseases of the circulatory system was 1.645 (1.02-2.52). Activity index was significantly associated with death, OR (95%CI) 1.99 (1.41-2.80) adjusted for age and gender.
Conclusion. PsA patients had a minor increase in SMR compared with the general population. Among patients, death was associated with activity index. In our study we found no association between PsA and the risk of developing an acute cardiovascular event such as stroke or AMI.

P62

PATIENTS WITH NR-AXSPA SHOW A STATISTICALLY HIGHER DISEASE BURDEN IN CLINICAL PRACTICE COMPARED WITH PATIENTS WITH RADIOGRAPHIC AXIAL SPA

Jacobsson L.T.[1], Husmark T.[2], Theander E.[3], Henriksson K.[4], Büsch K.[5]*, Johansson M.[5]*
*Contributed equally
[1]Dept. of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg; [2]Dept. of Rheumatology, Falu Hospital, Falun; [3]Dept. of Rheumatology, Skåne University Hospital Malmö, Lund University, Malmö; [4]Rheumatology City Clinic, Stockholm; [5]AbbVie AB, Stockholm, Sweden

Background. The ASAS axial SpA classification criteria was published in 2009 but so far there has been limited research on axial SpA patients in clinical practice. There is no diagnose code for non-radiographic axial SpA (nr-axSpA) and it is unclear which diagnosis these patients receive in clinical practice. Characterization of nr-axSpA patients in clinical practice is lacking in comparison with radiographic axial SpA (rad-axSpA).
Objective. The aim of this study was to characterize patients with axial SpA in clinical practice and to investigate similarities/differences between radiographic and non-radiographic axial SpA.
Methods. This is a prospective, cross-sectional, multi-center cohort study from Sweden. SpA patients (diagnosed with Psoriatic Spondylitis (M07.2), Ankylosing Spondylitis (M45), Spinal entesopathy (M46.0), Sacroiliitis, not elsewhere classified (M46.1), Other specified inflammatory spondylopathies (M46.8), or Inflammatory spondylopathy, unspecified (M46.9)) were consecutively recruited from the clinical settings of the participating study centers. Patients were followed for three months via an online questionnaire. At baseline, the rheumatologist assessed the ASAS axial SpA criteria and registered information on disease history, extra articular manifestations, and treatments.
The patients answered online questionnaires capturing patient demographics, disease activity and function (BASDAI, BASFI, HAQ-S, etc.), QoL (EQ-5D, AS-QoL), health care resource use, and work ability (WPAI). p-values, unadjusted for covariates, were calculated using chi-square tests for categorical variables and t-tests for continuous variables.
Results. 251 patients were included of whom 197 (78%) were classified as axial SpA. Of those, 125 (63%) were classified as rad-axSpA and 72 (37%) were classified as nr-axSpA according to the ASAS axial SpA criteria. The nr-axSpA patients were diagnosed with AS (35%), other specific inflammatory spondylopathies (31%), inflammatory spondylopathy unspecified (19%), psoriatic spondylitis (11%), and sacroilitis, not elsewhere classified (4%). Time between symptom onset and diagnosis was 9.0 (8.4) years for rad-axSpA and 6.7 (7.1) years for nr-axSpA. The nr-axSpA patients showed a higher disease burden compared with rad-axSpA patients, e.g. higher BASDAI (4.1 vs. 2.7), VAS global (4.3 vs. 2.9), VAS pain (4.4 vs. 2.9), and ASDAS (CRP) (2.3 vs. 1.9) (Table).

Variable	Radiographic Axial SpA n=125	Non-radiographic Axial SpA n=72	p-value
BASDAI, mean, n (%)	2.7 (65)	4.1 (61)	<0.001
BASDAI >4.0, %, n (%)	28 (65)	55 (61)	0.004
BASFI, mean, n (%)	2.5 (65)	3.0 (61)	0.29
VAS global, mean, n (%)	2.9 (65)	4.3 (61)	0.006
VAS pain, mean, n (%)	2.9 (65)	4.4 (61)	0.003
ASDAS CRP, mean, n (%)	1.9 (58)	2.3 (57)	0.03
ASDAS ESR, mean, n (%)	1.8 (58)	2.3 (56)	0.007
Current NSAID use, %, n (%)	60 (100)	71 (100)	0.13
Current MTX or SSZ use, %, n (%)	28 (100)	22 (100)	0.37
Current anti-TNF use, %, n (%)	50 (100)	40 (100)	0.17

Conclusions. In this study, from Swedish clinical practice, we included patients from rheumatology clinics with pre-specified diagnoses most likely to be classified as axial SpA. The results show that the nr-axSpA patients have a statistically higher burden of disease than patients with rad-axSpA.

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WORK PARTICIPATION IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS AND CHRONIC LOW BACK PAIN – CAFASPA 2 STUDY

van Hoeven L.[1,2], Boonen A.[3], Hazes J.M.W.[1], Weel A.E.A.M.[1,2]
[1]Rheumatology, Erasmus Medical Centre, Rotterdam; [2]Rheumatology, Maasstad Hospital, Rotterdam; [3]Rheumatology, Maastricht University Medical Centre, Maastricht, The Netherlands

Introduction/Aim. Chronic low back pain (CLBP) is one of the main complaints for consulting general practitioners. Recent studies show that up to 40% of the CLBP patients suffer from axial spondyloarthritis (axSpA). It is well known that CLBP influences work participation leading to work disability and increased health costs. However little is known about the relation between axSpA and work participation and whether this differs in CLBP patients. Therefore our aim is to observe the work participation in a large cohort of axSpA and CLBP patients derived from primary care.
Material and Methods. All patients of the CaFaSpA 2 study are used; a cross-sectional study in CLBP patients (18-45 years). Patients were checked for the presence of axSpA, split up in ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA) based on the ASAS criteria. Roland Morris Disability Questionnaire (RMDQ), BASDAI and ASDAS were collected. Work participation was assessed in the past 7 days using the Work Productivity and Activity Impairment (WPAI) questionnaire. Four sub scores (all percentages) were derived; absenteeism (health related inability to work), presenteeism (health related reduction in work productivity), work impairment (combines absenteeism and presenteeism) and impairment in activities performed outside of work. Higher percentages indicates worse work outcomes. Descriptive statistics are given.
Results. In total 579 primary care patients participated, (41% male, mean age 35.9 years). 95 (16.4%) patients were classified as axSpA, of which 24 as AS and 71 as nr-axSpA. Most patients (n=412; 71%) were employed. In the working population the mean absenteeism was 6.2%, mean presenteeism was 26.0% and mean work impairment was 29.7%.
Conclusions. To the best of our knowledge this is the first study that looked into the absenteeism and presenteeism in a cohort of CLBP and axSpA patients. AS seems to have a greater impact on absenteeism, presenteeism, work and activity impairment than nr-axSpA and CLBP.

Table I. Study characteristics.

	AS (n=24)	nr-axSpA (n=71)	CLBP (n=484)
Male, no. (%)	6 (25%)	30 (42%)	202 (42%)
Age, mean ± SD, years	38.6±5.8	36.8±6.6	37.3±6.5
Duration of low back pain, mean ± SD, years	9.3±9.9	9.6±7.4	9.2±7.7
RMDQ, mean ± SD	11.1±6.8	7.0±5.3	8.0±6.1
BASDAI, mean ± SD	4.9±2.1	3.9±2.1	4.2±2.3
ASDAS, mean ± SD	2.8±0.9	2.2±0.8	2.3±0.9
Working characteristics			
Working, no. (%)	15 (62.5)	55 (77.5)	342 (72.2)
Number of hours work per week, mean ±SD	24.4±14.6	29.3±16.2	29.2±15.5
Absenteeism, % ± SD (in working population)	7.7±19.7	4.9±19.0	6.4±20.4
Presenteeism, % ± SD (in working population)	31.3±38.5	21.8±31.9	26.5±30.7
Work impairment, % ± SD (in working population)	35.6±41.1	25.0±33.8	30.1±33.1
Activity impairment, % ± SD	44.6±37.9	31.1±32.5	34.4±32.4

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DO EXTRA-ARTICULAR MANIFESTATIONS INFLUENCE OUTCOME IN ANKYLOSING SPONDYLITIS? 12 YEAR RESULTS FROM OASIS

Essers I.[1], Ramiro S.[2,3], Stolwijk C.[1], Landewé R.[2,4], van der Heijde D.[5], Van den Bosch F.[6], Dougados M.[7], van Tubergen A.[1]
[1]Rheumatology, MUMC and CAPHRI, Maastricht; [2]ARC, Amsterdam, The Netherlands; [3]Rheumatology, Hospital Garcia, Almada, Portugal; [4]Rheumatology, Atrium MC, Heerlen; [5]Rheumatology, LUMC, Leiden, The Netherlands; [6]Rheumatology, Ghent University Hospital, Ghent, Belgium; [7]Rheumatology, Paris-Descartes University, Cochin Hospital, Paris, France

Introduction/Aim. To assess whether extra-articular manifestations (EAMs) are associated with worse functional disability, quality of life (QoL), and more radiographic damage in patients with ankylosing spondylitis (AS) over time.
Materials and Methods. 12-Year follow-up data from the Outcome in Ankylosing Spondylitis International Study were used, complemented with data on EAMs extracted from medical charts.
Function was assessed by Bath AS Functional Index (BASFI) and physical component of the Short form-36, QoL by ASQoL and EuroQoL, and radiographic damage by modified Stoke AS Spine Score (mSASSS). Time-adjusted generalized estimating equations analyses were performed to assess whether prevalent and incident EAMs, respectively, were associated with these outcomes over time.
Results. 216 Patients were included (154 (71%) men, mean age 43.6 years (SD 12.7), mean symptom duration 20.5 years (SD 11.7), and mean follow-up 8.3 years (SD 4.1)). At baseline, 39 (18%) patients had acute anterior uveitis (AAU), 15 (7%) inflammatory bowel disease (IBD), and 9 (4%) psoriasis (prevalent cases). During follow-up, 19 patients developed AAU, 9 IBD, and 5 psoriasis (incident cases). Psoriasis was not taken into account in further analyses, because of low prevalence and incidence in this cohort. Prevalent AAU was univariably associated with worse mSASSS (B=7.19, 95%-Confidence Interval [CI] 0.19 to 14.19, p=0.04), but not in a multivariable model. Incident IBD showed in multivariable analysis a trend towards worse BASFI over time (B=1.40, 95%-CI -0.04 to 2.84, p=0.06).
Conclusion. The presence of AAU and IBD was not associated with a worse QoL or radiographic damage in this longstanding AS cohort. Incident IBD showed a trend towards more functional disability.

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ANKYLOSING SPONDYLITIS AND RISK OF ISCHEMIC HEART DISEASE: A POPULATION-BASED COHORT STUDY

Essers I.[1,2,3], Stolwijk C.[1,2,3], Boonen A.[2,3], De Bruin M.L.[1], Bazelier M.T.[1], de Vries F.[1,3,4,5], van Tubergen A.[2,3]
[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht; [2]Rheumatology, MUMC+, Maastricht; [3]CAPHRI, Maastricht; [4]Clinical Pharmacy and Toxicology, MUMC+, Maastricht, The Netherlands; [5]MRC Lifecourse Epidemiology Unit, Southampton General Hospital, Southampton, UK

Introduction/Aim. For ankylosing spondylitis (AS), the literature on the risk of ischemic heart disease (IHD) and acute myocardial infarction (AMI) is relatively scarce and conflicting. We aimed to investigate the incidence and risk of IHD and AMI, including the role of NSAIDs on this risk, in patients with AS compared with population controls.
Methods. All patients with newly diagnosed AS (n=3,809) from the British Clinical Practice Research Datalink (1987-2012) were matched with up to 7 controls by year of birth, gender and practice (n=26,197). Incidence rate ratios (IRRs) and hazard ratios (HR) for development of IHD and AMI were calculated. Stepwise analyses were performed adjusting for age, gender, comorbidity, and drug use, including NSAIDs.
Results. At baseline, 4.3% of the patients had IHD and 1.8% had AMI, compared with 3.4% and 1.4% of the controls, respectively. After exclusion of pre-existing IHD or AMI, the overall IRRs were 1.18 (95%-confidence interval [CI] 0.96-1.46) and 0.91 (95%-CI 0.65-1.27) for IHD and AMI, respectively. Compared with controls, the overall age-gender adjusted HR for developing IHD was 1.20 (95%-CI 0.97-1.48), and for AMI 0.91 (95%-CI 0.65-1.28) for patients with AS. In female patients, the risk of developing IHD was increased (HR 1.81, 95%-CI 1.18-2.79), but after adjustment for all possible risk factors only a non-significant trend was found (HR 1.36, 95%-CI 0.86-2.14). In particular, recent NSAID use explained this change (HR IHD adjusted for age-gender-NSAID use 1.47, 95%-CI 0.93-1.36).
Conclusion. Female patients with AS are at increased risk of developing IHD, but this effect is associated with recent NSAID use. However, it cannot be excluded that NSAID use is (partly) a reflection of active disease.

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PATIENTS WITH AS DO NOT ADAPT TO THEIR DISEASE: EVIDENCE FROM THE 'THEN-TEST' IN PATIENTS TREATED WITH TNF-INHIBITORS

Essers I.[1], van Tubergen A.[1], Heldmann F.[2], Baraliakos X.[2], Braun J.[2], Boonen A.[1]
[1]MUMC+ and CAPHRI, Maastricht University, The Netherlands; [2]Rheumazentrum Ruhrgebiet, Herne, Germany

Introduction/Aim. Although never formally studied, rheumatologists feel that patients with ankylosing spondylitis (AS) tend to positively adjust to their disease. The 'then-test' is an approach to prove response shift. This theory states that patients that respond to treatment re-rate their former health as worse as initially thought, and that the magnitude of treatment response is associated with a larger gap between the initial and retrospective assessment of health. The aim of the present study was to understand whether patients with AS adapt to their disease, using the 'then-test'.
Materials and Methods. Data were retrieved from AS patients in the Evaluation of Recombinant Infliximab Therapy (ASSERT) and continued in the European AS Infliximab Cohort (EASIC). At enrollment into EASIC, patients were asked to re-rate their well-being before the start of infliximab in ASSERT using a 'then-test' for the Bath AS Global Score (retrospective BAS-G). Initial and retrospective BAS-G were compared using a paired t-test, and stability of the gap over time in EASIC was assessed using Mixed Linear Models. Linear regression analysis was performed to understand whether treatment response was associated with the gap between initial and retrospective score.
Results. 86/103 Patients (mean age 39.8 years (SD 10.4); mean disease duration 10.8 years (SD 8.5)) contributed to the analyses. Patients judged their BAS-G initial at 7.0 (SD 1.6), and by 'then-test' at 7.2 (SD 2.3) (p=0.45), resulting in a non-significant difference between the retrospective and initial BAS-G of 0.2 (SD 2.7). The 'then-test' showed to be stable over time (p=0.13). Multivariably, the gap was irrespective of treatment response, and only associated with initial BAS-G (p<0.01) and baseline disease activity (p=0.02).
Conclusion. Patients with AS were able to retrospectively judge their well-being, and irrespective of treatment response. In this setting, the 'then-test' could not prove adaptation by response shift in AS.

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DISEASE ACTIVITY STRONGLY INFLUENCES WORK PRODUCTIVITY AND PHYSICAL HEALTH RELATED QUALITY OF LIFE IN EARLY AXIAL SPONDYLOARTHRITIS: DATA FROM THE SPACE-COHORT

Roeterink A.[1], De Hooge M.[1], Van de Vijver J.[1], Van den Berg R.[1], Dagfinrud H.[2], Landewé R.[3], Van Oosterhout M.[4], Ramonda R.[5], Huizinga T.[1], Van der Heijde D.[1], Van Gaalen F.A.[1]
[1]LUMC, The Netherlands; [2]Diakonhjemmet Hospital, Norway; [3]AMC; [4]GHZ, The Netherlands; [5]University of Padova, Italy

Background. Not much is known about the relation between disease activity and work productivity loss (WPL) and health-related quality of life (HRQoL) in early onset axial spondyloarthritis (axSpA).
Objectives. To assess the relationship between disease activity and WPL and HRQoL in early axSpA.
Methods. The SPACE cohort recruited patients (n=345) with chronic back pain (≥3 months, ≤2 years, onset <45 years) in 5 European centres. In patients fulfilling the ASAS axSpA criteria (n=131), the following assessments were done: ASDAS and BASDAI (disease activity), BASFI (functional ability), SF-36 (HRQoL) and Work Productivity and Activity Impairment (WPAI). Patients were grouped according to ASDAS: inactive disease (<1.3), moderate disease (1.3-2.1), high disease (2.1-3.5) and very high disease activity (>3.5). BASDAI and BASFI scores ≥4 were considered as high disease activity and impaired function, respectively. HRQoL was reported as the SF-36 physical (PCS) and mental component summary (MCS) scores. Impact of disease on work productivity (WP) was defined as percentage of absenteeism and presenteeism and WPL (combines absenteeism and presenteeism) with greater scores indicating greater impairment.
Results. Figure 1 shows that PCS decreased significantly with increasing ASDAS. Moreover, absenteeism, presenteeism and WPL increased as ASDAS increased (figure 1b). MCS was not influenced by disease activity. PCS and WPL had a similar association with BASDAI and BASFI (low vs.high BASFI; PCS 46.3 vs. 47.2, p=0.76; WPL; 30.9% vs. 66.7%; absenteeism; 7.1% vs. 24.9%; presenteeism; 28.9% vs. 61.1%, all p<0.001).
Conclusions. In early axial SpA, disease activity highly influences physical HRQoL and work productivity. These findings support aiming for clinical remission in patients with early axial SpA.

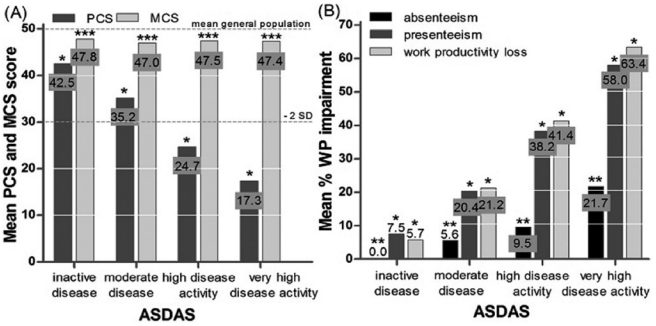

Fig. 1. PCS, MCS (A) and WPAI components (B) in association with ASDAS in patients with axSpA. *p<0.001; **p=0.02; ***p=0.97.

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SUBSTANTIAL DECREASE IN WORK PRODUCTIVITY AND PHYSICAL HEALTH-RELATED QUALITY OF LIFE IN CHRONIC BACK PAIN OF RECENT ONSET: DATA FROM THE SPACE-COHORT

Roeterink A.[1], De Hooge M.[1], Van de Vijver J.[1], Van den Berg R.[1], Dagfinrud H.[2], Turina M.[3], Van Oosterhout M.[4], Ramonda R.[5], Huizinga T.[1], Van der Heijde D.[1], Van Gaalen F.A.[1]
[1]LUMC, The Netherlands; [2]Diakonhjemmet Hospital, Norway; [3]AMC; [4]GHZ, The Netherlands; [5]University of Padova, Italy

Background. Ankylosing spondylitis is associated with work productivity loss (WPL) and a decreased health-related quality of life (HRQoL). Little is known about early axial spondyloarthritis.
Objectives. To determine the impact of chronic back pain (CBP) of recent onset on HRQoL and work productivity in young patients.
Methods. The SPACE-cohort includes patients with CBP (≥3 months, ≤2 years, onset <45 years) in 5 European centers (n=345). Patients who met the ASAS axial SpA criteria were classified as axSpA (n=131). Patients with 1 SpA feature were defined as possible SpA (n=167), and those with no SpA features as no SpA (n=47). The 36-item Short-Form (SF-36) and Work Productivity and Activity Impairment (WPAI) surveys were used to assess HRQoL and WP. SF-36 physical (PCS) and mental component summary (MCS) scores were compared to the general population (score of 50±10 SD represents the general population). Impact of disease on WP was defined as percentage of absenteeism, presenteeism and WPL (combines absenteeism and presenteeism) with greater scores indicating greater impairment.
Results. 304 patients completed the SF-36 and 230 the WPAI. Figure 1 shows a significant reduction of ≥2 SD in mean PCS scores in all subgroups compared to the general population while MCS approximated the general population.. Absenteeism was highest in no SpA and possible SpA (21.6% and 18.5%; p=0.10 and p=0.05, compared to axSpA 10.3%). Presenteeism was highest in no SpA and possible SpA (46.9% and 44.7%), compared to axSpA (34.7%). WPL was highest in no SpA and possible SpA (55.2% and 48.3%) compared to axSpA (37.5%),
Conclusion. WP and physical HRQoL are already greatly reduced in young patients with CBP of recent onset.

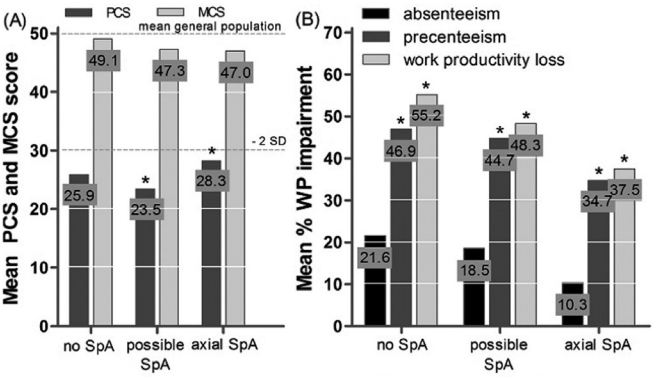

Fig. 1. PCS, MCS (A) and WPAI components (B) in patients with chronic back pain ≥3 months but ≤2 years and <45 years of age. *p<0.05 axSpA vs. possible SpA and axSpA vs. no SpA.

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RENAL DISEASE IN A COHORT OF AXIAL SPONDYLOARTHRITIS

Meirinhos T., Aguiar R., Ambrósio C., Barcelos A.
Rheumatology Dept., Centro Hospitalar do Baixo Vouga E.P.E., Aveiro, Portugal

Introduction. The association of IgA nephropathy with ankylosing spondylitis was established in the 1970's. However, the global prevalence of renal disease in patients with axial spondyloarthritis (aSpa) is unknown.
Aim. To evaluate the prevalence of renal disease in a cohort of patients with aSpa and to identify possible relations between its occurrence and disease features.
Patients and Methods. The medical records of all patients diagnosed with aSpa, followed at our department, were reviewed. Data collected included extra-articular involvement, disease activity radiological damage, urinalysis, CPR, creatinine, IgA, uricemia levels, relevant comorbidities (type II diabetes and high blood pressure) and NSAIDs use.
Statistical analysis was performed using SPSS version 17.0® and significance was set at 0.05.
Results. 93 patients were enrolled; 52 were male. Mean age was 45.7±15.1 years and mean disease duration was 10.7±11.2 years. Incidence of peripheral disease and uveitis was respectively 37.63% and 13.98%. HLA B27 was present in 38.71% of patients, absent in 31.18% and unknown in the remaining. Mean BASDAI was 3.47±2.49 and mean mSASSS was12.02±17.23; 31.18% of patients had high blood pressure and 8.60% had type II diabetes. Regarding urinalysis, it was abnormal in 13.98 % of patients: 10.75% had microscopic hematuria, 2.15% had proteinuria >500mg/24h and 1.1% had both. Mean serum creatinine, uricemia, CRP and IgA level were 0.82±0.21, 4.55±1.56, 0.68±0.92 and 264.74±110.21 mg/dL, respectively. No significant difference in serum creatinine, uricemia or IgA level was found between patients who had normal or abnormal urinalysis. Creatinine level was not significantly different amongst patients who had NSAIDs on demand, daily or no NSAIDs. No significant correlation was identified between disease activity, duration or radiological damage and any laboratory studies. Patients with urine abnormalities did not have higher disease activity and damage, or long disease duration.
Conclusion. Although a considerable prevalence of urinalysis abnormalities was found in this cohort, these changes did not correlate with disease characteristics. None of the patients was diagnosed with IgA nephropathy.

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CLINICAL PERFORMANCE OF SPONDYLOARTHRITIS CRITERIA IN PATIENTS AGED OVER 45 YEARS: WHICH OF THEM SHOULD BE APPLIED FOR DIAGNOSIS IN LATE-ONSET ANKYLOSING SPONDYLITIS?

Bendahan L.T., Mendes J.G., Klemz B.N.C., Gomes C.M.F., Oliveira T.L., Pinheiro M.M.
Universidade Federal de São Paulo (Unifesp/ EPM), Rheumatology Division, São Paulo, Brazil

Background. Recently, the classification criteria for axial and peripheral spondyloarthritis (SpA) have been validated in younger patients, according to ASAS group. However, there is no consensus about which criteria should be used in patients with late-onset back pain, arthritis or enthesitis.
Aim. To evaluate the clinical performance of SpA criteria for diagnosis in patients aged over 45 years.
Patients and Methods. A total of 329 patients were enrolled in this study. Ninety-seven patients with psoriatic arthritis were excluded. Thirty-three (10%) patients were over 45 years old when the first axial (ax) and peripheral (p) symptoms emerged. All of them were evaluated by a rheumatologist, according to the following classification criteria: modified New York (mNY), 1984; ESSG, 1990; Amor, 1991; ax-ASAS, 2009 and p-ASAS, 2010. Sacroiliac MRI was performed when necessary. Besides, it was applied 3 criteria (Calin, Berlin and ASAS) for defining inflammatory back pain (IBP). Comparisons among all the criteria were performed in order to assess specificity and sensitivity of each one. The mNY criteria was chosen as gold-standard. P<0.05 was set as significant.
Results. The average age and duration of symptoms were 57.6±7.9 years and 7.75±5.0 years. Eighteen (54,5%) patients were male and familial history of SpA was found in 20%. Almost 70% of patients had both axial and peripheral involvement. IBP was reported by 66.7% patients. Mean ASDAS-VHS, BASFI, BASMI, mSASSS were 3.0±1.2, 4.73±2.45, 4.37±2.46, 13.4±11.8, respectively. Extra-articular manifestations were found in 12 (36,6%) patients. The best sensitivity and specificity for SpA was verified for ax-ASAS (above 80%), followed by Amor and p-ASAS (above 70%) criteria.
Conclusion. Our data showed that symptoms of SpA might start after 45 years old, particularly in a world which aging has been faster. Thus, the ASAS criteria might be applied in SpA patients aged over 45 years for classification and diagnosis.

P71

MALE AND FEMALE PATIENTS WITH AXIAL SPONDYLOARTHRITIS EXPERIENCE DISEASE ACTIVITY DIFFERENTLY: RESULTS FROM THE GLAS COHORT

Arends S.[1,2], Maas F.[1], van der Veer E.[3], Bos R.[2], Efde M.[2], Leijsma M.K.[1], Bootsma H.[1], Brouwer E.[1], Spoorenberg A.[1]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen; [2]Rheumatology, Medical Center Leeuwarden; [3]Laboratory Medicine, University Medical Center Groningen, The Netherlands

Aim. To investigate whether there are differences in Bath AS disease activity index (BASDAI), AS disease activity score (ASDAS), and their individual components between male and female patients with axial spondyloarthritis (SpA).
Methods. All consecutive patients from the GLAS cohort who visited the outpatient clinic between January 2011 and December 2012 were included in this cross-sectional analysis. All patients fulfilled the modified New York criteria for AS (>90%) or the ASAS criteria for axial SpA. Disease activity was assessed using BASDAI (consisting of 6 questions on a numerical rating scale) and ASDAS (composite index from BASDAI questions 2, 3 and 6, patient global assessment of disease activity (GDA), and C-reactive protein (CRP)).
Results. Of the 467 included patients, mean age was 45 years (SD±13), mean duration of symptoms 17 years (range 0-61), 66% were male, and 80% HLA-B27+. Male patients were significantly older, had longer disease duration, and were more frequently HLA-B27+. Extra-articular manifestations, comorbidity, and medication use were comparable between both sexes.
BASDAI and ASDAS were significantly higher in female patients. Analyzing the BASDAI and ASDAS questions separately, significant differences were found for fatigue (Q1), spinal pain (Q2), enthesitis (Q4), duration of morning stiffness (Q6), and patient GDA, whereas no differences were observed for peripheral arthritis (Q3) and intensity of morning stiffness (Q5). Differences remained statistically significant after correcting for age, disease duration, and HLA-B27 status. CRP levels were comparable between sexes, indicating that the difference in ASDAS can be explained by subjective instead of objective aspects of disease activity.
Conclusion. This cross-sectional study in daily clinical practice shows that patient-reported measures of disease activity were significantly worse in female axial SpA patients. We recommend being aware of these differences when interpreting BASDAI and ASDAS results in research and clinical practice.
Acknowledgement. The GLAS cohort was supported by an unrestricted grant from Pfizer. Pfizer had no role in the design, conduct, interpretation, or publication of this study.

Table I. Disease activity in male and female patients with axial SpA.

	Males (n=309)	Females (n=158)	*p*-value
BASDAI	3.4 (1.8-5.2)	4.2 (2.4-6.4)	0.001
ASDAS	2.2 (1.5-2.9)	2.5 (1.8-3.3)	0.008
BASDAI Q1	4 (3-7)	6 (4-8)	0.000
BASDAI Q2	4 (2-6)	5 (3-7)	0.001
BASDAI Q3	2 (0-5)	2 (0-6)	0.784
BASDAI Q4	2 (1-5)	4 (1-7)	0.001
BASDAI Q5	4 (2-6)	4 (2-7)	0.088
BASDAI Q6	2 (1-5)	3 (1-6)	0.038
Patient GDA	3 (2-6)	4 (2-7)	0.011
CRP (mg/L)	3 (2-7)	3 (2-8)	0.733
CRP ≥5	115 (38%)	60 (39%)	0.814

Values are presented as median (IQR) or number of patients (%).

P72

DISEASE ACTIVITY IS THE MAJOR DETERMINANT OF QUALITY OF LIFE AND PHYSICAL FUNCTION IN PATIENTS WITH EARLY AXIAL SPONDYLARTHRITIS – RESULTS FROM THE ESPERANZA COHORT

Fernández-Carballido C.[1], Navarro-Compán V.[2], Moreno M.[3], Juanola X.[4], Mulero J.[5], de Miguel E.[2], on behalf of the ESPERANZA Study Group
[1]University General Hospital, Elda, Alicante; [2]University Hospital La Paz, Madrid; [3]Parc Taulí Hospital, Sabadell; [4]Bellvitge University Hospital, Barcelona; [5]Puerta de Hierro Hospital, Madrid, Spain

Aim. First, to describe health related quality of life (HRQoL) and physical function (PF) and in patients with early axial Spondyloarthritis (axSpA). Second, to analyse the associations between HRQoL and PF with disease activity and radiographic damage.
Methods. Baseline data from 259 patients (67% male) meeting ASAS axSpA criteria from the Esperanza cohort were used. Linear regression analyses were employed to evaluate the associations between disease activity (BASDAI, physician', patient' global and night pain VAS and CRP levels) and radiographic damage (BASRI-spine and mNY score for sacroiliac joints) with HRQoL (ASQoL), physical function (BASFI) and spinal mobility (BASMI).
Results. Mean (SD) values were: disease duration 13.3 (6.8) months, age 32.2 (6.9) years, BASDAI 3.8 (2.3), CRP 9.7 (13.2) and BASMI 1.4 (1.3). Outcome mean (SD) values were 5.9 (4.8) for ASQoL and 2.4 (2.3) for BASFI. ASQoL was associated with all disease activity parameters (BASDAI: Std β 0.645; $p<0.01$; CRP: β 0.272; $p<0.01$) and spine BASRI (β: 0.149; $p<0.05$) in the univariable analysis, but only with disease activity in the multivariable analysis (BASDAI: β 0.336; $p<0.001$). BASFI was associated with disease activity (BASDAI; β 0.691; $p<0.01$; CRP: β 0.300; $p<0.01$) and radiographic damage (BASRI-s: β 0.154; $p<0.05$; radiographic sacroiliitis degree: β 0.146; $p<0.05$). However, in the multivariable analysis, PF remained only associated with disease activity (BASDAI: β 0.473; $p<0.001$). Spinal mobility was mainly associated with radiographic damage (BASRI-s: β 0.322; $p<0.01$ and radiographic sacroiliitis: β 0.282; $p<0.01$) in the univariable models but only a trend was observed for this association in the multivariable analysis.
Conclusion. In patients with early axSpA, HRQoL and PF are already impaired. Both outcomes are mainly associated with disease activity.

Table I. Linear regression univariable analysis adjusted for age and gender.

	ASQoL		BASFI		BASMI	
	Std Beta	*p* value	Std Beta	*p* value	Std Beta	*p* value
CRP (mg/L)	0.272	$p<0.01$	0.300	$p<0.01$	0.187	$p<0.01$
ESR (mmHg)	0.113	$p<0.1$	0.186	$p<0.01$	0.074	Ns
VAS (0-10) physician	0.558	$p<0.01$	0.616	$p<0.01$	0.285	$p<0.01$
VAS (0-10) patient	0.640	$p<0.01$	0.650	$p<0.01$	0.117	$p<0.1$
VAS (0-10) night back pain	0.597	$p<0.01$	0.593	$p<0.01$	0.106	$p<0.1$
BASDAI	0.645	$p<0.01$	0.691	$p<0.01$	0.167	$p<0.01$
ASDAS	0.564	$p<0.01$	0.608	$p<0.01$	0.193	$p<0.01$
MASES	0.239	$p<0.01$	0.239	$p<0.01$	0.052	Ns
BASRI spine	0.149	$p<0.05$	0.154	$p<0.05$	0.322	$p<0.01$
Sacroiliitis xRay	0.078	ns	0.146	$p<0.05$	0.282	$p<0.01$

Table II. Linear regression multivariable analysis adjusted for age and gender.

	ASQoL		BASFI		BASMI	
	Std Beta	*p* value	Std Beta	*p* value	Std Beta	*p* value
CRP (mg/L)	0.107	0.07	0.126	0.02	0.032	0.7
VAS (0-10) physician	0.207	0.01	0.266	<0.001	0.246	0.02
VAS (0-10) night back pain	0.203	0.02	0.058	0.4	-0.085	0.4
BASDAI	0.336	<0.001	0.473	<0.001	0.043	0.7
MASES	0.096	0.1	0.078	0.2	-	-
BASRI spine	-0.011	0.9	-0.058	0.4	0.198	0.06
Sacroiliitis xRay	-	-	0.093	0.2	0.022	0.8

P73

THE IMPACT OF ANKYLOSING SPONDYLITIS ON WORK IMPAIRMENT – RESULTS FROM THE SCOTLAND REGISTRY FOR ANKYLOSING SPONDYLITIS (SIRAS)

Jones G.T., Dean L.E., Macfarlane G.J., on behalf of SIRAS
Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, UK

Introduction/Aim. The impact of ankylosing spondylitis (AS) on work status is substantial. While the majority of studies focus on absenteeism, decreased workplace productivity (presenteeism) is also important when assessing the impact of disease on work-life, yet remains relatively understudied.
The aim of the current study was to describe the prevalence of, and factors associated with, work impairment in AS.
Materials and Methods. SIRAS collects data on clinically diagnosed AS patients in Scotland. Clinical data, including BASDAI and BASFI, is obtained from medical records, and postal questionnaires provide patient-reported data, including pain and fatigue. Work impairment 'during the past week' was assessed using the Work Productivity and Activity Impairment questionnaire. Factors associated with work impairment were identified using logistic regression, and stepwise models were used to determine independent risk factors. Results are given as odds ratios with 95% confidence intervals. Additionally, the population attributable risks associated with independent risk factors were calculated.
Results. SIRAS includes clinical and patient-reported information on 959 patients (73% male; mean age 52yrs). 55% of participants were currently working, of whom 10% had missed work (during the past week) due to their AS. However, 71% of workers reported some workplace impairment during this time. Factors independently associated with work impairment (any versus none) were: moderate/severe fatigue (4.8; 2.4-9.4), poor physical function (BASFI≥4: 2.6; 1.2-5.6) and chronic widespread pain (3.7; 1.9-7.3). The population attributable risks associated with these factors were 19%, 9% and 13% respectively.
Discussion/Conclusions. The majority of employed AS patients did not report missing any recent absenteeism. However, many experienced impairment whilst working, the key identifiable drivers of which were fatigue, pain and poor physical function. Targeted, non-pharmacological treatments, such as cognitive behavioural therapy, in addition to traditional therapeutic targets, may help to improve overall work productivity. This may reduce the economic impact of the disease and, ultimately, could improve overall work retention.

P74

ENTHESITIS - PREVALENCE AND ASSOCIATION WITH CLINICAL VARIABLE IN AXIAL SPONDYLOARTHRITIS

Hax V., Moro A.L.D., Kohem C.L., Jost D., Wroblewski J., Guerra B., Xavier R.M., Mancuso A.C.B., Evaldt C.A., Copetti A.P., Prates D., Palominos P.E.
Rheumatology Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Introduction. Enthesitis characterized by focal inflammatory changes at the insertion of tendons, ligaments, or capsule into bones, is an important variable in the classification criteria of spondyloarthritides. The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) analyzes 13 anatomical sites and is a validated tool for assessing enthesitis.
Objective. Our goal is to report the frequency of enthesitis, its clinical impact and relation with the disease activity in patients with axial spondyloarthritis (SpA).
Patient and Methods. Cross-sectional study in a Rheumatology Clinic of the Hospital de Clínicas de Porto Alegre, Brazil, including patients fulfilling ASAS criteria for SpA. Data were extracted from medical records. Clinical, laboratory and demographic variables and disease indexes were investigated.
Results. Among the 115 patients included, 56,5% were male, 87,8% white, 66% HLA-B27 positive, with a mean age of 51,4 years and with a mean of 12,3 years since the diagnosis. Enthesitis was observed in 38,2% of the patients with a mean of 3,8 painful enthesis per patient, with the posterior iliac spine (21,4%) and first chondrosternal (20,7%) being the most commonly affected. Binary Poisson regression showed in the univariate analysis that patients with enthesitis presented higher mean scores of Bath Ankylosing Spondylitis Functional Index (BASFI; $p<0.001$) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; $p<0.001$). Enthesitis was also associated with a higher rate of nonsteroidal anti-inflammatory continuous use ($p=0.017$). Inflammatory markers, HLA-B27 and the use of DMARDs or biologics were not associated with MASES. However, multivariate analysis showed that MASES was associated only with BASDAI ($p<0.001$; RP: 1,344; IC 95%: 1,239–1,457).
Discussion. Enthesitis is a primary clinical feature in SpA and was a frequent manifestation in this observational study. MASES correlated with a higher score of disease activity and thus should be used routinely in clinical practice to improve patient care.

P75

DELAY TO DIAGNOSIS IN AXIAL SPA: NO IMPROVEMENT IN THE UK

Sykes M.P.[1], Doll H.[2], Sengupta R.[3], Gaffney K.[1]
[1]Rheumatology, Norfolk & Norwich University Hospitals NHS Foundation Trust, Norwich; [2]Oxford Outcomes, ICON Commercialisation and Outcomes, Oxford; [3]Rheumatology, Royal National Hospital for Rheumatic Diseases NHS Foundation Trust, Bath, UK

Introduction. Diagnostic delay has always been a major challenge in axial spondyloarthritis (axial SpA). We wished to determine whether there have been any recent improvements in the UK.
Methods. We established the time from symptom onset to diagnosis of axial SpA patients attending two large UK secondary care centres. The average delay was analysed against year of diagnosis.
Subgroup analyses were performed to identify if any patient characteristics predicted a shorter delay.
Results. Data were available on 1193 patients who had a physician-verified diagnosis of axial SpA (including 800 patients with ankylosing spondylitis). There was a 51% increase in new diagnoses in the last 5 years compared to the previous 5 year period (p<0.001). The mean delay to diagnosis was 8.53 years (SD 9.04), median delay 5.0 years (IQR 2-12) with no improvement in the last 5 years.
The presence of peripheral arthritis (p=0.025) or inflammatory bowel disease (p=0.024) was associated with a reduction in delay to diagnosis; those with peripheral arthritis being more likely to have been diagnosed within 2 years of symptom onset (OR 1.53; p=0.046).
Conclusions. The number of new cases of axial SpA has increased significantly, however there has been no improvement in delay to diagnosis.

P76

UNRAVELING THE FAMILIAL TENDENCY FOR ANKYLOSING SPONDYLITIS IN KOREA

Kim H.W.[1], Choe H.R.[2], Chang W.I.[2], Kim Y.G.[3], Yoo B.[3], Hur J.W.[1], Kim T.H.[4], Lee S.[5], Lee E.Y.[2]
[1]Dept. Internal Medicine, Eulji General Hospital, Seoul; [2]Dept. Internal Medicine, Seoul National University Hospital, Seoul; [3]Dept. Internal Medicine, Asan Medical Center, Seoul; [4]Dept. Internal Medicine, Hanyang University Hospital, Seoul; [5]Dept. Applied Statistics, Dankook University,Yongin, Korea

Introduction/Aim. Despite of the evidence of familial aggregation of ankylosing spondylitis (AS), familial tendencies are not fully explored. The purpose of this study was to examine the recurrence risk (RR) ratios in different degrees of relatives for Korean AS patients.
Patients and Methods. 526 consecutive unrelated AS probands (101 female, 425 male, mean age 35.5 years, mean disease duration 12.3 years, 88.7% HLA-B27 positive) fulfilling the modified New York criteria were face-to-face-interviewed by physicians, with elaborated questionnaire to investigate AS in other family members by the same criteria. A total of 12,051 relatives (2284, 5342 and 4425 for first, second and third-degree relatives (TDR), respectively) were included. The RR ratios for different degrees of relatives were elicited and subsequently stratified by gender and HLA-B27 status. The prevalence of AS among Korean in 2013 was estimated by the Korean National Health Insurance Service at 0.07%.
Results. The RR ratio was 53.8 for first-degree relatives (FDR) followed by 10.8, 9.0 for second-degree relatives (SDR) and TDR, respectively, indicating strictly decreasing in familiality. Among FDRs, siblings were more frequently affected than offspring or parents. For male probands, the overall RR ratio for FDR was 55.5, and 65 for female, implying higher familiality of female over male. Remarkably, all of affected SDRs and beyond were relatives of HLA-B27 positive probands.

Table. The relative recurrence risk ratio by gender in Korean AS patients.

Korean population prevalence (%)	Female 0.04		Male 0.09		All 0.07	
	RR % (95% CI)	RR ratio	RR % (95% CI)	RR ratio	RR % (95% CI)	RR ratio
Overall familial AS	0.8(0.5-1.0)	19.3	1.8(1.4-2.1)	19.5	1.3(1.1-1.5)	18.3
First degree	2.6 (1.7-3.5)	**65.0**	5.0 (3.8-6.3)	**55.5**	3.8 (3.0-4.5)	**53.8**
Parent	1.8 (0.6-3.0)	45.0	3.7 (2.0-5.3)	41.1	2.7 (1.7-3.8)	39.2
Offspring	2.5 (0.1-4.9)	62.5	5.1 (1.9-8.4)	56.6	3.9 (1.8-5.9)	55.3
Sibling	3.3 (1.7-4.8)	82.5	6.6 (4.3-8.9)	73.3	4.8 (3.4-6.1)	68.1
Second degree	0.4 (0.2-0.7)	**10.0**	1.1 (0.7-1.5)	**12.2**	0.8 (0.5-1.0)	**10.7**
Third degree	0.2 (0.0-0.4)	**5.0**	1.0 (0.6-1.4)	**11.1**	0.6 (0.4-0.9)	**9.0**

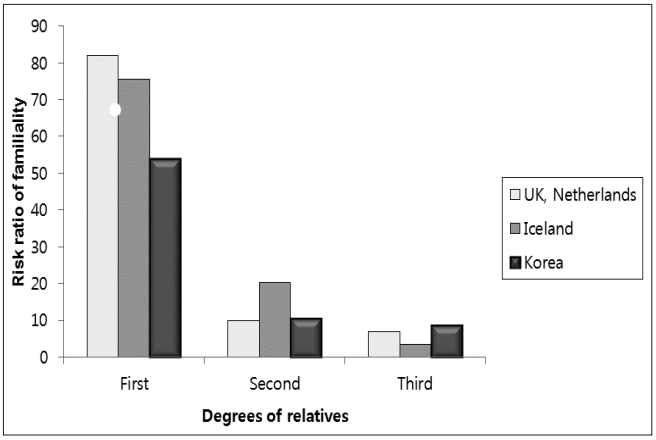

Fig. Recurrence risk ratios of familiarity in different countries. It shows familial tendency are decreasing as familial degree extends in order, though with lesser risk for FDR in our study.

Conclusion. We demonstrated strongest familiality of AS in FDRs, particularly in siblings. Despite of similar sharp decline pattern of familiality beyond SDR, lower RR ratio in FDR in our study, compared to previous Caucasian reports, indicates ethnic difference in heritance of the same disease. This study suggests familial tendency for AS can be explained by degrees of relationship, gender and HLA-B27, warranting further studies.

P77

EVALUATION OF A TRIAGE SYSTEM FOR PATIENTS WITH LOW BACK PAIN

Smet J.[1], Parijs R.[1], Vanheste R.[2], D'Haese K.[1], Van Boxstael A.[1], Vander Cruyssen B.[1], Ravelingien I.[1], Stubbe M[1]
[1]Dept. Rheumatology and Physiotherapy; [2]Dept. Radiology OLV Hospital, Aalst, Belgium

Introduction. Low back pain (LBP) is one the most common pain syndromes, 5-7% of the patients with LBP have spondyloarthritis (SpA). It is important to distinguish patients with SpA from other suffering from mechanical LBP. Early diagnosis and treatment allow to reduce discomfort, loss of function, costs and improve the prognosis. A minority of the patients is directly referred at the rheumatologist and the waiting time is often long; however his expertise is essential for the diagnosis and the treatment of these patients.
The objective of this study is to evaluate a triage system for patients with LBP which could be useful in the daily practice and improve the quality of care.
Methods. Patients younger than 60y with LBP for more than 3 months were included. Calin, Berlin, ASAS classification criteria and BASDAI score were collected by the rheuma nurse. Patients who fullfilled the Calin or Berlin criteria were seen by the rheumatologist (group A), the others by the physatrist (group B). Final diagnosis were collected and the proportion of patients with SpA among the 2 groups were analysed.
Results. Forty patients were already included, 17 in group A and 23 in group B. There was a majority of female (60% in group A and 77% in group B) and mean age ± SEM was 39±9y and 34±14y in groups A and B respectively. Response to NSAID was described by 82% of the patients in group A en 45% in group B as well as a positive famillial history for SpA in 76% and 13% in group A and B respectively. Prevalence of HLAB27 was 41% in group A. SpA was present among 11/17 (64,7%) patients in group A and 0/23 in group B.
Conclusions. The triage of the patients with LBP using paramedicals is largely feasible and powerful to refer early the patients with SpA at the rheumatologist. Such a system could be used as standard of care in the department of rheumatology.

P78

REMISSION IN SpA: ONLY ASDAS OR ALSO A BASDAI SCORING?

Nowik M., Simone D., Ferraccioli G.F., Gremese E.
Institute of Rheumatology & Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy

Aim. The BASDAI has been historically the most widely used clinical disease activity measure in spondyloarthritis. More recently, the ASDAS was introduced by the Assessment of SpA international Society. While BASDAI is a fully patient-oriented measure, ASDAS includes inflammatory markers among its items. In this study, we looked for an agreement between the definition of low disease activity assessed using ASDAS-CRP and BASDAI, and we tried to identify a cutoff value indicating remission on the BASDAI scale.
Patients and Methods. We evaluated a population of 187 patients meeting ASAS criteria for spondyloarthritis receiving follow-up at our division. For each patient, disease activity was assessed by BASDAI, ASDAS-CRP at the last available follow up. Receiver-operating characteristic (ROC) curves were drawn to identify the BASDAI cutoff indicating remission. The kappa coefficient was computed to evaluate agreement between the definition of remission according ASDAS and the previously indicated remission cutoff for BASDAI of 1 (1).
Results. In our population of 187 patients, of which 117 males (62.6%), mean BASDAI was 3.1±2.3, mean ASDAS-CRP was 1.8±1.0 mg/l. At the last follow up visit, 53 patients (28.3%) showed a BASDAI≤1 and 59 patients were in remission according to ASDAS (31.6%). This BASDAI cutoff (kappa coefficient 0.62), appeared to be more difficultly achieved in comparison to the ASDAS remission (p<0.001).
The ROC curve analysis showed that a value of 1.8 on the BASDAI scale was the cutoff indicating remission (AUC 0.91±0.02, p=0.02). The remission evaluated using BASDAI≤1.8 was achieved in 71 patients (38%) and good agreement was found between said cutoff and the definition of remission using ASDAS (kappa coefficient 0.72).
Conclusion. Our results show a good agreement between ASDAS remission and the previously indicated BASDAI remission ≤1. A value of BASDAI equal or less than 1.8 was found to have the strongest agreement with the ASDAS remission of 1.3.

Reference

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P79

GENETIC AND CLINICAL PREDICTORS OF RESPONSE TO TNF-BLOCKER IN AN ITALIAN AXIAL-SPA COHORT

Simone D., Canestri S., Nowik M., Messuti L., Miceli MC., Gremese E., Di Mario C., Tolusso B., Ferraccioli G.
Institute of Rheumatology & Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy

Introduction. Several genes besides HLA-B27 are associated to the development of different clinical manifestations within the spectrum of spondyloarthritides, while no one has ever been associated to a difference in the response, differently from other factors like sex and body mass index.
Aim. We aimed to evaluate the frequency of the polymorphism in the enhancer HS1/2A of the Ig Heavy 3'regulatory region, previously described as associated to autoimmune conditions (rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus), in patients with spondyloarthritis. We also aimed to identify the clinical features associated to this polymorphism and predictors of response to the anti-TNF treatment.
Methods. We evaluated 153 patients with a diagnosis of axial-Spa according to the 2009 ASAS criteria, on which, after informed consent, selective polymerase chain reaction of the region containing polymorphic HS1/2A alleles was performed. All patients in anti-TNF therapy were evaluated to identify predictors for disease-activity outcome.
Results. The frequency of allele *2 of the HS1/2A enhancer was significantly increased compared to healthy controls (65.7 vs 40.8%, p<0.001), while no difference was found within the different clinical subtypes of the disease. The logistic regression analysis showed that female patients and those with higher BMI were less likely to reach low disease activity [BMI:OR 40, 95%CI (4.2-333.3); sex:OR 142.8, 95%CI (8.9-1000)] or strong clinical response (BASDAI <1) [BMI:OR 7, 95%CI (1.6-31.2); sex:OR 1.8, 95%CI (1.1-6.3)] at 12 months follow up. Considering the mean time to reach BASDAI <1, female patients, patients with BMI>25 and not-carriers of the 2/2 genotype of HS1/2A showed to be slower responder to the anti-TNF.
Conclusion. Our data show an association in spondyloarthritis with the allele 2 of the gene enhancer HS1/2, similarly for what observed in other autoimmune diseases. Also, BMI, sex and the presence of a specific polymorphism of gene HS1/2A might influence the response to the anti-TNF therapy.

P80

VALIDITY OF ANKYLOSING SPONDYLITIS AND SPONDYLOARTHRITIS DIAGNOSES IN THE SWEDISH NATIONAL PATIENT REGISTER

Exarchou S.[1], Lindström U.[2], Sigurdardottir V.[3], Sundström B.[4], Askling J.[5], Eriksson J.K.[5], Forsblad d'Elia H.[2], Turesson C.[1], Kristensen L.E.[1], Jacobsson L.[2]
[1]Section of Rheumatology, Dept. of Clinical Sciences, Lund University, Lund; [2]Dept. of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, Gothenburg; [3]Dept. of Rheumatology, Falun Hospital, Falun; [4]Dept. of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå; [5]Clinical Epidemiology Unit, Rheumatology Unit, Dept. of Medicine, Karolinska Institutet, Stockholm, Sweden

Background. Using ICD-codes from the Swedish National Patient Register (NPR) offers unique opportunities for epidemiological studies of Ankylosing Spondylitis (AS) and undifferentiated Spondyloarthritis (uSpA). This study aims to validate the ICD-codes for AS and uSpA in the NPR against established classification criteria (modified New York - mNY, ASAS, Amor and ESSG criteria).
Methods. All patients with an ICD-code of AS or uSpA in the NPR 1966-2009 at a visit to a department of rheumatology or internal medicine, or corresponding hospitalization, were identified (n=20074). Following a structured procedure to achieve geographical representativeness, 500 random patients with a registered diagnosis of AS or uSpA in 2007-2009 were selected from 5 center in Sweden. A structured review of clinical records, with extraction of necessary information for the established classification criteria was performed and the positive predictive values (PPV) for fulfilling these were calculated.
Results. In this cohort 11472 (34% women) patients had received an AS diagnosis and 11004 (56% women) an uSpA diagnosis. The group having received both types of diagnoses had similar frequencies for fulfillment of mNY criteria, symptoms and signs of back disease as the group having been coded as AS only. Of those being coded as AS only, the PPV for fulfilling the mNY, any criteria set and any of the included criteria elements were 70%, 89% and 96% respectively. Of those with uSpA (without AS ever) the corresponding PPV values were 20%, 79% and 99% respectively.
Conclusion. AS or uSpA diagnoses in the NPR had a high validity, suggesting that case identification based on ICD-codes can be used for epidemiological studies of these diseases.

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COMPARISON OF HLA B27 TYPING BY FLOW CYTOMETRY AND POLYMERASE CHAIN REACTION ASSAY IN PATIENTS WITH ANKYLOSING SPONDYLITIS

Angeli R.S.[1], Duarte M.P.[3], Palominos P.E.[2], Zeni M.[3], Mancuso A.C.B.[4], Motta H.B.[3], Rojas B.[3], Gomes S.B.[3], Casagrande L.[3], Sgnaolin V.[5], Xavier R.M.[2], Schneider P.G.[2], Kohem C.L.[2]
[1]Federal University of Rio Grande do Sul, Porto Alegre; [2]Hospital de Clínicas de Porto Alegre, Dep. Rheumatology, Porto Alegre; [3]Federal University of Rio Grande do Sul, Porto Alegre; [4]Hospital de Clínicas de Porto Alegre, Dep. Statistic, Porto Alegre; [5]Biomedical Gerontology Graduate Program, São Lucas Hospital, Porto Alegre, Brazil

Introduction. HLA-B27 testing is of diagnostic value in Ankylosing Spondylitis (AS) since 90% of patients have the B27 gene compared to only 8% of healthy individuals. Flow cytometry (FC) and polymerase chain reaction (PCR) are techniques generally used for routine HLA-B27 typing. Only few work compared the agreement between both techniques and no study compared these methods in Brazilian patients.
Aim. To compare the results of FC and PCR in a sample of Brazilian patients with AS.
Patients and Methods. In this cross-sectional study, 56 outpatients with AS recruited from a University Hospital in Brazil were submitted to HLA-B27 typing by FC and PCR assay. The results of the two assays (allele presence or absence) were compared. The *kappa* statistic was used to define the agreement between the two methods. A p-value <0.005 was considered statistically significant.
Results. Concordance was observed in 48 patients (43 positive and 5 negative samples). Eight discrepant results were obtained: one patient had a positive result by PCR but a negative result by FC and 7 patients were considered HLA-B27 positive by FC but had negative results by PCR.
The *kappa*coefficient showed a moderate concordance (κ=0.481) between PCR and FC (p<0.001).
Discussion. In spite of the high sensitivity, the FC demonstrated low specificity, probably due to some interferent as the presence of antigens that cross-react with HLA-B27, such as HLA-B7. Only moderate agreement between the two techniques demonstrates that the gold standard method for the HLA-B27 typing needs to be further studied.

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THE RATIO OF PATIENTS WHO WERE DIAGNOSED WITH ANKYLOSING SPONDYLITIS BY SACROILIAC JOINT MRI

Seo Y.H., Choi S.J.
Division of Rheumatology, Dept. of Internal medicine, College of Medicine, Korea university, Seoul, Korea

Introduction. The Axial spondyloarthritis classification criteria includes sacroiliitis imaging, that can be X-ray, and MRI. But the MRI is very expensive study, so the routine use of MRI can't be recommended to many patients. The researchers of this study wanted to know how many ankylosing spondylitis (AS) patients could be diagnosed by the help of sacroiliac joint MRI.
Methods. We retrospectively reviewed 121 patients with AS in a single tertiary center in Korea between 2013 and 2014.
Results. In 121 AS patients, only 10 person had MRI study, and in those of them, 2 person showed normal or modified New York criteria grade 1 sacroiliitis in their sacroiliac (S-I) joint X-ray. That 2 person's MRI showed active inflammation, then they could be diagnosed with AS. The other 8 patients, who had MRI study, their S-I joint X-ray showed NY criteria grade 2 or suspicious 3, on one side or both side. None of whose X-ray showed NY criteria grade 3 or 4 had S-I joint MRI study.
Conclusion. In this study reveal only 2 person (1.7% of AS patients) could be helped by MRI study.
Discussion. We thought that the cost of MRI study can be the barriers to many people who suffer inflammatory back pain. So we are studying the lower cost study, digital tomosynthesis, to improve the diagnostic sensitivity of AS in people who have inflammatory back pain.

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DISEASE SEVERITY AS MEASURED BY PROMS OR NEED FOR SECOND LINE TREATMENT IN INFLAMMATORY BOWEL DISEASE ASSOCIATED ARTHROPATHY: COMPARISON TO OTHER SPONDYLOARTHRITIS SUBGROUPS

Drivelegka P.[1], Papachrysos N.[2], Petersson I.F.[3], Bremander A.[4,5], Jacobsson L.T.H.[1]
[1]Dept. of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg; [2]Dept. of Gastroenterology, Sahlgrenska University Hospital/Östra, Gothenburg; [3]Dept. of Orthopedics, Department of Clinical Sciences, Lund, Lund University, Lund; [4]Dept. of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund; [5]Research and Development Centre, Spenshult Hospital for Rheumatic Diseases, Halmstad, Sweden

Background. Inflammatory Bowel Disease associated arthropathy (IBD-aA) can cause impaired function but the level of activity limitations in comparison with other subgroups of spondyloarthritis (SpA) is unknown. Furthermore, data on the association of IBD-aA with the severity of bowel disease is limited.
Objectives. To compare disease severity as measured by patient reported outcome (PROMs): 1) in patients with IBD-aA with peripheral and axial musculoskeletal manifestations to those in Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA) respectively, 2) by severity of IBD-aA reflected by whether second line treatment had be given.
Methods. The SpA Scania cohort consists of all the subjects aged 15 years or older in the Skåne region (1.2 million inhabitants in southern Sweden) having recieved a diagnosis of any type of Spondyloarthritis during 2003-2007 at primary or specialised care visits (N=5771) recorded in the Skåne Health Care Register (SHCR). This included patients with Ankylosing Spondylitis (26%), Undifferentiated Spondyloarthritis (22%), Psoriatic Arthritis (39%) and IBD-aA (2.3%). A postal questionnaire was sent in 2009 to all the subjects aged 15 years or older including questions on PROMs with an overall response rate of 58%. Of the 65 patients with IBD-aA responding to the questionnaire a structured review of medical records verified both IBD and arthritis in 80% (N=52), from whom questionnaire data was used in the present analyses. The occurrence of axial or peripheral musculoskeletal disease and given second line therapy (surgery or treatment with TNF-inhibitor for IBD) were retrieved through the medical record review.
Results. Fifty-two patients records were analysed (17 men, mean age 39.8). Patients with axial IBD-aA (N=23) had comparable values for BASDAI (4.8 vs 4.0, p=0.19) and BASFI (4.1 vs 3.4, p=0.44) to AS patients (N=711). Patients with peripheral IBD-aA (N=44) had comparable values for global health (numeric rating scale) (4.5 vs 4.1, p=0.51) compared to PsA patients (N=1225). Severe bowel disease, defined as the need of anti-TNF-α therapy or surgery, was observed in 52% (n=27) of the patients with IBD-aA. Perceived health according to PROMs was similar in the patients with and without severe IBD (BASDAI: 5.1 vs 4.9 p=0.71, BASFI: 4.5 vs 3.3 p=0.13, global health: 4.8 vs 4.2 p=0.29).
Conclusions. Patients with IBD-aA tend to have worse perceived health compared to patients with AS and PsA. This warrants further and larger studies of this subgroup of SpA.

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THE IMPORTANCE OF TARGETING EDUCATION STRATEGIES FOR COMPLEMENTARY THERAPISTS DEALING WITH POTENTIAL AXIAL SPONDYLOARTHRITIS PATIENTS

Sengupta R.[1], Cook D.[2], Gaffney K.[3]
[1]Royal National Hospital for Rheumatic Diseases, Bath; [2]National Ankylosing Spondylitis Society; [3]Norfolk and Norwich University Hospitals, Norwich, UK

Introduction. There remains a significant delay in diagnosis of Axial Spondyloarthritis (AxSpA). Back pain is extremely common in the UK with 6-9% of UK adults visiting their GP annually for this specifically. Many healthcare professionals potential AxSpA patients including osteopaths, chiropractors, acupuncturists and masseurs. The objective of this survey was to determine the use and expertise of complementary therapists by AxSpA patients prior to them getting a diagnosis.
Methods. Prior to attending a UK based back pain education programme, osteopaths and chiropractors were sent a questionnaire regarding the assessment and management of patients with back pain. Additionally, patients attending an AxSpA clinic at the Royal National Hospital for Rheumatic Diseases, Bath were asked whether they had visited a complementary therapist after symptom onset and prior to their diagnosis of AxSpA.
Results. In total, 41 osteopaths and chiropractors completed the questionnaire (Figure 1). Whilst 89% (34/41) complementary therapists were confident/ very confident in assessing mechanical back pain, only 58% (23/40) were confident/ very confident in assessing inflammatory back pain.
Of the 276 patients that were asked whether they had visited an osteopath/ chiropractor/ acupuncturist/ masseur, 40% (110/276) had visited at least one of the aforementioned practitioners between the onset of their symptoms and diagnosis (Figure 2).

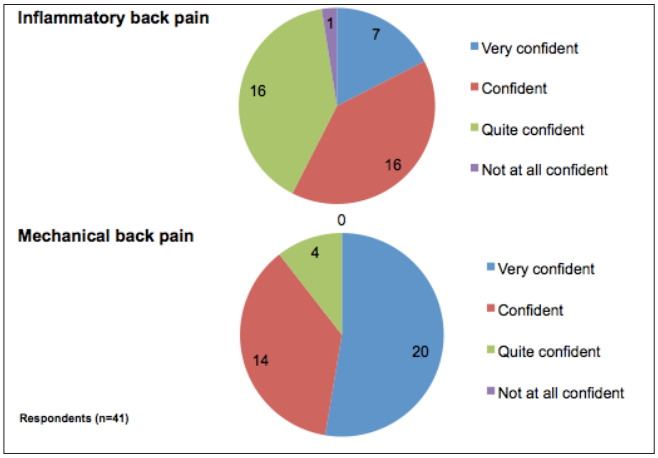

Fig. 1. Confidence of osteopaths and chiropractors in managing mechanical and inflammatory back pain

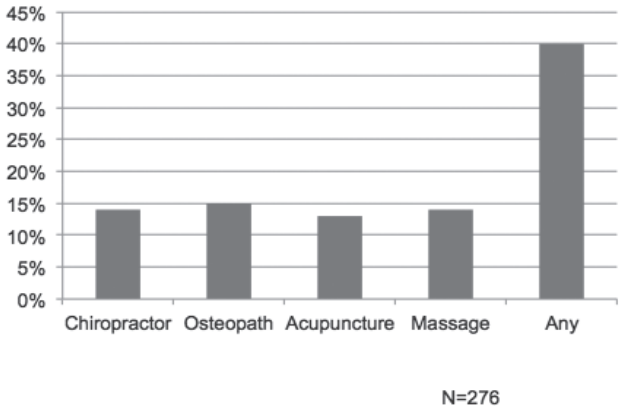

Fig. 2. The use of complementary therapies by patients prior to a diagnosis of AxSpA

Conclusions: The diagnosis of AxSpA remains a clinical challenge for most healthcare professionals. The survey highlights the lack of confidence reported by osteopaths and chiropractors when assessing back pain. In addition, this survey highlights the use of these care providers by patients between their onset of AxSpA symptoms and diagnosis. The education of these care providers is therefore essential to help reduce the delay in diagnosis of AxSpA in the UK.

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PATIENTS WITH SPONDYLOARTHRITIS HAVE HIGH CARDIOVASCULAR AND CEREBROVASCULAR MORTALITY: ONTARIO SPONDYLOARTHRITIS (ONSPA) STUDY

Haroon N., Haroon N.N., Li P., Paterson M., Inman R.D.
University of Toronto, University Health Network, Toronto Western Research Institute, Toronto, Canada

Introduction. OnSpA is a population-based study of spondyloarthritis (SpA) in Ontario that has a population of over 13 million. Patients with SpA have high risk of cardiovascular disease but it is unknown if they have excess vascular mortality. We explored risk of vascular mortality and the contributing factors in AS.
Methods. We performed a population-based, retrospective cohort study on incident SpA patients, age 15 or above, living in Ontario, Canada between April 1995 and March 2011. There were 21,878 cases and 87,504 controls (age, gender and socioeconomic status matched). Primary outcome was a composite event of cardiovascular and cerebrovascular deaths coded as the primary cause on death certificates. Cox proportional hazards model was used to estimate differences in vascular mortality between cases and controls. Crude and adjusted hazard ratios (HR) were calculated and adjustments were made for coronary and cerebrovascular disease (CAD, CVD), cancer, diabetes, dementia, inflammatory bowel disease, hypertension, CKD and peripheral vascular disease (PVD). Risk factors of vascular mortality were identified in the SpA cohort.
Results. The mean age of SpA patients (53% men) was 46 ±16 years and follow-up was 169,307 patient-years. Controls were followed for 692,499 patient-years. Cases and controls had similar prevalence of CAD, CVD, PVD, dementia or diabetes but IBD (6% vs 4%), hypertension (24% vs 18%) and CKD (2% vs 0.8%) were common in cases. Crude and adjusted HR (95%CI) for vascular deaths were 1.49 (1.26-1.77) and 1.36 (1.14-1.63) respectively indicating a 36-49% higher chance of vascular mortality in AS. Crude HR (95%CI) in males and females were 1.63 (1.31-2.03) and 1.31(1.00-1.71) respectively. Data is shown in table 2. The predictors of vascular death included age, male sex, low income, CKD and PVD in addition to CAD and CVD (Figure 1).
Conclusions. AS is a significant risk factor for vascular mortality. The results should prompt a strategy to more aggressively screen and treat vascular risk factors in AS patients.

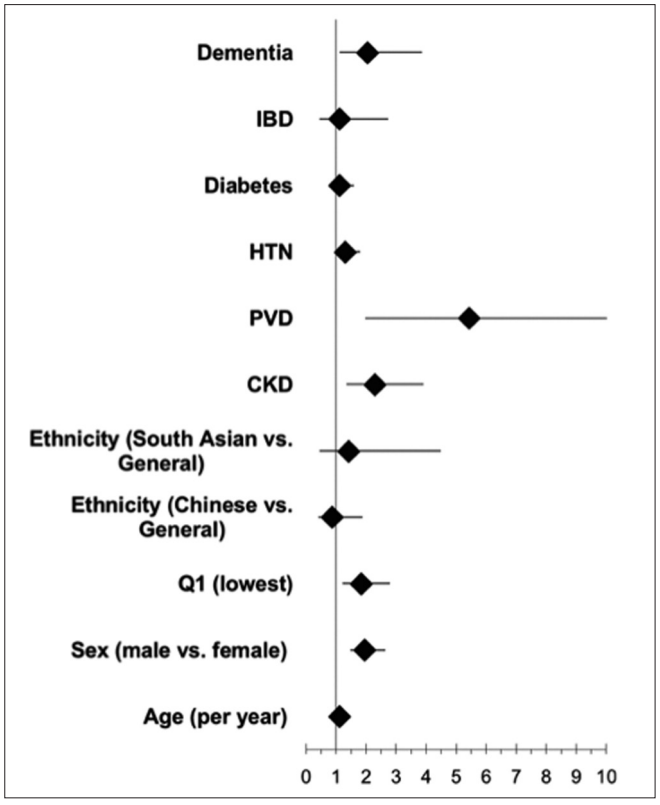

Fig. 1. Forrest plot showing hazard ratios of variables tested for association with vascular mortality in SpA.

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BASELINE CHARACTERISTICS IN EARLY SPONDYLOARTHRITIS: THE BEGIANT COHORT

Varkas G., Cypers H., Van Praet L., Carron P., Gyselbrecht L., Corluy L., De Bock W., Raeman F., Vanneuville B., Devinck M., Peene I, Elewaut D, Van den Bosch F.
BeGiant Consortium, Belgium

Background. The ASAS classification criteria for SpA allow us to classify SpA patients in early stages of disease (1), which raises the opportunity for early intervention and long term follow-up. However, identification of prognostic factors and biomarkers of disease activity are still a key research area.
Objectives and Methods. The BelGian Inflammatory Arthritis and spoNdylitis cohorT (BeGIANT) is a multicentre, observational cohort in which patients diagnosed with axial and/or peripheral SpA, and classified according to the ASAS criteria, are prospectively followed every 6 months. Patients fulfilling the modified New York criteria at baseline are excluded.
Results. Baseline characteristics of 160 newly diagnosed patients with non-radiographic (nr-ax Spa) and peripheral SpA are reported in Table I. Almost eighty-two and a half percent of the nr-ax SpA patients have a positive MRI of the sacroiliac joints, as defined by the ASAS criteria. Also, we found a high prevalence of women and high HLAB27 positivity in nr- ax spa. Considering extra-articular manifestations, psoriasis was more prevalent in peripheral Spa. Uveitis was more prevalent in nr- ax SpA. Inflammatory bowel disease had similar prevalence in early nr-ax Spa and peripheral SpA.
Also, inflammatory parameters are generally higher in peripheral Spa. Interestingly, the acute type of gut inflammation seems more prevalent in nr-ax Spa compared to the chronic type of inflammation, in contrast to our findings in ankylosing spondylitis (2). Nr-ax and peripheral Spa express similar burden of disease in early SpA.

Table I. Baseline characteristics of BeGiant cohort.

	Nr-axial SpA (n=101) (median [range])	Peripheral SpA (n=59) (median [range])
Age, years	32.24 [16.27-56.08]	40.41 [18.13-73.23]
Symptom duration, years	2.42 [0- 28.35]	0.19 [0.02-18.71]
HLA-B27 (+) (%)	69.00	55.30
Positive MRI SIJ (%)	82.4	29.4
Male (%)	46.50	55.90
CRP (mg/dl)	0.30 [0-5.30]	0.62 [0-20.20]
ESR (mm/h)	7.00 [1.00-71.00]	19.00 [1.00-99.00]

Conclusions. The BeGiant cohort is a well-defined cohort in early SpA. To our knowledge, this is the first cohort in which patients diagnosed with early SpA and classified according to the ASAS criteria are prospectively followed. Baseline characteristics are completely in line with other early SpA cohorts. An indisputable asset is the high prevalence of classification through the imaging arm of the ASAS criteria in up to 82,5%.

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PERSISTENTLY HIGH DISEASE ACTIVITY ACCORDING TO THE ASDAS IS ASSOCIATED WITH ACCELERATED RADIOGRAPHIC SPINAL PROGRESSION IN PATIENTS WITH EARLY AXIAL SPONDYLOARTHRITIS

Poddubnyy D.[1], Haibel H.[1], Braun J.[2], Rudwaleit M.[1], Sieper J.[1]
[1]Charité Universitätsmedizin Berlin; [2]Rheumazentrum Ruhrgebiet, Herne, Germany

Introduction/Aim. Recently an association between elevated disease activity according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) and radiographic spinal progression in advanced ankylosing spondylitis (AS) has been reported. The aim of the study was to investigate the association between radiographic progression and disease activity as assessed by the ASDAS in patients with early axial SpA.
Materials and Methods. Altogether 177 patients with definite axial SpA (100 with ankylosing spondylitis (AS) and 77 with non-radiographic axial SpA) from the German Spondyloarthritis Inception Cohort (GESPIC) were included in the current study. Spinal radiographs (cervical spine lateral views, lumbar spine lateral and anteroposterior views) were scored according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) system and for the presence of syndesmophytes.
Results. Rates of radiographic spinal progression were remarkably increased in patients with very high disease activity (time-averaged ASDAS>3.5) – table. Patients with very high disease activity had significantly higher odds for syndesmophyte formation as compared to patients with lower disease activity: odds ratio (OR)=5.5 (95%CI 1.89-16.04). In the logistic regression analysis, mSASSS progression by ≥2 points over two years was significantly associated with the time-averaged ASDAS: OR=1.58 (95%CI 1.02-2.44). Even stronger was the relationship between ASDAS and syndesmophyte formation/progression: OR=2.64 (95%CI 1.50-4.64). Interestingly, the association of ASDAS with syndesmophyte formation remained significant even after adjustment for time-averaged CRP: OR=2.16 (95%CI 1.13-4.11).
Conclusions. Persisting very high disease activity according to the ASDAS is associated with radiographic spinal progression in axial SpA patients with disease duration <10 years. As demonstrated in the multivariate analysis, this effect is at least partially independent of the effect of CRP.

Table. Rates of radiographic spinal progression over two years, and time-averaged BASDAI and CRP levels in relation to disease activity according to the time-averaged ASDAS.

	Inactive disease, ASDAS<1.3 N=32	Moderate disease activity, 1.3 ≤ASDAS <2.1 N=41	High disease activity, 2.1≤ASDAS ≤3.5 N=83	Very high disease activity, ASDAS >3.5 N=21	*p**
Δ mSASSS	0.47±1.16	0.48±1.89	0.70±2.65	1.91±3.76	0.14
mSASSS progression ≥2, %	12.5%	12.2%	14.5%	28.6%	0.33
Syndesmophyte formation, %	3.1%	7.3%	10.8%	33.3%	0.005
CRP, mg/l	2.5±2.8	4.8±5.3	8.6±8.0	18.8±13.3	<0.001
BASDAI (0-10)	1.6±0.7	2.5±1.2	4.4±1.6	6.1±2.0	<0.001

**p* for the inter-group comparison (ANOVA or chi-square test).

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REACHING A STATUS OF LOW DISEASE ACTIVITY SPONTANEOUSLY OVER TWO YEAR FOLLOW-UP IN ACTIVE PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS IN COMPARISON TO ANKYLOSING SPONDYLITIS NOT TREATED WITH TNF BLOCKERS

Poddubnyy D.[1], Haibel H.[1], Braun J.[2], Rudwaleit M.[1], Sieper J.[1]
[1]Charité Universitätsmedizin Berlin; [2]Rheumazentrum Ruhrgebiet, Herne, Germany

Introduction/Aim. The aim of the current analysis was to investigate the rates of remission/low disease activity states over two years without anti-TNF treatment in patients with nr-axSpA and AS who were candidates for anti-TNF treatment at baseline.
Materials and Methods. In total, 210 patients with early axSpA (115 with AS according to the modified New York criteria and symptom duration ≤10 years, and 95 with nr-axSpA and symptom duration ≤5 years) from the German Spondyloarthritis Inception Cohort (GESPIC) were evaluated at baseline and every 6 months thereafter till 2 years. Patients with axSpA were considered to be candidates for anti-TNF therapy at baseline if they had BASDAI ≥4 and elevated C-reactive protein (CRP, >6 mg/l). Patients who received at least one prescription of a TNF blocker were excluded. The following definitions for low disease activity were applied: BASDAI<4, BASDAI<4 and normal CRP, BASDAI ≤2, ASDAS inactive disease (<1.3).
Results. Eleven patients (11.6%) with nr-axSpA and 28 patients (24.3%) with AS were considered to be candidates for the anti-TNF therapy at baseline due to elevated BASDAI and CRP. One nr-axSpA patient and 6 AS patients received anti-TNF treatment during the follow-up and were excluded. Remaining patients in both groups (10 with nr-axSpA and 22 with AS) received conventional therapy. At year 2 BASDAI<4 was achieved by 50% of nr-axSpA patients and 38% AS patients, BASDAI<4 and normal CRP by 29% and 16%, BASDAI≤2 by 17% and 19%, and ASDAS inactive disease by 16.7% and 6.3% of the patients, respectively. BASDAI<4 at least 2 time points during 2 years of the follow-up was achieved by 57% of nr-axSpA and by 40% of AS patients, BASDAI<4 and normal CRP by 25% and 13%, BASDAI≤2 by 13% and 13%, and ASDAS inactive disease by 25% and 0% of nr-axSpA and AS patients, respectively. All differences were statistically non-significant.
Conclusions. Only a small proportion of patients (<25%) with nr-axSpA and AS reached a stricter definition of low disease activity over two years of follow-up without TNF-blocker treatment. The rates were numerically lower in AS if a combined definition of low disease activity with inclusion of CRP was used.

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FUNCTIONAL RELEVANCE OF THE IL-23 RECEPTOR GENE POLYMORPHISM RS10889677 IN ANKYLOSING SPONDYLITIS

Hermann J., Fessler J., Stradner M., Angerer H., I. Holzer, Graninger W.
Medical University Graz, Dept. of Internal Medicine, Division of Rheumatology and Immunology, Graz, Austria

Introduction. Multiple interleukin-23 receptor (IL-23R) gene variants are associated with ankylosing spondylitis (AS). For instance, the protective variant rs11209026 leads to impaired IL-23-induced Th17 cell response. We tested the functional relevance of rs10889677, another single nucleotide polymorphisms (SNP) in the IL-23 receptor (IL-23R) associated with AS.
Patients and Methods. Blood was drawn from 105 AS-patients attending the rheumatologic outpatient clinic and DNA was extracted to determine the SNPs rs10889677 (SNP1), rs11209026 (SNP2), rs11465804 (SNP3) and rs1343151 (SNP4) by polymerase chain reaction. To test the functional relevance of the SNP1 we performed intracellular flow cytometry and stained PBMCs with anti-CD3, CD4, CD8, IL-23R, pSTAT-3 and IL-17A. We assessed phosphorylation of STAT-3 (pSTAT-3) and intracellular IL-23R expression following IL-23 stimulation (100ng/ml) for 15 min and the prevalence of Th17 cells following IL-23 stimulation for 16 hours.
Results. We detected 10 (9.6%) homozygote and 49 (47.1%) heterozygote carriers of SNP1 in the cohort tested. Homozygote carriers of the SNPs 2 and 3 were not found but we identified 7 (6.7%) patients that carried the homozygote SNP4. Fifteen SpA patients were wild type (WT) for all four SNPs tested and 11 served as control group.
After stimulation of PBMCs with IL-23 (100ng/ml), the median frequency of $CD4^+$ TH17-cells was significantly higher in patients caring the SNP1 (1.3 [0.8-1.4]) than in patients caring the WT (0.7 [0.5-1.3]) ($p<0.05$). Stimulation of PBMCs with IL-23 (100ng/ml) in patients caring the SNP1 displayed a trend

towards higher frequency of IL-23R expressing CD4+ T-cells (40.2 [24.7-53.1]) compared to WT (27.8 [15.4-39.3] (p=0.057). In addition, the increase in pSTAT3 production was higher in patients homozygotic for the SNP1 (2.8 [1.7-6.6]-fold) compared to the WT cohort (1.9 [0.4-3.4-fold]) (p=057).
Conclusion. The SNP rs10889677 seem to promote the development of Th17 cells indicating a pro-inflammatory effect of this SNP in patients with AS.

P90

ERAP DEFICIENCY LEADS TO REDUCED B27/NP383-391 IMMUNO-DOMINANT FLU EPITOPE RESPONSE IN INFLUENZA INFECTED TRIPLE HLA TRANSGENIC MICE

Akram A.[1,2], Inman R.D.[1,2]
[1]University of Toronto, Faculty of Medicine, Dept. of Immunology and Institute of Medical Science; [2]University Health Network (UHN), Toronto Western Hospital (TWH), Dept. of Genetics and Development, Toronto, Canada

Introduction. The role of HLA-B27 in modulating host response to infection is undefined, yet B27 confers susceptibility to arthritis. Despite co-dominant expression of class I MHC alleles, immune response to viral infections is characterized by immunodominance (ImDc). Defining factors contributing to ImDc has proved difficult due to multiple MHC-I allele co-expression in humans and normal mice.
Materials and Methods. To overcome this limitation, we generated human MHC-I transgenic (Tg) mice deficient for endogenous mouse MHC-I molecules and express only one or two human MHC-I allele(s) in the presence or absence of ERAP expression.
Results. Studies with flu-infected B27/ERAP$^{-/-}$ Tg mice revealed a reduced B27/NP383-391 influenza response compared to B27/ERAP$^{+/+}$ mice. Studies with flu-infected B7/ERAP$^{-/-}$ Tg mice revealed no change in B7/NP418-426 influenza response compared to B7/ERAP$^{+/+}$ Tg mice. Subsequent flu-specific studies revealed that ERAP deficiency in B27/ERAP$^{-/-}$ is associated i) with a partial deletion of Vβ8.1^{+} B27/NP383-restricted CD8^{+} T cells, and ii) the generation of B27-restricted NP383-391 flu epitope is ERAP dependent. To determine whether co-expression of multiple MHC-I alleles (*i.e.*, HLA-B7 and HLA-B27) in the presence or absence of ERAP influences the pattern of anti-flu CTL epitope recognition and ImDc, we generated novel triple MHC-I Tg mice. Similar to CTL responses seen with B27/ERAP$^{-/-}$ Tg mice, in flu-infected B7/B27/ERAP$^{-/-}$ Tg mice a significantly reduced B27/NP383-restricted CTL response was detected while there was no change in the response level of B7/NP418-restricted CTL. Subsequent tetramer staining revealed co-expression of B7/B27 leads to deletion of B27/NP383-391 specific T cells in the absence of ERAP.
Conclusion. The selective deletion of B27-restricted T cells has important implications for models defining the role that HLA-B27 plays in susceptibility to reactive arthritis and ankylosing spondylitis.

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THE ASSOCIATION OF PPM1A WITH INFLAMMASOME ACTIVATION IN ANKYLOSING SPONDYLITIS

Kim Y.G.[1], Hong S.[1], Chang E.J.[2], Lee C.K[1], Yoo B.[1]
[1]Dept. of Rheumatology; [2]Dept. of Biomedical Sciences, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Introduction/Aim. Recently, it has been suggested that autoinflammatory responses can be responsible for inflammation in ankylosing spondylitis (AS). We have reported that immunity to protein phosphatase magnesium-dependent 1A (PPM1A), which has been known as intracellular regulator of TGF-β signaling, was associated with AS. Therefore, we tried to investigate the association of PPM1A with inflammatory response in AS and its role in the inflammasome activation.
Materials and Methods. The synovial expression of PPM1A was evaluated in the patients with AS, rheumatoid arthritis (RA) and osteoarthritis (OA). The concentrations of PPM1A were measured in the plasma from AS, RA and healthy control (HC) subjects by ELISA, and analyzed the association with inflammatory burdens including ESR, CRP, and BASDAI in AS patients. To address the inducible condition of PPM1A in AS, PPM1A expressions were evaluated using immunoblotting and FACS after stimulation with various cytokines (TGF-β, TNF-α, IL-17, IL-23, and IL-32). To verify the role of PPM1A on the inflammasome activation, the production of IL-1β and expression of inflammasome related proteins were measured in murine macrophages with/without PPM1A gene modulation.
Results. The synovial expression of PPM1A was elevated in AS compared to RA or OA. In AS plasma, the levels of PPM1A were significantly higher and were related significantly with the values of BASDAI, ESR and CRP. The expression of PPM1A was induced markedly by stimulation with TGF-β in immunoblotting and FACS analysis. Finally, when PPM1A knockdown macrophages were stimulated with LPS and ATP, IL-1β secretion was decreased and the expression of caspase-1 p20, ASC and NALP3 were significantly suppressed.
Conclusions. Our present study suggested that inflammasome activation could be regulated by intracellular PPM1A, which contribute to the pathogenesis of inflammatory responses in AS.

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DECREASED TH9 AND IMBALANCE OF TH9 AND TH17 IN SPONDYLOARTHROPATHY

Ryu H.J., Lee M.K., Seo M.R., Choi H.J., Baek H.J.
Dept. of Rheumatology, Gachon University Gil Medical Center, Incheon, South Korea

Introduction. CD4^{+}T-helper cells(Th) differentiate into effector subsets and regulate immunity and inflammation. Its subsets are identified by the potent production of specific cytokines. Th9 is known to be differentiated from Th2 by TGFβ and mainly secret IL-9. In the several animal models, it was reported to be related with autoimmune diseases. However, it is controversial and not clear in vivo. This study is to investigate the imbalance of Th subsets including Th9 in spondyloarthropathy(SpA).
Patients and Methods. CD4^{+}Th cells were isolated from peripheral blood of 22 SpA patients (male 63.6%, mean age 35.5 years), 24 rheumatoid arthritis(RA) patients(43.9%, 32.3 years), and 26 age- and sex-matched healthy controls(HC) by Ficoll-Hypaque gradient and magnetic negative selection. CD4^{+}Th cells were stimulated with PMA plus ionomycin. To identify the subsets, the specific transcriptional factors (TF) were used; T-bet for Th1, GATA3 for Th2, RORγ for Th17, Foxp3 for Treg, and PU.1 for Th9. The relative gene expressions of TFs were analyzed using real-time PCR. Data was analyzed by t-test and Pearson correlation.
Results. PU.1 expression (0.21±0.19) was significantly decreased in SpA compared with HC (0.36±0.21)(p=0.01), but there was no difference between RA and HC. GATA3 expression significantly increased in SpA (0.55±0.52) compared with HC (0.31±0.23)(p=0.03). The differences of expression in Foxp3, RORγ and T-bet between each group were not statistically significant. Ratio of T-bet to GATA3 in RA (7.45±11.11) was higher than in HC (1.83±1.56)(p=0.02), but there was no difference between SpA and HC. But the ratios of PU.1 to GATA3 and PU.1 to RORγ in SpA (0.67±1.07, 0.61±0.6) were lower than in HC (1.83±1.29, 1.03±0.57)(p=0.004). In SpA, there was no difference of TFs according to HLA-B27 positivity and the ratio of T-bet to GATA3 was negatively correlated with CRP (p=0.02).
Conclusion. Decreased the differentiation toTh9 and the imbalance of Th9 and Th2 were observed in SpA. Imbalance of Th9 and Th17 was also observed and the ratio of Th1 to Th2 was correlated with CRP negatively, although the ratio of Th1 and Th2 was not different from HC. This study suggests that decreased Th9 and the imbalance of Th9 and Th2 or Th17 may contribute to the development of SpA.

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PSORIATIC ARTHRITIS: CLINICAL AND SEROLOGICAL COMPARISON BETWEEN EARLY AND LATE ONSET

Delle Sedie A., Lodato C., Cioffi E., Sardano E., Bombardieri S., Riente L.
Rheumatology Unit, Pisa University, Pisa, Italy

Introduction. Psoriatic arthritis (PsA) typically presents at the age of 30 to 50 years but onset in older or younger age is frequent. Very few data about the clinical characteristics of early and late onset PsA patients are reported in the literature.
Aim. To compare clinical and serological characteristics between early and late onset PsA.
Materials and Methods. 100 patients affected by PsA, diagnosed according to the CASPAR criteria, were enrolled in the study. We classified the patients into two groups based on the age at onset: the first one (group A) included 50 patients with early onset PsA (<40 years) and the second one (group B) 50 patients with late onset PsA (>60 years). From our patient files we collected the demographic, clinical and serological data, both at disease onset and in the follow-up, of all the studied patients.
Results. The demographic, clinical and serological data of the patients are reported in Table I. The only statistically significant differences observed were in the frequency of elevated ESR or CRP values (higher in group B) and in the disease duration (longer in group A).
Discussion. We observed higher ESR and CRP values in group B but no statistically significant difference in the type of onset (peripheral arthritis in both groups), the presence of sacroiliitis or in the female/male ratio were detected.
Conclusion. Our study showed that the only clinically significant differences between group A and group B were related to the prevalence of pathological levels of ESR and CRP, which were higher in group B.

Table I.

	Group A	Group B	*p*-value
Mean age at onset (yrs)	30	67.7	<0.05
M/F ratio	32/18	26/24	
Disease duration (months)	94,9	34.8	<0.05
Prevalent peripheral involvement	44/50	45/50	
Bilateral sacroiliitis	3/50	2/50	
Lombalgia	15/50	13/50	
Oligoarthritis	41/50	41/50	
Dactilitis	14/50	9/50	
Psoriasis	47/50	45/50	
Rheumatoid Factor Positivity	3/50	4/50	
Pathologic CRP	33/50	44/50	<0.05
Pathologic ESR	30/50	43/50	<0.05

P94

PREVALENCE OF PERI-ARTICULAR MANIFESTATIONS (ENTHESITIS AND DACTYLITIS) AND DISEASE ACTIVITY IN PSORIATIC ARTHRITIS PATIENTS: IMPACT OF TREATMENT WITH TNF INHIBITORS IN A REAL-WORLD CANADIAN POPULATION

Rahman P.[1], Choquette D.[2], Bensen W.G.[3], Khraishi M.[1], Fortin I.[4], Chow A.[5], Sheriff M.K.[6], Vaillancourt J.[7], Sampalis J.S.[7], Nantel F.[8], Otawa S.[8], Lehman A.J.[8], Shawi M.[8]
[1]Memorial University of Newfoundland, St. John's, NL; [2]Institut de Rhumatologie de Montréal, Montreal, QC; [3]McMaster University, Hamilton, ON; [4]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC; [5]Credit Valley Rheumatology, Mississauga, ON; [6]Nanaimo Regional General Hospital, Nanaimo, BC; [7]JSS Medical Research, Montreal, QC; [8]Janssen Inc, Toronto, ON, Canada

Background. PsA is characterized by inflammatory arthritis and is commonly associated with peri-articular manifestations (PAMs) including enthesitis and dactylitis. The purpose of this analysis was to determine the prevalence of PAMs in PsA patients treated with anti-TNFs.
Methods. BioTRAC is an ongoing, prospective, registry of rheumatology patients initiating treatment for with infliximab or golimumab. A total of 91 PsA patients with available baseline information on PAMs were included: enthesitis (n=62), dactylitis of hands (n=76) or feet (n=77), nail pitting of hands (n=76) or feet (n=75).
Results. At baseline, mean (SD) age and disease duration were 48.7 (10.3) and 6.5 (6.9) years, respectively, while the mean (SD) DAS28-CRP score was 4.1 (1.2). 50 patients (54.9%) had a PAM at baseline. Dactylitis (feet - 39.0%; hands – 15.8%) was the most common PAM followed by enthesitis (27.4%), and nail pitting (hands – 26.3%; feet – 24.0%). Patients with enthesitis had greater DAS28-CRP (p=0.042) and HAQ-DI (p=0.076). Upon six months of treatment, significant improvement in all disease activity parameters was observed. The prevalence of PAMs decreased from baseline to six months post-treatment (p=0.001). Among the patients with available six-month information that had a PAM at baseline (n=33), 48.5% did not present any manifestation after six months.
Conclusions. In this real-world cohort of PsA patients, a high prevalence of PAMs was observed at treatment initiation. Patients with PAMs had increased disease activity. Treatment with infliximab or golimumab for six months was associated with a significant improvement in disease parameters and reduction in the prevalence of PAMs.

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IS SKIN DISEASE MORE IMPORTANT TO PATIENTS OR PHYSICIANS IN THE ASSESSMENT OF DISEASE ACTIVITY IN PSORIATIC ARTHRITIS?

Sholter D.[1], Rahman P.[2], Avina-Zubieta J.A.[3], Kelsall J.[4], Arendse R.[5], Khraishi M.[2], Shaikh S.[6], Bensen W.G.[7], Rampakakis E.[8], Sampalis J.S.[8], Nantel F.[9], Shawi M.[9], Otawa S.[9], Lehman A.J.[9]
[1]University of Alberta, Edmonton, AB; [2]Memorial University of Newfoundland, St. John's, NL; [3]Arthritis Research Centre of Canada, Richmond, BC; [4]Mary Pack Arthritis Centre, Vancouver, BC; [5]University of Saskatchewan, Saskatoon, SK; [6]McMaster University, St Catharines; [7]McMaster University, Hamilton; [8]JSS Medical Research, Montreal; [9]Janssen Inc., Toronto, ON, Canada

Introduction. The aim of this analysis was to assess the agreement between PtGA and MDGA, and to compare the correlation of PtGA or MDGA with the PASI in PsA patients treated with infliximab in a real world clinical practice setting.
Methods. BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid diseases with infliximab. Included were PsA patients treated with IFX between 2005 and 2012. The correlation between disease parameters was assessed with the Spearman's rho coefficient, while the intra-class correlation coefficient and Cronbach's alpha was used to assess internal consistency.
Results. 92 patients (52.2% male) were included with a mean (SD) age of 48.7 (9.9) years and disease duration of 6.8 (9.1) years. Mean (SD) disease parameters at baseline were: PASI: 3.3 (5.6); SJC28: 4.0 (3.8); TJC28: 5.9 (5.3); PtGA: 5.0 (2.8); MDGA: 5.8 (2.2). 71.7% of patients had been treated with MTX.
A strong agreement was observed between PtGA and MDGA (r=0.632). The correlation of PASI with PtGA was low (r=0.213), whereas it was moderate with MDGA (r=0.343). Multivariate linear regression supported the stronger association of MDGA with PASI. PtGA showed a very strong correlation with pain (r=0.885) and strong with HAQ-DI (r=0.596), whereas a strong correlation was observed between MDGA and both pain and HAQ-DI (r=0.652 and r=0.520, respectively).
Conclusions. The association of PASI is stronger with MDGA compared to PtGA. Patient-reported pain and HAQ-DI were better correlated with PtGA and MDGA when compared to PASI, suggesting that both patients and rheumatologists place more emphasis on pain and functional activity than on skin.

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ABSENCE OF ERAP PARTIALLY RESCUES THE FLU-SPECIFIC Vβ8.1+ CTL WHICH ARE NORMALLY DELETED IN B7/B27 CO-EXPRESSING HLA TRANSGENIC MICE

Akram A.[1,2], Inman R.D.[1,2]
[1]University of Toronto, Faculty of Medicine, Dept. of Immunology and Institute of Medical Science; [2]University Health Network (UHN), Toronto Western Hospital (TWH), Department of Genetics and Development, Toronto, Canada

Introduction. The role of HLA-B27 in modulating host response to infection is undefined, yet B27 confers susceptibility to arthritis. Despite co-dominant expression of class I MHC alleles, immune response to viral infections is characterized by immunodominance (ImDc). Defining factors contributing to ImDc has proved difficult due to multiple MHC-I allele co-expression in humans and normal mice.
Materials and Methods. To overcome this limitation, we generated human MHC-I transgenic (Tg) mice deficient for endogenous mouse MHC-I molecules and express only one or two human MHC-I allele(s) in the presence or absence of ERAP expression.
Results. Studies with flu-infected B27/ERAP$^{-/-}$ Tg mice revealed a reduced B27/NP383-391 influenza response compared to B27/ERAP$^{+/+}$ mice. Studies with flu-infected B7/ERAP$^{-/-}$ Tg mice revealed no change in B7/NP418-426 influenza response compared to B7/ERAP$^{+/+}$ Tg mice.
Subsequent flu-specific studies revealed that ERAP deficiency in B27/ERAP$^{-/-}$ is associated i) with a partial deletion of Vβ8.1^{+} B27/NP383-restricted CD8^{+} T cells, and ii) the generation of B27-restricted NP383-391 flu epitope is ERAP dependent. To determine whether co-expression of multiple MHC-I alleles (*i.e.*, HLA-B7 and HLA-B27) in the presence or absence of ERAP influences the pattern of anti-flu CTL epitope recognition and ImDc, we generated novel B7/B27/ERAP$^{-/-}$ MHC-I Tg mice.
Similar to CTL responses seen with B27/ERAP$^{-/-}$ Tg mice, in flu-infected B7/B27/ERAP$^{-/-}$ Tg mice a significantly reduced B27/NP383-restricted CTL response was detected while there was no change in the response level of B7/NP418-restricted CTL. The reduction in B27/NP383-391 CTL response, to our surprise, was not due to the complete absence of flu specific B27/NP383-391 Vβ8.1^{+}CD8^{+} T cells. These T cells were partially rescued. In spite of this, subsequent tetramer staining revealed reduced levels of B27/NP383-391 specific CD8^{+} T cells similar to levels seen with B27/ERAP$^{-/-}$ Tg mice. Taken together these results reveal that i) besides the NP383-391-specifc Vβ8.1^{+}CD8^{+} T cells, other Vβ8.1+ T cell populations whose specificity is still unknown contribute to the overall reduced B27/NP383-391 CTL response in B7/B27/ERAP$^{-/-}$ Tg mice, and ii) absence of ERAP alters the peptide pool available in the thymus thus affecting key thymic selection processes.
Conclusion. The selective deletion of B27-restricted T cells has important implications for models defining the role that HLA-B27 plays in susceptibility to reactive arthritis and ankylosing spondylitis.

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TRANSLATION AND CROSS-CULTURAL ADAPTATION OF THE ASAS HEALTH INDEX AND THE ENVIRONMENTAL ITEM SET INTO 15 LANGUAGES

Kiltz U.[1], van der Heijde D.[2], Boonen A.[3], Bautista W.[4], Burgos-Vargas R.[5], Chiowchanwisawakit P.[6], Duruoz T.[7], El-Zorkany B.[8], Essers I.[9], Gaydukova I.[10], Géher P.[11], Gossec L.[12], Grazio S.[13], Gu J.[14], Khan A.[15], Kim T.J.[16], Maksymowych W.[17], Marzo-Ortega H.[18], Navarro V.[19], Olivieri I.[20], Patrikos D.[21], Pimentel dos Santos F.M.[22], Van den Bosch F.[23], Zochling J.[24], Braun J.[1]
[1]Rheumazentrum Ruhrgebiet, Herne, Germany; [2]Dept. of Rheumatology, Leiden University Medical Center, Leiden; [3]Division of Rheumatology, Dept. of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands; [4]University Military Hospital, Bogotá, Colombia; [5]Universidad Nacional Autonoma de Mexico, Mexico City, Mexico; [6]Mahidol University, Bangkok, Thailand; [7]Marmara University Medical School, Istanbul, Turkey; [8]Cairo University, Cairo, Egypt; [9]Maastricht University Medical Center, Maastricht, The Netherlands; [10]Saratov State Medical University, Saratov, Russia; [11]Semmelweiss University, Budapest, Hungary; [12]UPMC University Paris, Dept. of Rheumatology, Paris, France; [13]Sisters of Mercy Hospital, Zagreb, Croatia; [14]University Guangzhou, Guangzhou, People's Republic of China; [15]Case Western Reserve University, Cleveland, Ohio, USA; [16]Gwangju Hospital, Gwangju, South Korea; [17]University of Alberta, Edmonton, Canada; [18]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, UK; [19]University Hospital La Paz, Madrid, Spain; [20]San Carlo Hospital, Potenza, Italy; [21]General Military Hospital, Athens, Greece; [22]Universidade Nova de Lisboa, Lisboa, Portugal; [23]Ghent University Hospital, Ghent, Belgium; [24]Menzies Research Institute, Hobart, Australia

Introduction. The ASAS Health Index (ASAS HI) is a unidimensional questionnaire measuring health and impairment in functioning in patients with spondyloarthritis (SpA). The ASAS HI is accompanied by a multidimensional item set aiming at measuring environmental factors (EF Item Set). The ASAS HI contains 17 dichotomous items addressing categories of pain, emotional functions, sleep, sexual function, mobility, self care, and community life and the EF Item Set contains 9 dichotomous items addressing categories of support/relationships, attitudes and health services. The aim is to translate and adapt the ASAS HI and the EF Item Set cross-culturally into 15 languages with 17 versions.
Methods. Translation and cross-cultural adaptation was done in 20 countries using forward-backward procedure in 5 steps: translation, synthesis of translation, back translation, expert committee review and field testing in patients with axial SpA. We paid attention to include patients across a broad spectrum of socio-demographic background (age, gender, education).
Results. The ASAS HI and EF Item Set was translated into Arabic, Chinese, Croatian, Dutch/Flemish, French, German, Greek, Hungarian, Italian, Korean, Portuguese, Russian, Spanish (Colombia, Mexico, Spain), Thai, and Turkish. 206 patients, 59.7% male, mean (SD) age 42.4 (13.9) years, 65% AS patients, 35% with non-radiographic axSpA, mean (SD) BASDAI 3.8 (2.3) with axSpA underwent qualitative interviews during field testing in 23 countries (19 non-English speaking countries, 4 English-speaking countries). Interviews showed the English questionnaire and the translations to be clear, relevant and comprehensive. All versions were accepted with minor modifications. Completion times for ASAS HI and for EF Item Set were respectively, 2.6±1.6 and 2.1±1.5 (mean ± SD) minutes.
Discussions. The ASAS HI and the EF Item Set were successfully translated into 15 languages with 17 versions. This study showed the ASAS HI items to be readily adaptable throughout countries, indicating the concepts covered may be meaningful in many cultures. In the other hand, more difficulties were experienced with the contextual factors indicating these concepts may be more culture-dependent. By investigating patients with axSpA with and without peripheral manifestations it could be shown that the ASAS HI and the EF Item Set are valid to be applied in patients with all forms of SpA.

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SHORT TERM EFFICACY OF TUMOR NECROSIS FACTOR INHIBITORS IN PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLARTHRITIS AND ANKYLOSING SPONDYLITIS

Cetin P.[1], Kalyoncu U.[2], Sari I.[1], Karadağ O.[2], Kiliç L.[2], Kiraz S.[2], Onen F.[1], Ertenli I.[2], Akkoç N.[1]
[1]Dokuz Eylul University School of Medicine, Dept. of Internal Medicine, Division of Rheumatology, Izmir; [2]Hacettepe University School of Medicine, Dept. of Internal Medicine, Division of Rheumatology, Ankara, Turkey

Introduction. Axial spondylarthritis (AxSpA) has been proposed as an umbrella term for ankylosing spondylitis (AS) and non-radiographic (nr) AxSpA). Disease burden in AxSpA patients with or without radiographic sacroiliitis have been shown to be similar in different cohorts, which suggest that both diseases should be treated with the same approach. Recent randomized clinical trials showed that TNF inhibitors (TNFi) are effective also in treating signs and symptoms of nr-AxSpA. However, the efficacy of anti-TNF agents in patients with nr-AxSpA remains to be shown in daily rheumatology practice.
Objectives. To compare the efficacy of TNF inhibitors in patients with AS and nr-AXSpA in daily clinical setting.
Patients and Methods:. A total of 174 patients with AxSpA (107 M; 40.8±10.0) from two centers were included in this study. Of these patients 115 had AS according to the *modified New York criteria*, 59 *patients fulfilled* the ASAS classification criteria for AxSpA.
Results. Baseline demographics and clinical characteristics are summarized in the table below. After treatment with TNF inhibitors mean BASDAI score decreased significantly from 6.15±1.76 at baseline to 3.28±2.1 at 3 months (p=0.049) in patients with nr-AxSpA; from 5.99±1.69 to 3.05±1.7 (p:0.008) in patients with AS and from 6.05±1.71 to 3.12±1.85 (p=0.001) in the whole group. Minimal clinical response (a decrease of 2 units in BASDAI) was observed in 63% of the patients with nr-AxSpA and in 68% of the patients with AS. Major clinical response (BASDAI 50) was achieved in 49% and 51% of the patients with nr-AxSpA and AS, respectively.
Conclusion. The results of our study suggest that TNFi, which have been clearly shown to be effective in treating signs and symptoms of AS, seem to be equally effective in the treatment of nr-AxSPA.

Table I. Demographics and clinical characteristics of the AxSpA and AS patients.

	Non-radiographic axial spondylarthritis (n=59)	Ankylosing spondylitis (n:115)	p value
Age	36 (±10)	43 (±11)	p<0.001
Disease Duration (years)	8.05 (±7.6)	14.15 (±8.8)	p<0.001
Diagnosis Duration (years)	3.6(±2.9)	8.6 (±7.3)	p<0.001
Female (%)	55.9	29.5	p<0.001
Elevated CRP (%)	68	85	p:0.013
Elevated ESR (%)	56	71	p:0.056
HLA B27 positivity, n1/n2 (%)	19/29 (66)	24/34 (71)	p:0.666
Sacroiliitis by MRI n1/n2 (%)	46/49 (94)	-	
DMARD use at last visit (%)	36	28	
Biologic drugs used			
Infliximab (%)	14	32	
Etanercept (%)	39	39	
Adalimumab (%)	37	19	
Golimumab (%)	10	10	

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ANKYLOSING SPONDYLITIS PATIENTS HAVE AN INCREASED PROPORTION OF CD16$^+$ MONONUCLEAR CELLS ABLE TO INDUCE CCR6 ON CD4$^+$ T CELLS

Wright P.B.[1], Utriainen L.[1], McEntegart A.[2], McCarey D.[2], McInnes I.B.[1], Siebert S.[1], Milling S.W.F.[1]
[1]University of Glasgow, Centre for Immunobiology, Glasgow; [2]Glasgow Royal Infirmary, Dept. of Rheumatology, Glasgow, UK

Introduction. IL-17-secreting cells appear to be important in driving pathology both in AS patients and in the HLA-B27 transgenic (B27-TG) rat model of SpA. Dendritic cells (DCs) activate naïve T cells and maintain the balance between activation and suppression of the immune response. If affected by HLA-B27, DCs are therefore likely to drive T cell-mediated pathology in AS. Studies in our laboratory, using B27-TG rats, uncovered deficiencies in DC populations that promote IL-17 production from T cells. We therefore aimed to characterise the functions of DCs in AS patients, to understand their role in pathogenesis.
Patients and Methods. T cell and DC subsets were isolated from AS patients and age-matched healthy controls and analysed using multiparameter flow cytometry. DC populations, purified by flow cytometric sorting, were co-cultured with allogeneic T cells; T cell proliferation and chemokine receptor expression were measured by flow cytometry. Plasma IL-23p19 was measured by ELISA. Correlations between clinical and immunological parameters were analysed using Kruskal Wallis Spearman correlative tests with Dunn multiple comparisons post-test.
Results. Compared to controls, blood from AS patients contained increased proportions of CD4$^+$ CCR6$^+$ activated T cells, a higher ratio of pro-inflammatory (CD16$^+$ CD14$^-$ CD11c$^+$) mononuclear cells compared to CD1c$^+$ DCs, and higher systemic concentrations of IL-23. In co-culture experiments, CD16$^+$ DCs induce CCR6 expression on responding naïve T cells. The frequency of circulating CCR6$^+$ and CCR9$^+$ CD4$^+$ T cells in AS patients increased with disease severity and inflammation respectively.
Discussion. CCR6-expressing T cells are associated with a Th17 phenotype. Along with increased systemic levels of IL-23 in AS patients, a shift in circulating myeloid populations towards the CCR6-inducing CD16$^+$ population may contribute to the induction of Th17 cell-mediated pathogenesis. Furthermore, we have identified potential roles for CCR6$^+$ and CCR9$^+$ T cells in disease pathogenesis.

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THE IMMUNOLOGICAL BASIS OF THE SEX-BIAS IN ANKYLOSING SPONDYLITIS: TH17 EXPANSION IS RESTRICTED TO MALE PATIENTS AND CORRELATES WITH SEX-RELATED ALTERATION IN VITAMIN D METABOLISM

Gracey E.[1,2], Green B.[2], Yip P.[2], Ayearst R.[2], Anton A.[2], Lin A.[2], Inman R.D.[1,2]
[1]Dept. of Immunology, University of Toronto; [2]University Health Network, Toronto, Canada

Background. The male sex-bias in ankylosing spondylitis (AS) has long been known, however the biological basis for it is not known. Genetic and immunologic studies have implicated the Th17-axis in AS pathogenesis, and recent clinical trials suggest efficacy of anti-IL-17A therapy. Prior studies have demonstrated a direct and indirect suppressive effect of vitamin D_3 on Th17 cells. In the present study we examine whether there is a sex-bias in the Th17-axis, and its possible relationship to vitamin D metabolism in AS.
Methods. Serum IL-6 and IL-17A were measured by ELISA and 25(OH) vitamin D_3 by mass-spectrometry in a cohort of 75 AS patients and 34 age- and sex-matched healthy controls. Whole blood gene expression for vitamin D_3-associated and Th17-associated genes was measured by RT-PCR. Th17 cells were measured by flow cytometry of peripheral blood mononuclear cells (PBMC) in a second, overlapping cohort of 38 AS patients and 30 healthy controls.
Results. Male AS patients had an elevated Th17-axis when compared to females as demonstrated elevated IL-6 (p=0.082), IL-17A (p=0.016) and Th17 cell levels (p=0.021). A trend was seen for lower serum 25(OH)D_3 in male AS patients and healthy controls relative to their respective female counterparts. Gene expression of *VDR* and *CYP27B1* (D_3 activating enzyme) were equivalent in male and female AS patients, whereas *CYP24A1* (D_3 inactivating enzyme) expression was significantly elevated in male AS patients. This was not seen in male *vs* female healthy controls. In male AS patients, serum 25(OH)D_3 was inversely proportional to whole blood *IL23R* expression (r=-0.43, p<0.05) and Th17 cell level (r=-0.014, p=0.085).
Conclusion: Elevated levels of Th17 cells in AS are restricted to male patients. This may be due to a sex-related alteration in the Th17 inhibitory factor vitamin D_3. This work demonstrates a biological basis for the observed sex-bias in incidence and in disease expression in AS.

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ELEVATED SERUM LEVEL OF CD14 IN ANKYLOSING SPONDYLITIS PATIENTS

Li Q., Lv Q., Chen X., Gu J.
Rheumatology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Introduction/Aim. CD14 (including mCD14:membrane CD14 and sCD14**:** soluble CD14) can recognize and bind LPS or LPS / LBP complex, mediate LPS stimulation monocytes to secrete TNF-α, IL-1 and other cytokines. TLR4 interaction with CDl4 was able to complete LPS signal transduction. Our previous study also showed that TLR4 expression in AS patients peripheral blood mononuclear cells is elevated.
AS is a chronic inflammatory disease. In this study we investigated the differences of genes and its expression in patients with AS, the more understanding of the pathogenesis of AS.
Methods. All the patients met the modified New York criteria (1984). Use the microarray to find difference genes in 21 cases of ankylosing spondylitis (AS) patients and 20 healthy controls peripheral blood mononuclear cells, and verify its expression in serum though protein chip. The total RNA was extracted from the peripheral blood mononuclear cells of 21 cases of AS patients and 20 healthy controls. CDNA microarray (Sentrix Human Ref-8_V2 Beadchips, Illumina, San Diego, CA) contains 20589 probes, 16283 genes. The microarray data was analysed by Arraytool. The differential expression genes (Fold>1.5 $p<0.05$) of microarray were validated on AS patients and healthy controls (each is 20 cases) serum through the protein chips of RayBic Human Cytokine Antibody Arrays, AAH-BLG-1000. Spss 20.0 was used for the protein chip dat, and statistical analysis method is the Mann-Whitney U test.
Results. We got a total of 63 differentially expressed genes (Fold> 1.5, $p<0.05$) between AS patients and healthy controls through the Arraytool software. After analyzed by Mann-Whitney U test, a different protein molecule sCD14 was found between AS and healthy control serum, sCD14 was significantly elevated in the serum of ankylosing spondylitis patients ($p<0.05$).
Conclusions. sCD14 was significantly elevated in the serum of AS patients, it may be a worthy of study inflammatory target.

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INFLUENCE OF HLA-B27 AND SPONDYLOARTHRITIS (SPA) ON THE DISTRIBUTION OF CIRCULATING TH1, TH-17 AND TREG CELLS

Bouiller I.[1,2], Leboime A.[3], Said-Nahal R.[3], Chiocchia G.[1,2], Araujo L.M.[1], Breban M.[1,2,3]
[1]Faculty of Health Sciences Simone Veil, and INSERM U987, University of Versailles-St-Quentin; [2]Université Paris Diderot, Sorbonne Paris Cité, Laboratoire d'Excellence, Paris; [3]Service de Rhumatologie, Ambroise Paré Hospital, France

Introduction/Aim. HLA-B27 is a major genetic risk factor for SpA, but the association between HLA-B27 and SpA still remains largely unexplained. Our objective was to evaluate the impact of HLA-B27 and/or SpA on circulating $CD4^+$ T cells phenotype in healthy subjects and patients.
Materials and Methods. $CD4^+$ T cells were isolated from peripheral blood mononuclear cells of 22 HLA-B27+ patients and 23 healthy controls (15 HLA-B27+ and 7 HLA-B27-) by Ficoll gradient and magnetic sorting. Flow cytometry was used to analyze the phenotypic markers of the $CD4^+CD45RO^+CD25^-$ memory T cells for Th1, Th2, Th17 and Treg subtypes, *ex-vivo* and following PMA/ionomycin stimulation.
Results. No significant difference was observed between HLA-B27+ and HLA-B27- controls. Before stimulation, the frequency of Th1 cells was significantly increased in PBMCs of patients, as compared to HLA-B27+ and all controls (p=0.01 and 0.009, respectively). The Th17 frequency was similar between control groups and patients. Interestingly, inducible T cell costimulator (ICOS) expression was increased in Th17 cells from patients, as compared to both control groups (p=0.02). Treg frequency was decreased in HLA-B27+ patients as compared to HLA-B27- controls (p=0.04). The frequency of Th2 cells was similar between control groups and patients. After 6h of PMA/ionomycin stimulation, reduced frequency of Treg persisted in patients, as compared to HLA-B27- controls. No differences were observed for others subsets. After 24h of stimulation, a significantly higher proportion of Th1 cells was confirmed in patients, as compared to all controls (p=0.008).
Discussion. A higher frequency of Th1 and lower frequency of Treg was observed in HLA-B27+ SpA, as compared to controls. A lack of difference in relation to HLA-B27 in control, indicated that those changes were linked to the SpA context rather than to HLA-B27 by itself.

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BROMODOMAIN INHIBITORS REDUCE TH17-TYPE RESPONSES IN SPONDYLOARTHRITIS IN VITRO

Hammitzsch A.[1], de Wit J.[1], Ridley A.[1], Al-Mossawi M. H.[1], Knapp S.[2], Bowness P.[1]
[1]Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford; [2]Target Discovery Institute, Nuffield Dept. of Clinical Medicine, University of Oxford, UK

Introduction/Aim. Bromodomains bind acetylated lysine residues of histones and are part of epigenetic mechanisms regulating transcription. A small molecule inhibitor of the bromodomains of BET (bromodomain and extra-terminal) polypeptides, (+)-JQ1, has been shown to inhibit human and murine Th17 differentiation in vitro and ameliorated Collagen-induced arthritis and experimental autoimmune encephalomyelitis in mice. SGC-CBP30 is a novel highly selective p300 bromodomain inhibitor. We compared the efficacy of SGC-CBP30 with (+)-JQ1 on Th17-type responses in ankylosing Spondylitis (AS), psoriatic Arthritis (PsA) and healthy controls (HC) was tested in vitro.
Materials and Methods. CD4+ T cells were selected using magnetic beads from PBMC of AS and PSA patients or HC and cultured under Th17-polarizing conditions. Cells were treated with either SGC-CBP30 or (+)-JQ1 from day 0 on. Effects of the inhibitors were assessed by IL-17A and IFNγ ELISA and a LUMINEX assay on day 3 tissue culture supernatants. Toxicity was controlled with Annexin-V/7-AAD staining and a CFSE-proliferation assay. QT-PCR was performed on day 4.
Results. SGC-CBP30 showed a favorable toxicity profile compared with (+)-JQ1 when looking at apoptosis and proliferation. SGC-CBP30 and (+)-JQ1 reduced IL-17A measured by ELISA on day 3 by more than 50% in AS and PSA patients and HC. (+)-JQ1 additionally abrogated IFNγ production in all groups. GM-CSF and IL-10 reduction was more pronounced in (+)-JQ1 treated samples compared to SGC-CBP30 (Luminex). No significant effects of either of the inhibitors were observed on TNFα (Luminex). QT-PCR showed reduced transcripts for Th17 signature genes (Il17a, Il21 and Rorc) for both inhibitors in AS patients and HC, whereas Tbx21 was not affected and Il23r only lowered by (+)-JQ1.
Discussion. Both inhibitors effectively reduced Th17-type responses. However, SGC-CBP30 was less toxic and more selective compared to (+)-JQ1.
Conclusions. SGC-CBP30 should be further evaluated as a potential new drug in AS and PSA.

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PATTERN RECOGNITION RECEPTOR INDUCED CYTOKINE PRODUCTION IN MACROPHAGES FROM PATIENTS WITH SPONDYLOARTHRITIS

Liu Y.P.[1], Eickhoff J.[2], Bomkamp A.J.[3], Khan M.[4], Smith J.A.[1]
[1]Dept. of Pediatrics, University of Wisconsin (UW)-Madison School of Medicine and Public Health (SMPH), Madison; [2]Dept. of Biostatistics and Medical Informatics, UW-Madison SMPH, Madison; [3]Dept. of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [4]Dept. of Pathology and Laboratory Medicine, UW-Madison SMPH, Madison, USA

Introduction/Aim. Increasing evidence implicates cytokine dysregulation in the pathogenesis of ankylosing spondylitis (AS) and related spondyloarthritides (SpA), in particular dysregulation of the IL-23/IL-17 pathway. We investigated whether macrophages from AS and non-AS SpA subjects produce excessive cytokines in response to multiple pattern recognition receptor (PRR) agonists. Biochemical signaling events underlying excess cytokine production were also assessed.
Methods. CD14+ monocytes from 12 control, 12 AS and 12 non-AS SpA subjects were differentiated into macrophages and stimulated with agonists for Toll-like receptor (TLR) 4, TLR7/8, TLR2, and Dectin-1. Culture supernatant was analyzed for IL-6, IL-8, IL-10, IL-23 and TNF-α. Macrophage lysates were assessed for phosphorylated ATF2 and NF-κB activation.
Results: IL-23 exhibited the greatest differences between groups for multiple agonists, followed by TNF-α. SpA macrophages generally produced more cytokine than AS and control macrophages, except for peptidoglycan-induced IL-8, where only AS macrophages produced more than controls. pIκBα (measure of NF-κB activation) correlated positively with IL-23 production (r=0.41-0.55, $p<0.01$) in SpA and AS subjects. pATF2 was differentially regulated in AS and SpA, correlating positively with cytokine production in SpA (r=0.68-0.79, $p<0.03$), but not AS. Clusters of 2-4 subjects displayed strikingly similar patterns of cytokine production in response to different PRR agonists.
Conclusions. Cytokine responses of AS and SpA groups to one agonist/cytokine did not carry across to other agonists or cytokines. These findings have implications for design and interpretation of future studies. Cytokine and biochemical analyses revealed differences between narrowly defined AS and other SpA groups, suggesting that combining these groups under "spondyloarthritis" might be problematic in pathogenesis studies. Finally, we identified distinct "patterns" of PRR responses, perhaps reflecting shared variations at immunomodulatory gene loci.

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SUPPRESSION OF IN-VITRO TYPE-17 RESPONSES IN SPA PATIENTS USING SMALL MOLECULE ROR-γT INHIBITORS

De Wit J.[1], Al-Mossawi M.H.[1], Huhn M.[2], Arancibia C.V.[2], Powrie, F[2], Bowness P.[1]
[1]University of Oxford, Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford; [2]University of Oxford, Nuffield Dept. of Medicine, Oxford, UK

Introduction. $CD4^+$ T helper cells producing the pro-inflammatory cytokine IL-17A (Th17) have been associated with various inflammatory arthritides, including Ankylosing spondylitis (AS), psoriatic arthritis (PsA) and also rheumatoid arthritis (RA). IL-17A has therefore become a new target of interest to suppress the inflammatory responses in these diseases. Key in the type-17 responses is the specific transcription factor retinoid-related orphan nuclear receptor (ROR)-γt, which maintains Th17 phenotype and drives IL-17A production. Inhibition of ROR-γt shows promising results in repressing IL-17A responses in various mouse models. Here we investigate the *in vitro* effect of two different small molecule ROR-γt inhibitors on human type-17 responses of patients with inflammatory arthritides.
Methods. Peripheral blood and synovial leukocytes were obtained from patients with AS, PsA and RA. Using low strength anti-CD2/3/28 stimulation and recombinant IL-2, type-17 T cells were expanded in a 7 day culture system. Intracellular cytokine staining and ELISA were used to determine the effect of two different ROR-γt inhibitors.
Results. A consistent suppression with both ROR-γt small molecule inhibitors of approximately 50% was observed in IL-17A producing $CD4^+$ T cells from blood, synovial fluid and synovial tissue in AS, RA and PsA. IL-17A production by $CD8^+$ T cells was similarly reduced by both inhibitors. No significant effects on single producers of IFN-γ, TNF, GM-CSF, IL-17F and IL-22 were observed, implying specific IL-17A suppression. Cell viability or proliferation was not adversely affected by the ROR-γt compounds in our culture system.
Conclusions. Our results demonstrate that small molecule ROR-γt inhibitors specifically suppress IL-17A production in SpA (and RA) patient-derived lymphocytes from blood and synovium. These compound may there for be a next step in treatment of inflammatory arthritides.
Acknowledgements. Merck Laboratories, research funding and inhibitor compounds.

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IDENTIFICATION AND PHENOTYPING OF INNATE LYMPHOID CELLS PRESENT IN THE DISEASED JOINTS OF PATIENTS WITH SPONDYLOARTHRITIS, RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS

Al-Mossawi M.H., Manou-Stathopoulou S., De Wit J., Kendrick B., Gundle R., Bowness P.
University of Oxford, Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford, UK

Introduction. Innate lymphoid cells (ILCs) have been recently identified at a number of different tissues and are thought to be an important class of innate immune cells involved in the initiation of the inflammatory response during health and disease.
Methods. Matched synovial fluid and peripheral blood mononuclear cells from patients with spondyloarthritis (SpA) and psoriatic arthritis (PsA) were isolated and phenotyped using flow cytometry. In addition, cells from explanted orthopaedic surgical tissue samples were obtained from patients with SpA, PsA and rheumatoid arthritis (RA) and cultured in media containing interleukin-2 and interleukin-7.
Results. A population of lineage-negative (ie negative for CD3, CD5 CD8, CD11b, CD11c, CD14, CD19, CD20, TCR-γδ) CD45 positive, IL-7R positive cells was identified in the synovial fluid and tissue of diseased human joints. Further phenotyping showed these to be either C-KIT positive ILC3 cells or C-KIT negative ILC1 cells. CRTH2 positive ILC2 cells were not detected. Comparison of matched blood and synovial fluid cells showed ILC3 populations were enriched in the joint.
Discussion & Conclusions. ILC populations (type 1 and type 3) are pre present in the synovial fluid and synovial tissue of inflamed SpA, PsA and RA joints. These cells are capable of rapid cytokine release and are potentially highly inflammatory. Understanding the role of ILCs in health and disease is important for deciphering the processes taking part in early SpA pathogenesis.

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AFTER SURGERY WITH PROSTHESIS THE INFECTION RATES IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED BY TNF ALPHA BLOCKADE COMPARED TO CONVENTIONAL NSAIDS

Lee S.H., Hong S.J., Chung S.W.
Dept. of Rheumatology, School of Medicine, Kyung Hee University, Seoul, Korea

Objective. Some patients with severely advanced ankylosing spondylitis (AS) need to replace the destructed joints or correct them. Among these patients, some patients who don't respond to conventional NSAIDs have to be treated by anti TNF alpha blockades. We reviewed these patients to know how many patients had infection after surgery which had used prosthesis.
Methods. We reviewed retrospectively the patients with AS by medical chart who experienced the surgery in Kyung Hee university hospital at Gangdong in Seoul, South Korea from Mar 2006 to May 2014.
Results. Total 307 patients underwent the surgeries such as total hip replacement (THR) or corrective osteotomy of spine. Among them, 25 patients have been treated by TNF alpha blockades. 9 patients also have been treated by TNF alpha blockade from before the surgeries. Total follow up period are 4.3±2.3 years per person. Their average ages on surgeries are 35.6±10.7 years. Among them, 13 patients had THR the others had corrective osteotomy in spine. 11 patients have been treated by adalimumab, 9 patients have been treated by etanercept and 5 patients have been treated by infliximab. There was no wound complication associated with infection after the surgery until now. But in the group of patients who had been treated by conventional NSAIDs, one patient had wound infection after spine surgery. His age was 62 and had uncontrolled DM.
Conclusion. They're in no increased risk of infection after the surgeries using prosthesis in patients with AS who treated by TNF alpha blockade compared to the patients treated by conventional NSAIDs.

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FAT METAPLASIA IS A KEY INTERMEDIARY IN THE DEVELOPMENT OF SACROILIAC JOINT ANKYLOSIS FOLLOWING REPAIR OF EROSIONS IN PATIENTS WITH SPONDYLOARTHRITIS

Maksymowych W.P.[1], Wichuk S.[1], Chiowchanwisawakit P.[3], Lambert R.G.[2], Pedersen S.J.[4]
[1]Medicine and [2]Radiology, University of Alberta, Canada; [3]Medicine, Mahidol University, Thailand; [4]Copenhagen Center for Arthritis Research, University of Copenhagen, Denmark

Introduction. Fat metaplasia develops after resolution of inflammation in spine and sacroiliac joints (SIJ). Tissue with bright signal on T1W MRI, termed backfill (BF), may also fill areas of excavated bone along the SIJ joint space and is thought to reflect repair of erosion. Imaging OF the spine has indicated that fat metaplasia predicts development of new bone. We tested the hypothesis that SIJ ankylosis develops following repair of erosion and that fat metaplasia is a key intermediary step in this pathway.
Methods. We used the SPARCC SIJ Structural Score (SSS) method to assess fat metaplasia (FAT), erosion (ER), BF, and ankylosis (ANK). Four readers assessed 45 pairs of MRI scans blinded to time point (baseline, 2 years) from cases in a prospective cohort (exercise 1). In exercise 2, two readers independently assessed 147 pairs of scans blinded to time point (baseline, 2 years). Multivariate regression analyses focused on identifying significant MRI predictors of change in ANK scores, adjusted for age, sex, symptom duration, treatment, CRP (baseline and 2-year change), SPARCC SIJ inflammation score (baseline and 2-year change), and baseline SSS scores for FAT, ER, BF, and ANK.
Results. Resolution of ER was significantly correlated with the development of new ANK (p=0.045) in exercise1. In the second study, resolution of erosion also correlated significantly with the development of new fat metaplasia (p<0.0001) and new ANK (p=0.0001) at 2 years. New fat metaplasia also correlated significantly with development of ankylosis (p=0.0005). Significant independent predictors of new ANK in the multivariate model (adjusted $R^2 = 0.28$, F ratio = 14.4, p<0.0001) were 2-year change in BF score (p=0.0005), decreased erosion score (p=0.0001) and development of new fat metaplasia (p=0.0005).
Conclusion: Ankylosis in the SIJ develops following repair of erosion and fat metaplasia is a key intermediary step in this pathway.

P109

COMORBIDITIES IN PSORIATIC ARTHRITIS: COMPARISON WITH RHEUMATOID ARTHRITIS AND PSORIASIS

Nas K.[1], Karkucak M.[2], Durmus B.[3], Karatay S.[4], Capkin E.[2], Kaya A.[5], Ucmak D.[6], Akar Z.A.[1], Cevik R.[1], Ozgocmen S.[7]
[1]Dept. PMR, Faculty of Medicine, Dicle University, Diyarbakir; [2]Karadeniz Technical University, Trabzon; [3]Inonu University, Malatya; [4]Ataturk University, Erzurum; [5]Firat University, Elazig; [6]Dept. Dermatology, Dicle University, Diyarbakir; [7]Division of Rheumatology, Dept. PMR, Erciyes University, Kayseri, Turkey

Aim. To assess comorbidities in a Turkish cohort of psoriatic arthritis (PsA) and to compare with rheumatoid arthritis (RA) and psoriasis (PsO).
Materials and Methods. Patients recruited from Anatolian Group for the Assessment in Rheumatic Disease (ANGARD) cohort which consists five university centers. Patients should meet CASPAR criteria and underwent clinical, radiological and laboratory evaluation and examined by using standardized protocol. Co-morbid conditions were recorded. Controls were consecutively recruited patients with RA and PsO.
Results. A total of 173 patients with PsA (75M, 98F, mean age=41.8) and 157 controls (67 RA,90 PsO) (60M and 97F, mean age=43.5) were included. Arthritis antedated psoriasis in 16.6% of patients with PsA and majority had psoriasis vulgaris (79.8%). There was also 2.6 years diagnostic delay in PsA. Patients with PsO+RA had higher risk for overall arterial hypertension, HT (OR=2.46; 95% CI 1.13-5.34, p=0.023) and cataract/glaucoma surgery (OR=12.33; 95% CI 1.46-103.8, p=0.021) but not for overall diabetes mellitus, DM (OR=1.34; 95% CI 0.61-2.96, p=0.464) in logistic regression analysis adjusted for duration since diagnosis, current smokers, BMI and steroid use. Patients with PsO had younger age (36.1 vs 41.9, p=0.004), longer symptom duration (11.5 vs 8.9, p=0.042), lower BMI (25.2 vs 27.1, p=0.007) and higher glucocorticoid use (41.8% vs 20.2%, p=0.001) than patients with PsA. Patients with PsA had higher risk only for overall HT (OR=4.26; 95% CI 1.27-14.23, p=0.018) than PsO (adjusted for age, symptom duration, BMI and steroid use).
Conclusion. Patients with PsA had lower risk of DM, HT and cataract/glaucoma surgery compared to the control group composed of patients with RA and PsO. The higher risk in RA+PsO group may be related to the higher prevalence of glucocorticoid and NSAID use.

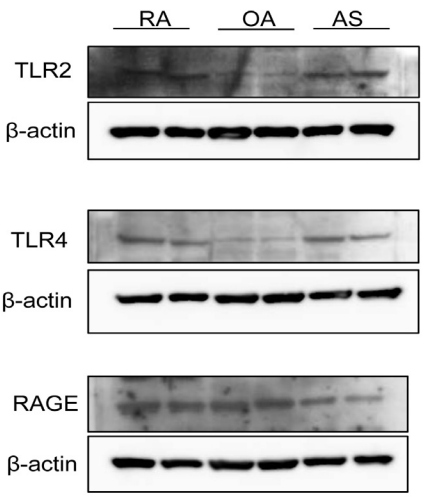
P110

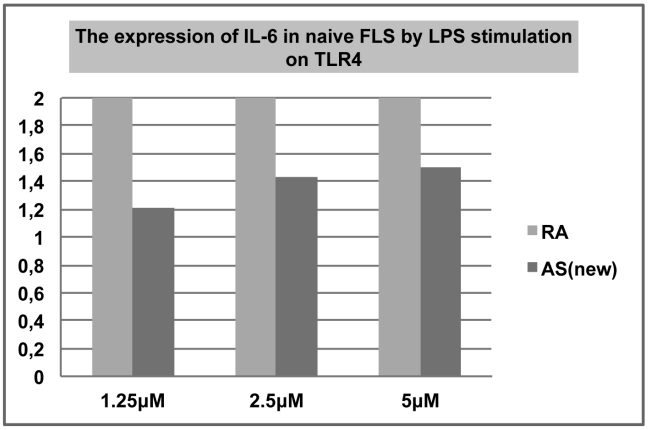
IL-6 MAYBE A CRUCIAL ROLE IN PERIPHERAL ARTHRITIS OF ANKYLOSING SPONDYLITIS BY TOLL-LIKE RECEPTOR 2 AND 4

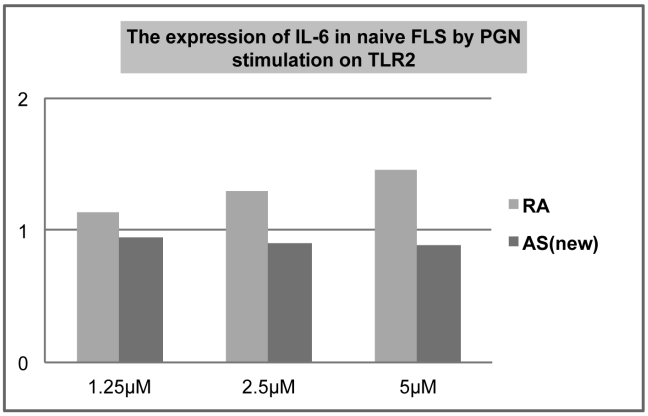
Lee S.Y.
Dong--A university, Pusan, South Korea

Background. The blocking of IL-6 therapy is not effective treatment of AS in recent report, but the role of blocking IL-6 on peripheral joint in non-radiographic axial AS is unknown. So we studied the blocking of IL-6 in peripheral arthritis of non-radiographic axial AS.
Methods. Synovial fibroblast (FLS) were obtained from knee of eight non-radiographic axial AS patients who were high BASDAI score (>6), and six RA patients who were moderate DAS28 score (>3.2). The expression of IL-6 was analyzed by real-time polymerase chain reaction and multiplex secretary protein analysis technology, Bio-plex assay, also the expression of toll like receptor (TLR) in FLS was detected by western blot.
Results. The expression of TLR 2 and TLR 4 were observed on AS and RA FLS. The administration of peptidoglycan for TLR 2 and LPS for TLR 4 increased the level of IL-6 in AS and RA FLS. The treatment of AS FLS with IL-6 inhibitor, tocilizumab, resulted in reduced expression of TLR 2 and TLR 4 in AS FLS and re-administration of peptidoglycan for TLR 2 and LPS for TLR 4 treatment did not increased the expression of IL-6, TLR 2 and TLR 4 in AS FLS.
Conclusion. Our results suggest that IL-6 maybe crucial role in peripheral arthritis of non-radiographic axial AS and blocking of IL-6 may ameliorate peripheral arthritis of AS by regulating TLR 2 and TLR 4, so inhibition of IL-6 maybe a potential therapeutic strategy in peripheral arthritis of non-radiographic axial AS.

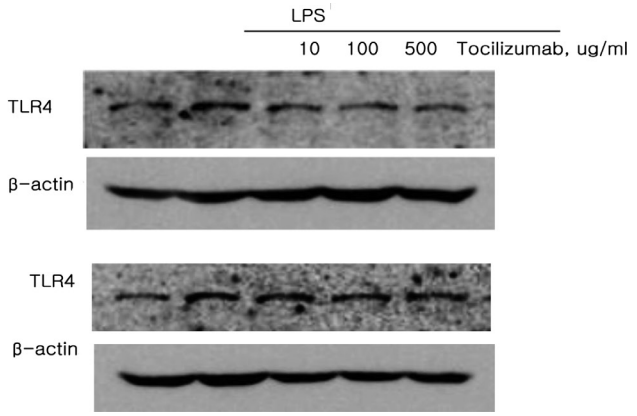
The expression of TLR2, TLR4 in AS synovial fibroblast by western blot, compared with OA, RA synovial fibroblast.



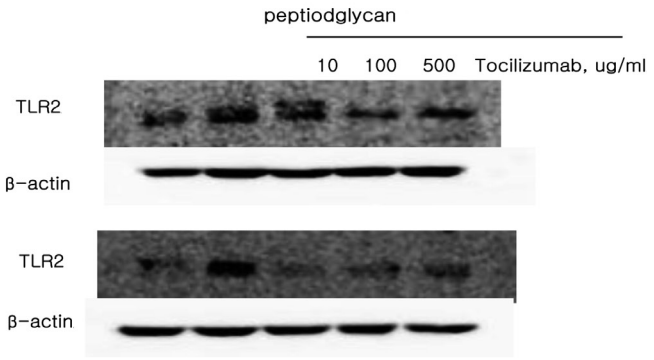




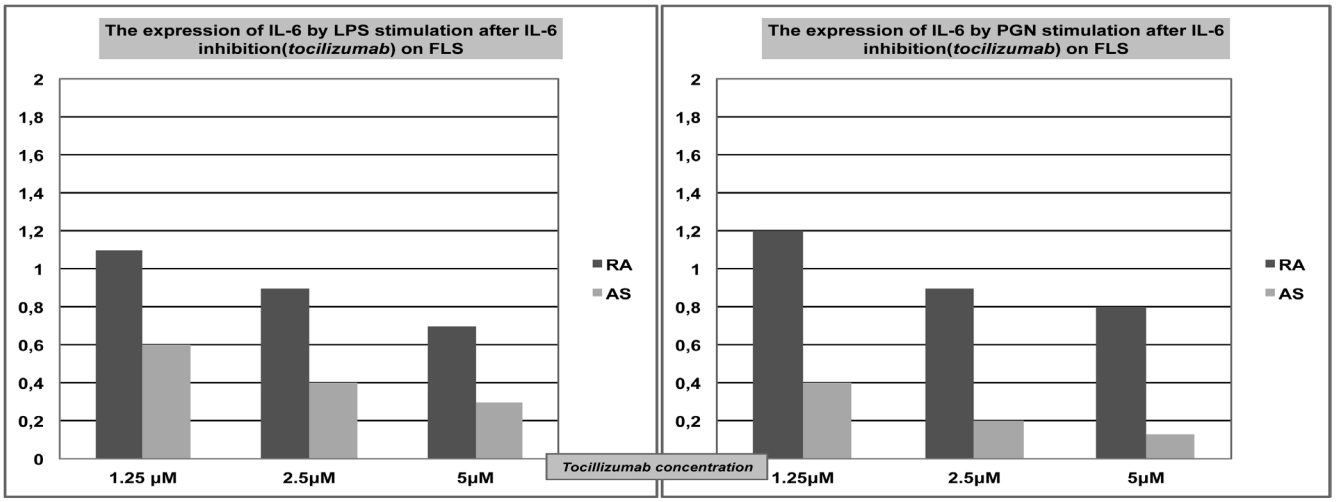
The expression of IL-6 in OA and AS naïve synovial fibroblast, stimulated by LPS for TLR2 and peptidyglycan for TLR4.



The expression of TLR 4 blocking by IL-6 inhibitor (tocillizumab) and stimulated by LPS: no interval change in expression of TLR 4.



The expression of TLR 2 blocking by IL-6 inhibitor (tocillizumab) and stimulated by peptidoglycan: decreased expression of TLR 2.



The expression of IL-6 was decreased after treatment of IL-6 inhibitor (tocillizumab). in AS and RA synovial fibroblast

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ANKYLOSING SPONDYLITIS ASSOCIATED ERAP1 VARIANTS TRIGGER THE UNFOLDED PROTEIN RESPONSE

Zhang Z., Haroon N.
University Health Network, University of Toronto and Toronto Western Research Institute, Toronto, Canada

Introduction. Endoplasmic reticulum aminopeptidase 1 (ERAP1) has recently been identified to be strongly associated with HLA-B27 positive AS. We have shown that the 730E ERAP1 variant with decreased function is associated with increased free heavy chain (FHC) expression on monocytes of AS patients. Unfolding of HLA-B27 and the formation of FHC can cause the release of inflammatory cytokines by triggering the unfolded protein response (UPR). We tested if ERAP1 variants can affect the UPR.
Methods. Endogenous ERAP1 was silenced in C1R-HLA-B27 cells with ERAP1-shRNA ($C1R^{ERAP1sh}$). Scrambled sequence shRNA ($C1R^{ERAP1scrambled}$) was used as control. We then transfected either the common variant ERAP1 ($ERAP1^{WT}$) or one of the two AS-associated ERAP1 variants, K528R or Q730E into the $C1R^{ERAP1sh}$ cells. Lentivirus expression vector alone was used as control and exogenous ERAP1 expression was tracked with HA-tag. UPR was measured using PCR for spliced variants of XBP-1 and by qRT-PCR and western blot for BiP, CHOP, PERK and ATF-6.
Results. Ninety-five percent of C1R cells that were selected by antibiotics were GFP positive indicating stable ERAP1-shRNA expression. Using WB we noted more than 90% suppression of ERAP1 and more than 85% suppression by qRT-PCR in $C1R^{ERAP1sh}$, compared to $C1R^{ERAP1scrambled}$. Anti-HA WB showed uniform strong expression of $ERAP1^{WT}$ and variant forms of ERAP1 in the respective cell lines.
Spliced XBP1, a marker of UPR, was upregulated in the $C1R^{ERAP1sh}$ cells. Re-introduction of ERAP1 ($C1R\text{-}ERAP1^{WT}$ cells) reduces the UPR response while $C1R\text{-}ERAP1^{K528R}$ and $C1R\text{-}ERAP1^{Q730E}$ cells expressing the ERAP1 variants had higher UPR activation compared to $C1R\text{-}ERAP1^{WT}$ cells. Other UPR markers including BiP, CHOP PERK and ATF6 expression followed the same pattern with AS-associated variants leading to higher UPR. After immunoprecipitation with antibody HC10, more FHC-bound BiP was seen in $C1R^{ERAP1sh}$ cells than other stable cells by Western Blot.
Conclusion. AS-associated ERAP1-variants, which are known to have reduced function, leads to more UPR compared to $ERAP1^{WT}$.

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CD74 AS AN AUTOANTIGEN IN SPONDYLOARTHRITIS

Witte T., Wintering O., Kniesch K., Klose K., Baerlecken N.
Dept. of Immunology and Rheumatology, Medical University Hannover, Germany

Introduction. Recently, we have described IgG autoantibodies against CD74 as a new diagnostic marker in SpA. The aim of this study was to characterize IgM antibodies against CD74 in SpA, to study the expression of CD74 on monocytes of SpA patients and to identify CD74 as a T cell antigen.
Methods. Sera of 20 newly diagnosed axSpA patients and 20 blood donors were obtained after written consent. PBMCs were isolated from the blood of 29 patients with axSpA (n=29), RA (n=20) and healthy controls (n=17). The cells were stained for CD3, CD14, CD19, HLA-DR and CD74. The MFI of CD74 on T-cells, B-cells and monocytes was compared between the groups using ANOVA. IgG and IgM antibodies against recombinant CD74 were measured by ELISA. PBMC of 37 SpA patients, 20 RA patients and 13 healthy controls were incubated overnight with recombinant CD74 or a control protein in the presence of brefeldin. Then, the intracellular production of TNFalpha and of IFNgamma was measured in $CD4^+$ T cells using flow cytometry.
Results. IgM antibodies against CD74 were present in 50 % of the axSpA patients and in 1/20 controls. The axSpA patients with IgM antibodies mostly had a disease duration of less than 2 years. The expression of CD74 was significantly lower on monocytes of axSpA patients compared to blood donors (p=0.047). Subgroup analysis revealed, that the reduced expression of CD74 was associated with not receiving a TNF inhibitor (p=0.019) and with IgG antibodies against CD74 (p=0.036). A higher subset of $CD4^+$ T cells of SpA patients produced IFNgamma (p=0.0003) or TNFalpha (p=0.0013) compared to RA patients and controls, in particular the subset of SpA patients with a disease-duration of less than five years.
Conclusions. CD74 is an autoantigen for both B and T cells in axSpA. Functional studies with the isolated CD74 antibodies will help to identify their role in the pathogenesis of SpA.

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THE KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR KIR3DL2 BINDING TO HLA-B27 LICENCES PATHOGENIC T CELL DIFFERENTIATION IN ANKYLOSING SPONDYLITIS

Ridley A., Hatano H., Wong-Baeza I., Shaw J., Wynn K., Al-Mossawi H., Ladell K., Price D., Bowness P., Kollnberger S.
Botnar Research Centre, Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, UK

Introduction. Ankylosing Spondylitis (AS) is associated with possession of HLA-B27 and also with increased numbers of circulating NK and Th17 cells expressing the killer cell immunoglobulin-like receptor KIR3DL2. The KIR3DL2 gene, found in all KIR haplotypes, encodes a receptor that binds strongly to β2m-free heavy chain forms of HLA-B27 (B27). We investigated how KIR3DL2 expression is induced on T cells. We also determined the effect of KIR3DL2 binding to HLA-B27 on Th17 cell differentiation.
Methods. We studied induction of KIR3DL2 and T cell transcription factors by purified naïve and CD4 T cells activated with mitogens, superantigen and by TCR crosslinking by, qPCR, western blot and flow cytometry. We characterised expression of Th17, activation and gut homing markers by KIR3DL2 CD4 T cells in 30 AS patients and healthy and disease controls by qPCR and flow cytometry. We compared the TCR repertoire of FACS-sorted KIR3DL2 CD4 T cells in AS patients and controls by template-switch anchored RT-PCR.
Results. Cellular activation induces expression of KIR3DL2 on naïve and effector $CD4^+$ T cells. Subsequently, KIR3DL2 binding to HLA-B27-expressing cells "licenses" Th17 differentiation by promoting expression of the Th17 transcription factor RORγt. Targeting HLA-B27 KIR3DL2 interactions with antibodies inhibited T cell IL-17 production. AS patient $KIR3DL2^+CD4^+$ T cells are enriched for T cell activation markers and have a TCR repertoire that is oligoclonal and which can share common sequences with KIR3DL2- cells, suggesting antigen-driven KIR3DL2 expression. AS patient $KIR3DL2^+CD4^+$ T cells were also enriched for the gut homing marker CCR9.
Conclusions. Our results suggest that KIR3DL2/HLA-class I interactions play both a general role in determining the fate of activated T cells, and drive pathogenic Th17 differentiation in AS. These findings also highlight the therapeutic potential of targeting HLA-B27-KIR3DL2 interactions for the treatment of B27-associated disease.

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CLINICAL MANAGEMENT IN ANKYLOSING SPONDYLITIS REMISSION

Myasoutova L., Lapshina S.
Kazan State Medical University, Kazan, Russia

Purpose. Evaluating the effectiveness of etanercept and the possibility of reducing the frequency of administration of the drug in the long term treatment of patients with AS and their achievement of remission.
Methods. We observed 15 AS patients (male -11, female - 4, mean age 32.9 years), onset of symptoms in 9 of them was not more than 5 years, the remaining 6 - disease duration ranged from 6 to 17 years. Initially, all patients had high activity (mean values ASDAS CRP- 3, 9; BASDAI - 6, 9), and HLA-B27- positive. Etanercept was administered at a dose of 50 mg once a week, in remission we reduced frequency of administration to 50 mg once in 2 weeks. Duration of etanercept therapy ranged from 18 to 42 months. Efficacy was evaluated by ASAS criteria.
Results. After 12 weeks of treatment, all patients achieved improvement ASAS 40 criteria, partial remission matched 11 (73.3%) patients, of which 9 had symptoms for less than 5 years. Patients who reached remission increased intervals between drug administration up to 2 weeks. After 24 weeks criteria ASAS partial remission was achieved in 14 (93.3%) patients, 1 patient with AS duration more than 10 years observed improvement ASAS40. There was a decrease (p<0.05) mean values of BASDAI (1,9), BASFI (1,6), ASDAS CRP (1,1). In all reached remission patients etanercept was administered 50 mg once in 2 weeks. On the background of long-term treatment with etanercept (12, 18, 24 and 42 months), partial remission (ASAS) was preserved in 12 (80%) patients, 2 patients with AS duration more than 6 years speakers had periods of exacerbation. Partial remission criteria were observed in all 9 patients with disease duration of less than 5 years and 3 (50%) of 6 persons with symptoms lasting more than 6 years serious side effects were not reported.
Conclusion. AS treatment with etanercept leads to a rapid and clinically significant improvement on the basic parameters. Reducing multiplicity of administration when the clinical wellbeing to two injections per month can store remission in the majority of patients, especially in light of limitation disease.

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A MOLECULAR BASIS FOR THE KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR KIR3DL2 BINDING TO HLA-B27 FREE HEAVY CHAIN DIMERS

Hatano H., Shaw J., Marquardt K., Zhang Z., Gauthier L., Chanteux S., Rossi B., Li D., Mitchell J., Kollnberger S.
Botnar Research Centre, Nuffield Dept. of Rheumatological and Musculoskeletal Sciences, Oxford University, Oxford, UK

Introduction. The killer cell immunoglobulin-like receptor KIR3DL2 binds more strongly to HLA-B27 (B27) β2m-free heavy chain (FHC) dimers than other HLA-class I heavy chains and ligands. B27 binding more strongly to KIR3DL2 has been proposed to play a role in Ankylosing Spondylitis by promoting the survival of pathogenic Natural Killer (NK) and Th17 cell subsets. We determined a molecular basis for the stronger binding of B27 FHC dimers to KIR3DL2.
Methods. We modelled B27 FHC dimer binding to KIR3DL2 using MODELLER and HADDOCK molecular docking programs. We studied production of IL-2 by KIR3DL2CD3e Jurkat reporter cells when KIR3DL2 binds to ligand. We identified key contact residues in KIR3DL2 by alanine mutagenesis and also studied the effect of mutating potential contact residues to the corresponding amino acids in the related molecule KIR3DL1. IFNγ production was measured by ELISA and cytotoxicity of $KIR3DL2^+$NK cells was measured by using flow cytometry to monitor expression of CD107a and killing of CFSE-labelled target cells.
Results. B27 FHC dimers triggered production of higher IL-2 by KIR3DL2 reporter cells compared to other heavy chains. Only KIR3DL2-HLA-B27 FHC interactions inhibited natural killer cell cytotoxicity and IFNγ production significantly compared to KIR3DL2 binding to other class I FHC.
Our molecular modelling and mutagenesis data provides an explanation for the stronger binding of B27 dimers to KIR3DL2 identifying non-symmetrical complementary contacts of KIR3DL2 D0 and D1 domains with the α1, α2 and α3 domains of both B27 heavy chains in the B27 dimer. The D2 domain contacts residues in the α2 domain of one B27 heavy chain.
Conclusions. These findings provide novel insights into the molecular basis of KIR3DL2 binding to HLA-B27 and other ligands. They also suggest an important role for KIR3DL2 HLA-B27 interactions in controlling the function of NK and other KIR3DL2+expressing leukocytes in HLA-B27+ patients with Ankylosing Spondylitis.

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FUNCTIONAL IMPLICATIONS OF THE ENDOPLASMIC RETICULUM AMINOPEPTIDASE 2 (ERAP2) ASSOCIATION WITH ANKYLOSING SPONDYLITIS AND CROHN'S DISEASE: IMPACT ON THE UNFOLDED PROTEIN RESPONSE

Zhang Z., Ciccia F., Yee K., Guggino G., Abdullah H., Inman R.D., Alessandro R., Raimondo S., Triolo G., Haroon N.[1]
[1]University of Toronto, University Health Network, Toronto Western Research Institute, Toronto, Canada

Introduction. Endoplasmic Reticulum Aminopeptidase 2 (*ERAP2*) has found to be associated with AS and Crohn's Disease (CD). The functional implications of this association have not been explained to date. We tested levels of HLA-B27 and MHC-I Free Heavy Chain (FHC) in AS patients with the ERAP2 null allele. We further tested if ERAP2 suppression in an *in vitro* system results in changes in B27 misfolding and UPR.
Methods. A total of 40 B27-positive AS patients were typed for the rs2248374 polymorphism. Peripheral Blood Mononuclear Cells (PBMC) were isolated and stained with antibodies to CD19 (B cells) and CD14 (Monocytes). Staining with HC10 antibodies to assess MHC-I FHC expression and ME-1 antibody for intact HLA-B27 was performed. Mean Fluorescence Intensities (MFI) for FHC and B27 expression was assessed by flow cytometry.
C1R-B27, a human B lymphoblastoid cell line stably transfected with HLA-B27, were treated with 2 separate shRNAs to suppress endogenous ERAP2. Changes in UPR were assessed by PCR for BiP, CHOP and PERK. Protein expression of CHOP was assessed by western blot and semi-quantitative XBP-1 splicing assay was done by PCR.
Results. AS patients with no ERAP2 expression (homozygous for the minor allele of rs2248374) had higher FHC expression on the surface of PBMCs (p=0.019). When corrected for ME1 expression there was significantly lower ratio of intact-B27:FHC ratio in PBMC as well as specifically on monocytes.
PCR showed more than 20-fold increase in CHOP levels with ERAP2 suppression and between 1.2-1.5 fold increase in BiP and PERK. CHOP protein levels increased more than 3 fold while XBP1s increased 20-fold.
Conclusions. ERAP2 deficiency in AS patients are associated with higher MHC-I FHC expression on PBMCs. Suppression of ERAP2 in an *in vitro* system led to significant increase in UPR markers. Changes in ERAP2 expression could influence the pathogenesis of AS and CD.

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HISTOLOGIC AND IMMUNOLOGIC CHARACTERIZATION OF INFLAMED GUT AND SACRO-ILIAC JOINTS OF PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

Ciccia F., Rizzo A., Guggino G., Alessandro R., Triolo G.
University of Palermo, Italy

Introduction. An important link between gut inflammation and sacroiliac joints SIJs inflammation has been recently demonstrated. We aimed to evaluate the immunologic signature of gut and SIJs inflammation in patients with nrAxSpA.
Methods: SIJs biopsy samples were obtained from 5 patients with nrAxSpA and from 5 patients undergoing to BM biopsy for uncertain MGUS. Ileal expression of IL-23, IL-17, IL-22 IL-9, IL-and 36a was evaluated by RT-PCR and immunohistochemistry (IHC) in paired gut samples obtained from the same patients and from 5 normal controls. BM biopsies were evaluated by IHC for the expression of CD3, CD8, CD68, TNF-α, IL-17, IL-23p19, IL-36a, IL-22 and IL-9. Density visual count of CD34-stained microvessels and trabecular bone area as a fraction of total trabecular tissue area (marrow and bone) and the perimeter of marrow-bone interface were measured in the same microscopic field.
Results. Plasma cells were less than 10% on bone marrow examination in all patients and displayed a normal phenotype. Infiltration of inflammatory mononuclear cells was observed in all the bone marrow biopsies of nrAxSpA patients, with patients displaying a higher number of $CD4^+$ cells compared to controls. In 4 out of the 5 nrAxSpA patients the infiltrating inflammatory cells were aggregated in lymphoid follicles with germinal centres cuffing central marrow vessels. No lymphoid follicles were observed in controls. Microvessel density was also clearly increased in nrAxSpA compared with normal controls. Finally we observed structural changes of osseous trabeculae showing a reduction in trabecular bone volume (TBV) in nrAxSpA patients compared to controls. Immunologically, a fully developed IL-23/Th17 signature characterizes the bone marrow of nrAxSpA patients with the over-expression of IL-23p19, IL-17, IL-22, IL-36a and IL-9.
Conclusion. Profound morphological and immunological changes characterize the inflamed bone marrow of patients with early spondylitis. A different immunological signature seems to be present in the gut and in the bone marrow of nrAxSpA patients.

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WHAT HAVE WE LEARNED ABOUT NON-CLASSICAL FORMS OF HLA-B27 AND ITS ROLE IN THE PATHOGENESIS OF SPONDYLOARTHROPATHIES?

Rysnik O.J.[1], McHugh K.[1], Bowness P.[1], van Tok M.[2], van Duivenvoorde L.M.[2], Baeten D.[2]
[1]NDORMS, University of Oxford, Nuffield Orthopaedic Centre NHS Trust, Oxford, UK; [2]Academic Medical Center and University of Amsterdam, Amsterdam, The Netherlands

Introduction. The strong association of the human leukocyte antigen HLA-B27 (B27) with the Spondyloarthropathies (SpA), particularly with Ankylosing Spondylitis (AS), was discovered more than four decades ago, yet the role of B27 plays in disease remains unclear. Our research group discovered that B27 free heavy chains (B27 HC) can form dimers ($B27_2$) and/or non-classical B27 molecules (NC-B27), which can bind innate immune receptors in non-conventional way, compared with other MHC class I molecules. We therefore investigated the pathogenic role for these forms of B27 in AS.
Materials and Methods. We used a novel HD6 antibody, generated against $B27_2$, alongside the conventional HC10 and ME1 antibodies to examine surface expression of NC-B27 in AS patient and healthy control primary cells and B27 transgenic (tg) rat model using flow cytometry and confocal microscopy. We investigated the expression patterns of NC-B27 in spondyloarthropathy (SpA) and control synovial tissues, as well as HLA-B27 tg rat joints using immunohistochemistry.
Results. AS patient monocyte-derived dendritic cells (moDCs) expressed higher levels of free-heavy chains compared with healthy controls. Confocal microscopy data suggested that AS patient moDCs express low levels of $B27_2$, however HD6 expression can be further induced by brief low pH treatment. Our preliminary data from B27 tg rat model showed that expression of classical and NC-B27 depends on animal's age. Moreover, B27 HC are present in the immune system and circulation before the disease onset. B27 HC are abundantly expressed in the inflamed joints of both B27 tg rats and SpA patient synovial tissue.
Conclusions. We showed that B27 HC expression on AS moDCs is significantly increased compared with healthy controls. Our preliminary data for the first time has demonstrated elevated levels of B27 HC in the inflamed SpA synovial tissue and B27 tg rat joints as well as in circulation. A better understanding of HLA-B27 behavior at the cell surface will aid the development of therapeutic strategies for treatment of AS.

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HUMAN MAST CELLS ENGULF AND STORE EXOGENOUS IL-17A

Noordenbos T.[1,2], Paramarta J.E.[1], Blijdorp I.C.[1,2], van Mens L.J.[1], Stap J.[3], Hoebe R.[3], Mul E.[4], Yeremenko N.G.[1,2], Baeten D.L.[1,2]
[1]Amsterdam Rheumatology and Immunology Center; [2]Laboratory of Experimental Immunology; [3]Dept. of Cell Biology and Histology; [4]Sanquin Research and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Background. IL-17A plays an important role in pathophysiology of spondyloarthritis, as IL-17 blocking therapy was effective in the first phase II trial. Analysis of inflamed synovium revealed an abundant presence of IL-17A-positive mast cells. This population was specifically increased in patients with SpA compared to RA and was not modulated by TNF-blocking therapy, suggesting that IL-17A-positive mast cells are specific for the pathophysiology of SpA and that they act upstream of general inflammation.
Objectives. As mast cells are not known to produce IL-17A in mice, we aimed to investigate the mechanism of IL-17A expression by human mast cells.
Methods. mRNA and protein expression was assessed ex vivo and after PMA/ionomycine stimulation in primary human mast cells from tonsil and synovium. Internalization of exogenous IL-17A was assessed by Western blot, imagestream, live imaging and confocal microscopy. Release of IL-17A was assessed by ELISA.
Results. Immunostaining and western blot analysis confirmed the presence of IL-17A protein in primary human mast cells. However, in contrast to T cells, mast cells did not express RORC protein, the indispensable transcriptional factor controlling IL-17A expression. Accordingly, *IL17A*, *IL17F*, and *RORC* gene expression was readily detectable in sorted T lymphocytes but not in mast cells, even after stimulation. Given the discrepancy between the presence of IL-17A protein and absence of its transcriptional machinery, we investigated the uptake of recombinant IL-17A. Western blot and imaging studies indicated that both primary mast cells and the LAD2 mast cell line engulf and store exogenous IL-17A. This uptake can be blocked by inhibiting receptor-mediated endocytosis. Engulfed IL-17A can be released back to the milieu upon external stimuli.
Conclusions: Human mast cells do not produce IL-17A but engulf and store exogenous IL-17A and possess ability to release the IL-17A back to the milieu.

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CALPROTECTIN (S100A8/9) AS SERUM BIOMARKER FOR CLINICAL RESPONSE IN PROOF-OF-CONCEPT TRIALS IN AXIAL AND PERIPHERAL SPONDYLOARTHRITIS

Turina M.C.[1], Yeremenko N.[1], Paramarta J.E.[1], De Rycke L.[2], Baeten D.B.[1]
[1]Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam; [2]Reumatologie, Tergooi, Hilversum, The Netherlands

Introduction. Biomarkers complementing clinical evaluations may help to reduce the length and size of proof-of-concept (PoC) trials aimed to obtain quick "go/no go" decisions in the clinical development of new treatments. We aimed to identify and validate serum biomarkers with a high sensitivity to change upon effective treatment in spondyloarthritis (SpA) PoC trials.
Methods. The candidate biomarkers high sensitive-C-reactive protein (hs-CRP), interleukin-6 (IL-6), pentraxin-3 (PTX-3), alpha-2-macroglobulin (alpha-2-MG), matrix metalloproteinase-3 (MMP-3), calprotectin, and Vascular Endothelial Growth Factor (VEGF) were determined by ELISA in healthy controls (n=20) and SpA patients before and after 2 weeks of infliximab (n=18) or placebo (n=19) treatment in cohort 1. Clinical outcome was evaluated at week 12. Results were validated in ankylosing spondylitis (AS) with infliximab (cohort 2, n=21) and peripheral SpA with etanercept (cohort 3, n=20).
Results. Serum levels of calprotectin, hs-CRP, PTX-3, VEGF (all $p<0.001$) and MMP-3 ($p=0.062$), but not IL-6 and alpha-2-MG, were increased in SpA versus healthy controls. Treatment with infliximab, but not placebo, significantly decreased calprotectin ($p<0.001$) and hs-CRP ($p<0.001$) levels, with a similar trend for MMP-3 ($p=0.063$). The Standardized Response Mean (SRM), which reflects the ability to detect changes over time, was high for calprotectin (-1.26), good for hs-CRP (-0.96) and moderate for MMP-3 (-0.52), whereas the SRMs in the placebo group were below -0.30. Calprotectin and hs-CRP, but not MMP-3, were good biomarkers of treatment response in axial SpA as evaluated in 2 separate cohorts. All 3 markers reflected response to etanercept treatment in peripheral SpA with SRMs above 0.5. These results were confirmed in cohort 2 and 3.
Conclusions. Calprotectin and hs-CRP are good serum biomarkers with high sensitivity to change upon effective treatment at the group level in small-scale, short term PoC trials in SpA.

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INCREASED PRODUCTION OF INTERLEUKIN-17 OVER INTERLEUKIN-10 BY REGULATORY T CELLS IMPLICATES ICOS MOLECULE IN EXPERIMENTAL SPONDYLOARTHRITIS

Araujo L.M.[1,2], Fert I.[1,2], Jouhault Q.[1,2], Labroquère K.[3], Andrieu M.[3], Chiocchia G.[1,2], Breban M.[1,2,4]
[1]Faculty of Health Sciences Simone Veil, and INSERM U987, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux; [2]Université Paris Diderot, Sorbonne Paris Cité, Laboratoire d'Excellence, Paris; [3]Institut Cochin, INSERM U1016, CNRS UMR8104; [4]Service de Rhumatologie, Ambroise Paré Hospital, University of Versailles Saint-Quentin-en-Yvelines, Boulogne, France

Introduction/Aim. HLA-B27/human β2m transgenic rats (B27-rats) develop an inflammatory disorder resembling spondyloarthritis, with accumulation of pro-inflammatory Th17 cells. Since regulatory T cells (Treg) and Th17 cells have opposing effects on inflammatory disorders, we investigated whether biased expansion of Th17 cells could result from altered Treg frequency and/or function in the B27-rats.
Material and Methods. We characterized the phenotype and function of Treg in B27-rats, in comparison with controls nontransgenic and B7-rats, by examining their expression of cell surface markers, suppressive activity, cytokines production, and differentiation pattern.
Results. In B27-rats, the preferential accumulation of $CD4^+$ effector T cells (Teff) over Treg was not associated with a defect in Treg differentiation or suppressive activity. The expression of Treg markers was similar between B27- and control rats, to the exception of the inducible costimulator (ICOS) molecule that was overexpressed in the B27-rats. High level of ICOS is considered as a hallmark of Treg with heightened suppressive activity and IL-10 expression. Paradoxically, the production of IL-10 by Treg was reduced in the B27 rats, whereas that of IL-17 was enhanced. Moreover, addition of anti-ICOS mAb during Treg differentiation in the presence of B27 rat dendritic cells reversed this cytokine profile, restoring the balance between IL-10/IL-17 in B27 rat Treg.
Conclusion. We report here a dysregulated IL-10/IL-17 production by Treg from B27 rats that may contribute to disease development. Moreover, our data highlight a key role for ICOS signaling in the generation of IL-10/IL-17 imbalance production by Treg, in this experimental model of spondyloarthritis.

P122

LOW-DOSE OF IL-2 FAILS TO PREVENT SPONDYLOARTHRITIS DEVELOPMENT IN EXPERIMENTAL MODEL

Araujo L.M.[1,2], Jouhault Q.[1,2], Fert I.[1,2], Bouiller I.[1,2], Chiocchia G.[1,2], Lebouteiller C.[3], Breban M.[1,2,4]
[1]Faculty of Health Sciences Simone Veil, and INSERM U987, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux; [2]Université Paris Diderot, Sorbonne Paris Cité, Laboratoire d'Excellence, Paris; [3]Exploratory Unit, Sanofi-, Toulouse; [4]Service de Rhumatologie, Ambroise Paré Hospital, University of Versailles Saint-Quentin-en-Yvelines, Boulogne, France

Introduction/Aim. HLA-B27/human β2m transgenic rats (B27-rats), a model of SpA develop an inflammatory disorder resembling spondyloarthritis with dysregulated IL-10/IL-17 production by regulatory T cells (Treg). Treg play a major role in controlling the pathogenic inflammatory process. Interleukin 2 (IL-2), a cytokine which promotes T reg cell survival and function, may thus have therapeutic efficacy in SpA. Here, we tested this hypothesis using low-dose of IL-2 treatment in B27 rats.
Material and Methods. B27-rats aged of 4 weeks (before disease onset) and nontransgenic (NTG) litermates were treated i.p. with 2.000 U of recombinant human IL-2 (Sanofi) or saline every-other day, during 8 weeks. Assessment of treatment effect was performed, based on clinical (weight, diarrhœa, arthritis) and histological (proximal and distal colon, caecum, ileum and joint) scores and the proportion of Treg in the spleen and lymph nodes was assessed.
Results. IL-2 treatment had no effect on weight gain, either in B27- or NTG rats. Over the 8 weeks of investigation, clinical disease score worsened similarly in both IL-2 and saline-treated groups of B27-rats. The macroscopic and histologic evaluation of gut showed differences between B27- and control rats, however, no change related to IL-2 treatment was observed. In the B27-rats, the percentage of Treg was mildly increased after IL-2 treatment in the spleen, but neither in mesenteric nor peripheral lymph nodes.
Conclusion. Our data demonstrate that low dose of IL-2 administered before disease onset was moderately effective for boosting Treg but failed to prevent rat-SpA development in B27-rats.

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INNATE IMMUNE STIMULATION TRIGGERS ALTERED IL-1A/B GENE EXPRESSION AND EXPERIMENTAL SPONDYLOARTHRITIS IN HLA-B27/HUB2M TRANSGENIC RATS

Van Tok M.N.[1], van Duivenvoorde L.M.[1,2], Satumtira N.[2], Dorris M.[2], Taurog J.D.[2], Baeten D.L.[1]
[1]Academic Medical Center, Dept. of Clinical Immunology and Rheumatology, Amsterdam, The Netherlands; [2]UT Southwestern Medical Center, Rheumatic Diseases Division, Dept. of Internal Medicine, Dallas TX, USA

Background. Spondyloarthritis (SpA) does not display the typical features of autoimmune diseases such as presence of autoantibodies and clinical response to T- and/or B cell targeting biologicals. Moreover, despite the strong association with MHC class I, CD8 T cells are not required for induction of SpA-like disease in the HLA-B27/huβ2m transgenic rat model. Therefore, we propose that SpA may be primarily driven by the innate immune response. Using the HLA-B27/huβ2m transgenic rat model,[1] we investigated this hypothesis by studying the effect of innate immune stimulation.
Methods. Splenocytes from HLA-B27/huβ2m, HLA-B7/huβ2m -transgenic rats and wild-type controls were analyzed for cytokine expression after in vitro stimulation. *In vivo* HLA-B27/huβ2m and HLA-B7/huβ2m -transgenic rats were immunized with low doses of *Mycobacterium tuberculosis*.
Results. *In vitro* stimulation of splenocytes with zymosan and with *M. tuberculosis*, but not with LPS, strongly induced gene expression of pro-inflammatory cytokines such as TNF, IL-1alpha, IL-1beta and IL-6 in all 3 rat strains. IL-1alpha and IL-1beta, but not TNF or IL-6, were increased in the HLA-B27/huβ2m transgenic cells as compared to both HLA-B7/huβ2m transgenic and wild-type controls upon ex vivo stimulation. In vivo, non-immunized HLA-B27/huβ2m transgenic males spontaneously develop arthritis and spondylitis after 4-6 months of age with an incidence of 70% and 40%. Immunization of 6 weeks old male HLA-B27/huβ2m transgenic rats with 30 μg *M. tuberculosis* respectively was sufficient to induce development of arthritis and spondylitis within 2-3 weeks with an incidence of 80-100%.
Conclusions. The transgenic over-expression of HLA-B27/Huβ2m increases the sensitivity to innate immune stimulation as evidenced by increased IL-1alpha and IL-1beta expression ex vivo and development of arthritis and spondylitis in vivo. These data indicate that innate immune activation can trigger experimental SpA.

Reference

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INFLAMMATORY BOWEL DISEASE ASSOCIATED ARTHROPATHY: CHARACTERISTICS OF THE DISEASE AND VALIDITY OF DIAGNOSES BASED ON ICD-CODING IN SWEDEN

Drivelegka P.[1], Papachrysos N.[2], Petersson I.F.[3], Bremander A.[4,5], Jacobsson L.T.H.[1]
[1]Dept. of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg; [2]Dept. of Gastroenterology, Sahlgrenska University Hospital/Östra, Gothenburg; [3]Dept. of Orthopedics, Dept. of Clinical Sciences, Lund, Lund University, Lund; [4]Dept. of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund; [5]Research and Development Centre, Spenshult Hospital for Rheumatic Diseases, Halmstad, Sweden

Background. Epidemiological studies of IBD-associated arthritis (IBD-aA) are scarce, but both axial and peripheral musculoskeletal manifestations are considered to be more common in IBD-aA than in the general population.
Objectives. To determine: 1) the validity of ICD-10 codes for IBD-aA in administrative databases, 2) the frequency and characteristics of axial and peripheral arthritis by type of IBD.
Methods. The SpA Scania cohort consists of all the subjects aged 15 years or older in the Skåne region (1.2 million inhabitants in southern Sweden) having received a diagnosis of any type of Spondyloarthritis during 2003-2007 at primary or specialised care visits (N=5771) recorded in the Skåne Health Care Register (SHCR). This included patients with Ankylosing Spondylitis (26%), Undifferentiated Spondyloarthritis (22%), Psoriatic Arthritis (39%) and IBD-aA (ICD-codes: M07.4, M07.5, 2.3%). Medical records were reviewed following a structured protocol in the subgroup of IBD-aA patients (N=65) that also responded to a postal survey sent to the Spa Scania cohort in 2009.
Results. Of the 65 patients with IBD-aA diagnosis in the register, 80% (n=52) and 94% had both IBD and arthritis according to the medical records when requiring ≥1 or ≥2 visits with diagnoses of IBD-aA respectively. Of the 52 patients (80%) where IBD and rheumatic disease could be verified (17 men), the mean age at the time of onset of arthritis symptoms was 39.8 years (SD: 13.9). Of the 29 patients with ulcerative colitis (UC) 83% had peripheral and 45% had axial arthritis. For Crohn's disease (CD) (n=23) the corresponding figures were 91% and 48%. In 78% of the patients, bowel disease preceded the arthritis symptoms. Only in 8 patients (15,4%) the onset of arthritis preceded the IBD and 7 of them had axial arthropathy. Overlap between peripheral and axial arthritis was found in 18 patients (34,6%). In women peripheral arthritis was more common than axial (91% vs 40%), whereas in men a more equal distribution was observed (76% vs 65%).
Conclusions. The ICD10 codes for IBD-aA had a high validity supporting larger epidemiological studies. Peripheral arthritis was more common than axial disease in both UC and CD.

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ETANERCEPT INCREASES BONE MINERAL DENSITY IN ANKYLOSING SPONDYLITIS, BUT DOES NOT PREVENT VERTEBRAL FRACTURES

Van der Weijden M.A.C[1,2], Van Denderen J.C.[2], Lems W.F.[1,2], Nurmohamed M.T.[1,2], Dijkmans B.A.C[1,2], Van der Horst-Bruinsma I.E.[1,2]
[1]VU University Medical Center, Dept. of Rheumatology, Amsterdam; [2]Jan van Breemen Research Institute / Reade, Dept. of Rheumatology, Amsterdam, The Netherlands

Introduction. Ankylosing spondylitis (AS) is characterized by chronic inflammation often leading to ankylosis of the spine, but also by a decrease of bone mineral density (BMD) and high prevalence of vertebral fractures (VF). Treatment with TNF blocking agents decreases inflammation and has shown to be effective in increasing BMD. We studied the effects of etanercept on BMD and VF in AS patients after two years of treatment. Furthermore we studies changes in bonemarkers (CTXI, CTXII, RANKL, OPG, Osteocalcin) and radiological damage.
Methods. Patients with active AS, treated with etanercept for two years, were included. BMD lumbar spine and hips was measured at baseline and after two years, as well as the radiological damage (mSASSS, including thoracic spine), VF (Genant method) and change in bone-markers.
Results. Forty-nine AS patients were included (Table). After two years of etanercept, hip BMD raised with 2.2% (p=0.014) and lumbar spine BMD with 7.0% (p<0.001). The BASDAI decreased significantly (p<0.001) as well as CRP and ESR (p<0.001). Despite etanercept therapy, the number of patients with vertebral fractures more than doubled (from 6 to 15 patients, p=0.004) as well as the severity. Also the radiological damage mSASSS+ThSpine increased significantly over time (from 12.1 to 18.5, p<0.001). No significant change in bone-markers was found.

Clinical characteristics n=49	Baseline	after 2 years etanercept
Men[a]	40 (81.6)	
Age[b], years	41.8 (9.2)	
Disease duration[b], years	12.2 (9.1)	
ESR[c], (mm/hr) [<20]	20.0 (6.0-39.0)	6.5 (3.0-16.0)*
CRP[c], (mg/l) [<10]	14.0 (3.0-39.0)	2.5 (1.0-9.8)*
BASDAI[b], (0-10)	5.7 (1.6)	2.9 (2.1)*
BASFI[b], (0-10)	5.7 (2.1)	3.5 (2.9)*
BASMI[b], (0-10)	4.4 (2.3)	4.0 (2.4)
Total mSASSS[c], (0-72)	10.0 (3.8-35.5)	15.5 (5.5-42.5)*
Total mSASSS+ThSpine[c], (0-90)	12.1 (6.8-42.7)	18.5 (8.7-52.0)*
sBMD hip[b]	0.903 (0.152)	0.921 (0.146)*
sBMD L2-L4[b]	1.141 (0.203)	0.213 (0.200)*
number vertebral fractures[a]	8 (16.3)	21 (42.9)*
patients with vertebral fractures[a]	6 (12.2)	15 (30.6)*

[a]number (%), [b]mean (SD), [c]median (IQR), *significant change p<0.05.

Conclusions. This prospective longitudinal observational cohort study in AS patients showed that after two years etanercept treatment, BMD of the hip and spine increased significantly. However, the number and severity of vertebral fractures increased, as well as the radiological progression, including the thoracic spine. Thus, the favourable effect of etanercept on BMD in AS is accompanied by unfavourable outcomes on vertebral fractures and radiological damage.
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INDUCED PLURIPOTENT STEM CELLS AS A TOOL FOR EVALUATING DISEASE-MEDIATING CELL TYPES IN SPONDYLOARTHRITIS

Layh-Schmitt G., Lu S., Navid F., Gadina M., Colbert R.
NIAMS, NIH, Bethesda, USA

Introduction/Aim. Many different cell types are involved in the axial inflammation, trabecular bone loss, and aberrant bone formation that result in ankylosing spondylitis. However, key cell types such as osteoblasts and hematopoietic progenitors are not readily accessible for study. Our aim was to reprogram fibroblasts from patients with axial spondyloarthritis (AxSpA) into pluripotent stem cells (induced pluripotent stem cells or iPSC), and then determine the capacity of these cells to differentiate into various lineages.
Methods. Dermal fibroblasts from 7 AxSpA patients and 3 healthy controls (HC) were reprogrammed using Sendai virus encoding Oct4, Sox2, Klf4 and Myc. One AxSpA and one HC fibroblast line were reprogrammed in two different labs to assess technical reproducibility. Virus-free iPSCs were differentiated into mesenchymal stem cells (MSCs) using a TGF-β inhibitor. MSCs were differentiated into osteoblasts, chondrocytes, and adipocytes using a differentiation kit (Millipore), and defined cytokine cocktails were used to differentiate iPSC into monocytes.
Results. iPSC derived MSCs expressed CD105, CD73, CD90 and CD44, but lacked CD45, CD34, CD11b, CD19, and HLA-DR as determined by antibody staining. MSCs differentiated into mineralizing osteoblasts (Alizarin-Red staining), chondrocytes (Alcian-Blue), and adipocytes (Oil Red O), and induced differentiation of peripheral blood monocytes into osteoclasts (TRAP staining) when co-cultured. iPSC derived monocytes/macrophages expressed HLA-DR, CD14, CD86, CD80, CX3CR1 and CD45 (flow cytometry), and were capable of phagocytosing. Preliminary comparison of mineralization potential revealed that osteoblasts from both AxSpA patients tested, exhibited 3-fold higher mineralization than HC (Alizarin Red staining). Independently derived iPSC lines behaved similarly.
Discussion/Conclusions. We successfully derived iPSC from AxSpA patient fibroblasts that could be differentiated into MSCs capable of differentiating into mature osteoblasts, chondrocytes and adipocytes, and inducing osteoclast formation. We also generated hematopoietic cells that could differentiate into monocytes and functional macrophages. Although preliminary, it is of interest that MSCs from AxSpA patients consistently demonstrated greater mineralization capacity. iPS cells provide a powerful tool to examine disease-relevant cell types involved in SpA pathogenesis.

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HLA-B27 PREVALENCE IN A COHORT OF BRAZILIAN PATIENTS WITH PSORIATIC ARTHRITIS AND ANKYLOSING SPONDYLITIS

Goldenstein-Schainberg C., Carrasco S., Saad C.G., MoraesJ.C.B, Gonçalves C.R., Sampaio-BarrosP., Parra E.R.
Disciplina de Reumatologia, Faculdade de Medicina da Universidade de São Paulo, Brazil

Introduction. Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) share common characteristics including an association with HLA-B27 antigen, which is positive in 20-60% and >90% patients respectively. Geographical HLA-B27 prevalence in general population varies from >50% in Canadian Indians and virtually 0% in Africans. HLAB27 may be detected by different methods with similar sensibility and specificity including serological (luminex system, solid phase assay), ADCC, molecular biology (PCR) and flow cytometry.
Aim. To establish the prevalence of HLA-B27 in Brazilian patients with PsA and AS from a single center using a low cost flow cytometry test.
Patients and Methods. Patients followed at our SpA clinic at Hospital das Clinicas, University of São Paulo were evaluated. HLA-B27 was analyzed in peripheral blood lymphocytes by flow cytometry using FacsCalibur (BD). Fifty µl of heparinized blood from patients and controls were incubated with 30µl HLA-B27/CD3 antibody (BD) for 30minutes in the dark followed by red cell lysis with 2ml of lysis solution (BD). All samples were washed twice with PBS and fixed with 250µl of 1% paraformaldehyde. Statistical analysis was performed using Fisher's test and $p<0.005$ considered significant.
Results. A total of 182 patients (94 PsA, 88 AS) and 72 controls were studied. Axial involvement occurred in 97% AS and 50% PsA patients, whereas 63% AS and 89% PSA had peripheral disease. HLA-B27 was positive in 83% (73/88) AS, 33% (31/94) PsA and 2.7% (2/72) controls. In AS, HLA-B27+ was associated with axial but not peripheral involvement (96% vs 61%, $p=0.047$). Conversely, HLA-B27 was positive in 90% peripheral PsA vs. 55% axial PsA ($p=0.003$).
Conclusion. The prevalence of HLA-B27 in Brazilian patients with PsA and AS by flow cytometry was similar to worldwide occurrence proving to be a reliable inexpensive method. HLA-B27 association with axial manifestation was confirmed in AS but not in PsA suggesting that HLA-B27 testing is of little value in predicting axial PsA.

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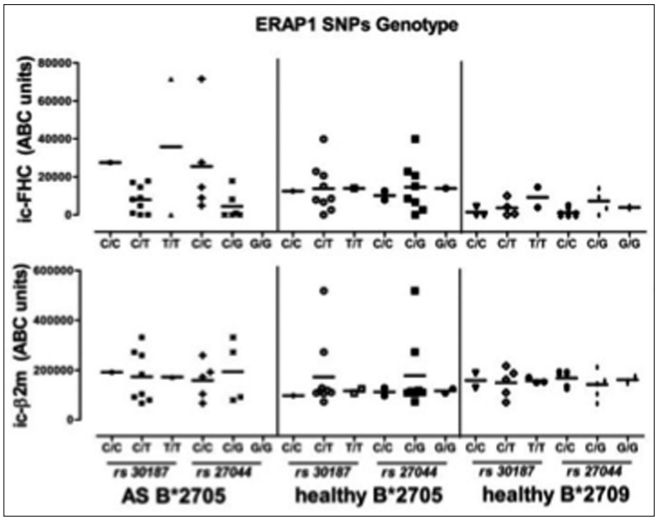
THE AMOUNT OF FREE HEAVY CHAIN AND β2M IN THE CYTOPLASM OF B*2705 ANKYLOSING SPONDYLITIS PATIENTS (AS) COMPARED TO B*2705 AND B*2709 HEALTHY SUBJECTS DOES NOT SUPPORT THE UPR THEORY – INFLUENCE OF ERAP1 POLYMORPHISMS

Cauli A.[1], Dessole G.[1], Porru G.[1], Cassotta A.[2], Piga M.[1], Vacca A.[1], Ibba V.[1], Fiorillo M.T.[2], Sorrentino R.[2], Mathieu A.[1]
[1]Rheumatology Unit, University of Cagliari; [2]Dept. Biology, University of Rome, Italy

Introduction. Several theories have been proposed to explain the B27 association with AS. The unfolded protein response (UPR) theory suggests that the tendency of B27 trimeric complex to misfold determines free heavy chain (FHC) accumulation in the endoplasmic reticulum, leading to a stress response and activation of pro-inflammatory pathways.
Aim. To investigate intracellular (ic) level of FHC and β2m in PBMC and the possible influence of ERAP1 allelic variance in HLA-B27 positive AS and healthy subjects (HSs) bearing the AS-associated (B*2705) and the non-AS-associated (B*2709) alleles.
Patients and Methods. The ic amount of FHC and β2m in CD14+ cells was evaluated in 12 HLA-B*2705 patients with AS, 12 HLA-B*2705 HSs and 12 HLA-B*2709 HSs by flow cytometry analysis. HC10 and TU99 clone monoclonal antibodies were used to detect FHC and β2m, respectively, and quantified by comparison with standard beads (ABC units). Cells were fixed and permeabilized by the Intraprep Permeabilization technique. Patients and controls were also genotyped for two ERAP1 SNPs associated with AS (rs27044C/G and rs30187C/T).
Results. FHC expression in AS patients was 37486±30346 compared to B*2705 HSs 35673±16723 and B*2709 HSs 26683±10592 (p=ns). β2m quantity was also not significantly different in AS patients 174930±90441 compared to B*2705 HSs 156471±123855 and B*2709 HSs 153478±42117 (p=ns). The majority of AS patients and HSs were heterozygous for both rs27044C/G and rs30187C/T SNPs; icFHC and icβ2m appeared not influenced by ERAP1 allelic distribution, as shown in the figure below:



Conclusion. This study shows equal amount of FHC and β2m in the cytoplasm of B*2705 AS patients compared to B*2705 and B*2709 healthy controls, regardless of ERAP1 allelic variance. These data do not provide support to the UPR theory in the pathogenesis of AS.

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ANTXR2 MIGHT BE A SUSCEPTIBILITY GENE OF ANKYLOSING SPONDYLITIS IN CHINESE HAN

Li Q., Lv Q., Wu X., Zhang P., Li X., Zheng X., Gu J.
Rheumatology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Introduction/Aim. ANTXR2 gene encodes a receptor for anthrax toxin,the receptor can bind to collagen IV and laminin which suggest that it may be involved in extracellular matrix adhesion. ANTXR2 gene was found to have a relationship with AS in GWS study and linkage analysis in the past years. However, the differences SNPs of ANTXR2 between AS patients and healthy controls has not been validated. Our study looked for disease susceptibility genes in southern Chinese Han patients with ankylosing spondylitis (AS).
Methods. We recruited 58 patients with AS (meet modified New York criteria (1984) and 90 age- and sex-matched controls of southern Chinese Han. The salting out method is used to extract DNA. Exon sequencing was done by the chip (Illumina, Inc)). SNPs of the sequencing results were selected (maf> 0.005, SNPs with <0.1 missing, Hardy-Weinberg test >0.001, sample false positive rate <0.1. These SNPs were validated on 292 cases of AS (meet modified New York criteria (1984) and 205 matched healthy controls through mass spectrometry method.
Results. In exon sequencing results, there have 5 SNP loci (rs78740643, rs11098964, rs28688624, rs4389526, rs7689197) of ANTXR2 gene meet maf> 0.005, miss <0.1, hwe> 0.001 and sample false positive rate <0.1. Verified by mass spectrometry, Chi-square analysis showed differences only rs11098964 ($p<0.05$) between AS in southern Chinese Han and matched healthy controls.
Conclusion. Our study found the ANTXR2 might be a susceptibility gene of Ankylosing Spondylitis.

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SPA-ASSOCIATED POLYMORPHISMS OF ERAP1 ARE CORRELATED WITH GENE EXPRESSION AND ENZYMATIC ACTIVITY OF THE AMINO-PEPTIDASE

Costantino F.[1,2], Talpin A.[1], Evnouchidou I.[3], Kadi A.[1], Said-Nahal R.[2], Leboime A.[2], Bonilla N.[4], Letourneur F.[4], Leturcq T.[1], Ka Z.[1], van Endert P.[3], Garchon H.J.[1,2], Chiocchia G.[1], Breban M.[1,2]
[1]INSERM U987, UFR Simone Veil, Versailles-Saint Quentin University; [2]Ambroise Paré Hospital (AP-HP), Boulogne-Billancourt; [3]INSERM, U1013, Université Paris Descartes, Sorbonne Paris Cité, Paris; [4]Institut Cochin, INSERM U1016, Paris, France

Introduction/Aim. Several polymorphisms in ERAP1 have been associated with SpA. A specific ERAP1 haplotype, rs17482078/rs10050860/rs30187-CCT, is strongly associated with increased risk of SpA, whereas the -TTC haplotype is associated with reduced risk. The aim of the present work was to determine whether SpA-associated ERAP1 polymorphisms might modify gene expression, protein level and enzymatic activity.
Methods. The discovery cohort included 9 HLA-B27+ SpA patients and 10 healthy controls. The replication cohort consisted of 14 HLA-B27+ SpA patients and 34 controls (13 HLA-B27+ siblings of patients and 21 additional independent controls (10 HLA-B27+ and 11 HLA-B27-). In both cohorts, we derived dendritic cells from monocytes (MD-DCs) and stimulated them or not with lipopolysaccharide. In all the studied populations, we investigated the relation between ERAP1 haplotype and mRNA expression level with multifactorial ANOVA. Additionally, enzymatic activity was determined using a fluorogenic assay in a subset of 8 subjects harbouring various haplotypes.
Results. In MD-DCs, there was a strong association between ERAP1 mRNA expression level and ERAP1 haplotypes with higher levels in subjects harbouring the susceptibility haplotype in both cohorts (p=0.001 and $5.6x10^{-7}$ respectively). A significant correlation was found between levels of susceptibility conferred by haplotypes and enzymatic activity ($r^2 = 0.96$; p=0.001).
Conclusions. Overall, these data provide strong evidence that SpA-associated ERAP1 polymorphisms affect the level of gene expression and aminopeptidase activity. How an increased production/activity of ERAP1 influences susceptibility to SpA remains to be determined.

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ANKYLOSING SPONDYLITIS-ASSOCIATED SNPS AT THE *IL23R-IL12RB2* INTERGENIC REGION ARE FUNCTIONALLY IMPORTANT

Roberts A.R., Cohen C.J., Vecellio M., Bowness P., Wordsworth B.P.
University of Oxford, Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Oxford, UK

Introduction/Aim. Genome-wide association studies have revealed at least 41 susceptibility loci for ankylosing spondylitis (AS). The next challenge is to identify the corresponding functional genetic variants, the molecular mechanisms by which they act, and the cellular pathways they modulate. Here, we have investigated functional variants in three putative regulatory regions at the *IL23R-IL12RB2* intergenic region.
Materials and Methods. We integrated the genetic data from the recent Immunochip study with publically available epigenetic datasets from the ENCODE project to identify candidate functional SNPs in regulatory regions. These regions each contain at least one SNP that is associated with AS independently of the functional coding SNP rs11209026. We have validated the function of AS-associated SNPs using luciferase reporter assays in HEK293T cells and Jurkat cells, and electrophoretic mobility shift assays using Jurkat cell nuclear extract.
Results. In HEK293T cells and Jurkat cells we observed enhancer activity and possible silencer activity in the regulatory regions overlapping AS-associated SNPs. The AS-associated SNPs rs6677188 and rs11209032 reduced this activity. The AS-associated SNP, rs6677188, differentially affects the binding of transcription factor/s to the corresponding regulatory region. There was 82% increased binding of transcription factor/s to a 387 bp fragment corresponding to the 'A' risk allele. The addition of IRF4 antibody interfered with the formation of this DNA-protein complex, suggesting involvement of IRF4. The binding of BATF and JunD was unaffected. A 20% increase in binding of IRF4 to a 31 bp fragment from the 'A' risk allele was observed (p<0.001), confirming the involvement of IRF4.
Discussion/Conclusion. We confirmed regulatory activity in the *IL23R-IL12RB2* intergenic region. We show functional effects of the AS risk allele for rs6677188 in a gel-shift protein binding assay. Future studies will focus on whether these effects are primarily on the *IL23R* gene or the neighbouring *IL12RB2* gene. This type of genetic-bioinformatic-epigenetic methodology has broad implications for the study of other loci associated with AS.

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FROM SNPs TO FUNCTION: TRANSCRIPTIONAL REGULATION OF RUNX3 IN ANKYLOSING SPONDYLITIS

Vecellio M.L., Roberts A.R., Cohen C., Bowness P., Wordsworth B.P.
University of Oxford, Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Oxford, UK

Introduction/Aim. Among the many genes associated with ankylosing spondylitis (AS), several (*RUNX3, EOMES, TBX21, ZMIZ1, IL7 and IL7R)* affect lymphocyte development and activation. To move from these genetic associations to a fuller understanding of the functional effects of genetic variation at associated loci is one of the greatest challenges in complex polygenic diseases. Here we focus on how two SNPs at the *RUNX3* locus affect the regulation of this gene. We highlight how a combination of SNP associations, data from the ENCODE project, and *in vitro* functional studies can be valuable in characterizing the effects of particular genetic variants, providing critical functional evidence for their role in AS.
Materials and Methods. We analysed SNPs function using several molecular biology approaches. These included (1) luciferase reporter assay on Hek293 and Jurkat cells transfected with plasmid constructs containing WT or AS allele, to test if the different sequences regulate gene expression; (2) electrophoretic mobility shift assays (EMSA) looking for differences in binding of specific transcription factors (TFs) involved in T-cell regulation (IRF4, BATF, JunD); (3) allele-specific Chromatin ImmunoPrecipitation (ChIP) to evaluate the enrichment for TFs and histone modifications (H3K4me1, H3K4me3 etc.) in the AS-associated allele compared with the WT allele.
Results. There were significant differences in transcriptional activity between the AS-associated and wild type SNPs in the luciferase assay (2.8 and 5 fold respectively). TF binding for SNPs at the *RUNX3* locus, evaluated by EMSA (45 bp DNA fragments), in *naïve* as well as in stimulated cells, clearly demonstrated differential allele-dependent binding for specific TFs, with IRF4 (AS/WT ratio: -37%) and JunD (AS/WT ratio: -41%) both involved. In contrast, BATF seems to be not implicated.
Discussion/Conclusion. We have identified functional differences in the transcriptional regulation of RUNX3 associated with SNPs at this locus already known to be associated with AS. The pathological implications of these results require additional study but could provide further insights into potential therapeutic targets.

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MULTIWAY TRANSCRIPTOMIC ANALYSIS OF MONOCYTE-DERIVED DENDRITIC CELLS (MD-DCs) DISCRIMINATES EFFECTS OF DISEASE AND OF HLA-B27 IN SPONDYLOARTHRITIS (SpA)

Chaplais E.[1], Talpin A.[1], Costantino F.[1], Desjardin C.[1], Bonilla N.[2], Leboime A.[3], Said-Nahal R.[3], Letourneur F.[2], Jacques S.[2], Chiocchia G.[1,4], Breban M.[1,3,4], Garchon H.J.[1,4]
[1]INSERM U987, Montigny-le-Bretonneux; [2]INSERM U1016, Paris; [3]Ambroise Paré Hospital, Rheumatology Division, Hospital, Boulogne-Billancourt; [4]University of Versailles Saint-Quentin, France

Introduction. The strong association of HLA-B27 in SpA only partly explains the disease risk. Whereas antigen-presenting cells, most notably dendritic cells, are believed to play a key role in SpA pathogenesis, the precise mechanisms underlying disease development and particularly the role of HLA-B27 remain poorly understood. To identify other involved genes and pathways, we carried out a transcriptome analysis of MD-DCs from patients and healthy controls, also considering the HLA-B27 status.
Methods. Whole-genome transcriptomic profiles (Affymetrix HumanGene 1.0 ST platform) of MD-DCs stimulated or not with endotoxin were obtained from 23 independent HLA-B27+ SpA patients, and from 44 controls (23 HLA-B27+ and 21 HLA-B27-). Analysis of differentially expressed (DE) genes was conducted with LIMMA, accounting for both the disease and the HLA-B27 status (p-value <5%), followed by quantitative gene set enrichment analyses (quSAGE) and functional pathway annotation.
Results. We performed three comparisons to identify DE genes related to HLA-B27 or SpA status, thus generating three lists: A, including 800 DE genes between HLA-B27+ patients and HLA-B27- controls; B, including 673 DE genes between HLA-B27+ controls and HLA-B27- controls; and C, including 466 DE genes between HLA-B27+ patients and HLA-B27+ controls. Subtracting A–B left 656 genes, of which 68 are in list C, thus yielding a robust list of genes affected by SpA without irrelevant genes affected by HLA-B27 only. quSAGE and functional annotation revealed that DE genes associated with SpA were mainly involved in metabolic, immune system and cellular processes.

Conclusion. Our study allowed us to identify a list of MD-DC genes and functions differing between SpA and controls, controlling for HLA-B27. Furthermore, HLA-B27 appeared to alter expression of an unexpectedly large number of genes in a manner independent of SpA.

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ANTXR2 IS ASSOCIATED WITH ANKYLOSING SPONDYLITIS

Karaderi T.[1], Keidel S.[1], Appleton L.H.[1], Evans D.M.[2,3], Wordsworth B.P.[1]
[1]National Institute for Health Research Oxford BRC and Musculoskeletal BRU, Oxford; [2]MRC Integrative Epidemiology Unit, University of Bristol, UK; [3]University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Queensland, Australia

Introduction. *ANTXR2* variants have been associated with ankylosing spondylitis (AS) in two previous genome-wide association studies (GWAS) ($p\sim9x10^{-8}$). However, a genome-wide significant association ($p<5x10^{-8}$) was not observed and the coverage of the locus was incomplete. We conducted a more comprehensive analysis of *ANTXR2* in an independent UK sample to confirm and refine this association.
Materials and Methods. A replication study was carried out with 2978 cases and 8365 controls. These were also combined with non-overlapping samples from the two previous GWAS in a meta-analysis. *HLA-B*27* stratification was also performed to test for evidence of genetic interaction.
Results. Five out of nine single nucleotide polymorphisms (SNPs) were associated ($p<0.05$) with AS in the replication study. In the meta-analysis, eight SNPs showed strong evidence of association; the most associated SNP was rs12504282 (OR=0.9, $p=6.7x10^{-9}$). Seven of the SNPs showed evidence for association in the *HLA-B*27*-positive subgroup, but no statistically significant interaction was detected between *HLA-B*27* and *ANTXR2* variants.
Discussion. *ANTXR2* variants are clearly associated with AS. The most associated SNPs from TASC (rs4333130), WTCCC2 (rs4389526) and this study (rs12504282) are in strong linkage disequilibrium ($r^2\sim0.8$). The associated SNPs lie near a putative regulatory region at this locus but may regulate genes quite physically distant from *ANTXR2*. ANTXR2 has a role as a receptor for the anthrax toxin but is also known as a capillary morphogen. As yet there is no biologically plausible role for ANTXR2 itself in AS.
Conclusions. We have confirmed the association of genetic variants at *ANTXR2* with AS but further studies are required to clarify their functional role.

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INVESTIGATION OF MODE OF INHERITANCE IN THE CHINESE HAN FAMILIES WITH ANKYLOSING SPONDYLITIS

Jiang Y., Lv Q., Li Q., Zhai J., Lin Z., Liao Z., Zhang Y., Yang M., Xu Y., Gu J.
Dept. of Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Introduction/Aim. Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that mainly affects the spine and sacroiliac joints. This disease shows familiar aggregation, but genetic mode remains unclear. Segregation analysis is among the most common methods of medical genetics, including the estimation of segregation ratio and comparison between expected segregation ratio and observed segregation ratio, to determine the relevant mode of inheritance. This study was to determine the mode of inheritance in Chinese Han families with Ankylosing Spondylitis through 12 Chinese Han families.
Patients and Methods. AS families with 5 or more than 5 patients diagnosed by 1984 modified New York criteria together with at least 3 generations with blood relatives alive were recruited from department of rheumatology in the third affiliated hospital of Sun Yat-sen University. Physical examinations and relevant laboratory tests of family members were acquired by our research group, and then formed pedigree charts of each family. S.A.G.E. software was used for complex segregation analysis to determine the mode of inheritance of AS.
Results. 12 Chinese Han AS families with a total number of 497, involving 65 male patients and 45 female patients were recruited in this study. Complex segregation analysis with multivariate logistic regression was performed to evaluate the mode of inheritance of Ankylosing Spondylitis. Mendelian dominant model fitted best compared with general model in 5 AS families respectively ($p>0.05$). However, after applying complex segregation analysis to 9 families, Tau AB free model fitted best, with p value of 0.24.
Conclusion. Our study shows that Mendelian dominant mode does exist in some AS pedigrees, and a non-Mendelian mode called tau AB free model may explain inheritance mode in certain families, thus providing theoretical basis to studies on genetic susceptible genes.

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ASSOCIATION OF EDIL3 GENE POLYMORPHISMS WITH ANKYLOSING SPONDYLITIS IN CHINESE HAN

Wu X., Lv Q., Zhang P., Zhang Y., Yang M., Lin Z., Liao Z., Zheng X., Gu J.
Dept. of Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Introduction. EDIL3 encoded the protein as an integrin ligand. It involves in mediating angiogenesis and influendes endothelial cell behavior. Our GWAS study in Han Chinese had found the gene has relationship with ankylosing spondylitis. In this study, we analysed SNPs in EDIL3 by sequencing to find more susceptibility loci for ankylosing spondylitis.
Method. According to the 1984 modified New York criteria for ankylosing spondylitis, we selected 350 cases and 295 age- and sex-matched controls of Chinese descent. At the first stage,58 cases and 90 controls were used exome sequencing to find and analyze the single nucleotide polymorphisms (SNPs) in EDIL3 according to the protocol of TruSeq (Illumina). After case/control association analysis, significant SNPs ($p<=0.05$) and new SNPs were validated on 292 cases and 205 matched controls through Mass Spectrometry method.
Results. There are 118 SNPs sequenced of EDIL3 gene in the exome sequencing results. 4 of them were new mutations: 5:83362489, 5:83239429, 5:83259039,5:83238287 (hg19). We didn't find non-synonymous mutition.
Then we verified 3 significant SNPs, rs12522953, rs10473882, rs72776512 and 5:83238287 by mass spectrometry. Case-control association analysis showed rs12522953 having relationship with AS ($p=0.01938$,OR=1.407 95%CI=1.056-1.875). Genotypic test revealed an increase in the risk AS under the AA VS GG model (OR=2.795, 95%CI=1.328-5.884, POR=0.00525). it was similar in the AA VS AG+GG model (OR=2.684, 95%CI=1.297-5.554, POR=0.005984). The selected single nucleotide polymorphisms showed association with AS.
Conclusion. our study verified the EDIL3 may be a candidate gene of ankylosing spondylitis and rs12522953 was a susceptibility loci for ankylosing spondylitis.

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BACH2 MIGHT BE A SUSCEPTIBILITY GENE OF ANKYLOSING SPONDYLITIS IN CHINESE HAN

Lv Q., Li Q., Wu X., Zhang P., Zheng X., Li X., Gu J.
Dept. of Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Introduction. BACH2 was known as a B cell-specific transcriptional repressor which plays a significant role in B cell maturation. A number of previous studies proved the clinicopathological significance of BACH2 expression in diffuse large B cell lymphoma. And there was also robust evidence for an association of RA susceptibility with genes involved in B cell differentiation (BACH2). In this study, we investigated whether BACH2 was susceptibility genes in southern Chinese Han patients with ankylosing spondylitis (AS).
Methods. A total of 58 patients who fulfilled the Modified New York Criteria for Ankylosing Spondylitis (1984) and 90 southern Chinese Han healthy volunteers with age and sex matched were included. Genomic DNA of each sample was separated by salting out method. Exon sequencing was performed to analyze the single nucleotide polymorphisms (SNPs) in BACH2 according to the protocol of TruSeq (Illumina). SNPs fulfilled significant SNPs ($p<=0.05$) were validated on 292 cases of AS and 205 matched healthy controls through mass spectrometry method.
Results. In exon sequencing results, there have 138 SNPs, 5SNP loci, rs72928026, rs9111, rs1065273, rs1065272, and rs3857493 of BACH2 gene meet maf> 0.005, miss <0.1, hwe> 0.001 and sample false positive rate <0.1. Verified by mass spectrometry, Chi-square analysis showed differences of rs72928026 and rs9111 between AS in southern Chinese Han and matched healthy controls.
Conclusion. Our study found the SNP loci rs72928026 and rs9111 of BACH2 might be a susceptibility gene loci of Ankylosing Spondylitis.

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SNPS ANALYSIS OF THE HAPLN1 GENES ON ANKYLOSING SPONDYLITIS PATIENTS AND HEALTHY SUBJECTS

Li Q., Wu X., Lv Q., Huang Z., Li H., Zhang Y., Lin Z., Liao Z., Yang M., Zhang P., Zheng X., Gu J.
Dept. of Rheumatology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Introduction/Aim. HAPLN1 (also known as link protein and CRTL1) is a member of the hyaladherin family of hyaluronic acid (HA) binding proteins. In cartilage, HALPN1 forms a ternary complex with HA and aggrecan. Our GWAS study in Han Chinese had found the gene has relationship with ankylosing spondylitis. In this study, 1) we analysed SNPs of HAPLN1 by sequencing to find more susceptibility loci for ankylosing spondylitis; 2) Analysed SNPs of HAPLN1 in different races.
Methods. A total of 350 patients who fulfilled the Modified New York Criteria for Ankylosing Spondylitis (1984) and 295 southern Chinese Han healthy volunteers with age and sex matched were included in the exon sequencing analysis. Genomic DNA of each sample was separated by salting out method. 58 cases and 90 controls were used exome sequencing to find and analyze the single nucleotide polymorphisms (SNPs) in HAPLN1 according to the protocol of TruSeq (Illumina). SNPs of the sequencing results were selected according to one of the conditions 1) significant SNPs (p<=0.05) in association analysis 2) non-synonymous or utr-3 mutition 3) new mutation (db137). 4) rare various .maf<1%.These SNPs was validated on 292 cases of AS and 460 matched healthy controls through mass spectrometry method. The controls was divided to several groups, which include 205 Chinese Han, 90 Chinese Hui, 76 Chinese Xinjiang, 27 German and 57 Japanese.
Results. In exon sequencing results, we found 84 SNPs loci in HAPLN1 gene, rs180793962, rs187955793 was non-synonymous mutition or utr3 various, 5:82934652 was a new SNP, the three SNPs and rs72771293, rs72772933 were rare variouses. The 5 SNPs were verified by mass spectrometry, cases/controls association analysis showed no differences between AS in southern Chinese Han and matched healthy controls (5:82934652, p=0.3906; rs187955793, p=0.375; rs180793962, p=1, rs72771293, p=0.06346 and rs72772933, p=0.4013), but their MAF still were less than 1%. Besides, we analyzed distribution of SNPs in controls of different races (Table I).

Table I. Compare rs72772933 and rs72771293 in different races.

Race.	Chr.	Gene	SNP	Ref.	Allele Frequence	OR (95%CI)	p
Japanese/Han	1	HAPLN1	rs72771293	G	0.222/0.0923	2.81 (1.591-4.961)	0.000242
german/Han	1	HAPLN1	rs72772933	A	0.03846/0.3439	00.7631 (0.0183-0.3182)	7.18e-06
german/Han	1	HAPLN1	rs72771293	G	0.25/0.09231	3.278 (1.603-6.702)	0.000668
uighur/Han	1	HAPLN1	rs72772933	A	0.1429/0.3439	0.318 (0.1308-0.7727)	0.008075
kazak/Han	1	HAPLN1	rs72772933	A	0.2353/0.3439	0.587 (0.3557-0.9686)	0.0357

Conclusion. Our study found the SNP loci in HAPLN1 gene might not be a susceptibility gene of Ankylosing Spondylitis, but variations are present in the SNP loci rs72772933, rs72771293 of HAPLN1 in different races.

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SNPs OF FCGR2A GENES IN ANKYLOSING SPONDYLITIS PATIENTS AND HEALTHY SUBJECTS

Zhang P., Li Q., Lv Q., Wu X., Gu J.
Dept. of Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Introduction. FCGR2A encodes one member of a family of immunoglobulin Fc receptor genes found on the surface of many immune response cells. The protein encoded by this gene is involved in the process of phagocytosis and clearing of immune complexes. Previous studies proved that FCGR2A polymorphism is associated with susceptibility to SLE, and with the response to infliximab treatment in rheumatoid arthritis. But there are scarce studies about FCGR2A in Ankylosing Spondylitis (AS). The aim of this study was to investigate SNPs in FCGR2A among AS and healthy subjects of different races.
Methods. A total of 350 patients who fulfilled the Modified New York Criteria for Ankylosing Spondylitis (1984) and 295 southern Chinese Han healthy volunteers with age and sex matched were included. Genomic DNA of each sample was separated by salting out method. 58 cases and 90 controls were used exome sequencing to find and analyze the single nucleotide polymorphisms (SNPs) in FCGR2A according to the protocol of TruSeq (Illumina). SNPs of the sequencing results were selected according 1) significant SNPs (p<=0.05) incase/control association analysis 2) non-synonymous or utr-3 mutition 3) new mutation. These SNPs was validated on 292 cases of AS and 460 matched healthy controls through mass spectrometry method. The controls were divided to several groups, which include 205 Chinese Han, 90 Chinese Hui, 76 Chinese Kazak, 27 German and 57 Japanese.
Results. In exome sequencing results, we found 29 SNP loci in FCGR2A gene, rs1542042 was a significant SNP (p<=0.05), rs1801274 was non-synonymous mutition, 1:161488855 was a new SNP. The 3 SNPs were verified by mass spectrometry, cases/controls association analysis showed no differences between AS in southern Chinese Han and matched healthy controls (rs1801274, p=0.03921; rs1542042, p=0.5263 and 1:161488855, p=0.6616). Besides, we analyzed distribution of SNPs in controls of different races. We found that differences of Allele frequence are significant in the 2 SNP loci, they are rs1801274 between Japanese and Han race (p=0.008699), and rs1542042 between Japanese and Han race (p=0.01999). 1:161488855 in different populations [G/A: German 3 (5.77%)/49 (94.23%); Japanese 2 (1.75%%) 112 (98.25%); Hui nationality 5 (2.78%)/175 (97.22%); Uygur 2(4.76%)/40 (97.24%); Kazak 3 (2.94%)/99 (97.06%)].
Conclusion. Our study found the SNP loci in FCGR2A gene might not be a susceptibility gene of Ankylosing Spondylitis, but Variations are present in the SNP loci rs1801274 and rs1542042 of FCGR2A in different races.

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RNA SEQUENCING IN ANKYLOSING SPONDYLITIS IDENTIFIES A NOVEL DISEASE-SPECIFIC TRANSCRIPTOME AND SPLICE VARIANTS

Haynes K.H., Cuddihy T., Le Cao K., Bradbury L., Brown M.A., Thomas G.P.
The University of Queensland Diamantina Institute, Translational Research Institute, Woolloongabba, Australia

Introduction/Aim. Previous ankylosing spondylitis (AS) transcriptional profiling studies utilised microarrays confined to known genes. With the advent of next-generation sequencing RNA sequencing (RNAseq) has enabled the full transcriptome of samples to be characterised with all known genes as well their splice variants including novel isoforms. A full catalogue of non-coding RNAs (ncRNAs) can also be identified and quantified. With a large proportion of the 43 independent genetic loci identified as being associated with AS occurring in intergenic, intronic or other untranslated regions of the genome, comprehensive definition of the AS transcriptome will greatly enhance our understanding of the biology underlying many of these genetic associations.
Materials and Methods. We sequenced 70 AS cases and 80 controls to a depth of 56 million reads which is sufficient for identification of known and novel transcripts except very rare RNA species. It also enables a detailed splicesome to be generated detailing both known and novel differential exon usage.
Results. We identified over 550000 transcripts of which ~3500 of the known transcripts were differentially expressed at a corrected p-value <0.05. Gene ontology analysis identified a number of immune-associated pathways. Analysis of exon usage showed a total of ~450000 exons being expressed with 500 differentially spliced genes identified including HLA-B, MICA and TLR genes. Again gene ontology analysis of the differentially spliced genes identified immune-associated pathways.

Discussion. This is the first application of RNAseq to transcriptional profiling in AS. Our analysis has defined a transcriptome and splicesome that clearly differentiates between AS cases and controls. We will now extend our studies to validate known differentially expressed genes and splice variants. We will also generate the "novel transcriptome" which will identify the novel ncRNAs and transcripts that have not been previously annotated. These combined analyses will generate the most comprehensive AS transcriptome yet developed and contribute significantly to elucidating the functional mechanisms underlying many GWAS hits.

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EPIGENETIC STUDY OF ADVANCED ANKYLOSIS IN PATIENTS WITH ANKYLOSING SPONDYLITIS

O'Rielly D.D., Zhang Y., Al-Ghanim N., Ardern R., Hamilton S., Zhai G., Rahman P.
Faculty of Medicine, Memorial University, St. John's, Canada

Objectives. To determine if epigenetic modifications may account for differences in the degree of ankylosis in ankylosing spondylitis.
Methods. AS patients satisfying the New York criteria with at least 4 continuous ankylosed vertebrae were categorized as advanced ankylosis. Control AS patients had absence of syndesmophytes on plain radiographs. All patients were Caucasians of Northern European Ancestry. Genome-wide DNA methylation profiling was performed on the blood DNA samples from 23 AS.
Patients with advanced ankylosis and 25 patients with no syndesmophytes. The profiling was performed using Illumina HumanMethylation450k Beadchip, which measures up ~480,000 different CpG sites per sample and covers 96% of RefSeq genes. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).
Results. Advanced ankylosis patients were predominantly males (22/23), with mean of disease onset at age 21.9 years and age at time of assessment was 43.72. Meanwhile, AS patients with no syndesmophytes were also predominantly males (24/25), with mean of disease onset at age 24.6 years and age at time of assessment was 44.1 years. Methylation data were normalized using BMIQ.
Method. Analysis was performed on 382,232 autosomal CpG sites after quality controls. Analysis revealed 100 locations where there was a difference between patients with and without spinal ankylosis, after correction for multiple testing. The three locations that differentiated the most included CPG sites in KIAA0319 (hypomethylated) (p=1.7x10-5); JAKMIP3 (p=6.4x10-5) and LYG2 (p=9.6x104). Based on functional relevance to AS pathogenesis, particularly antigen presentation, cytokine signalling, and bone remodeling, 5 candidate genes (4hypomethylated; 1hypermethylated) emerged: IL18RAP (beta diff=-0.1473; p=0.01), SMAD3 (beta diff=-0.16664; p=0.047), MCF2L (beta diff=-0.10894; p=0.009), DDAH2 (beta diff=0.11494; p=0.007), and NLRC5 (beta diff=-0.11542; p=0.052).
Conclusions. These preliminary results demonstrate that the global DNA methylation pattern in advanced ankylosis differs from AS patients with no spinal damage. High priority candidate genes identified in this study warrants further validation.

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ULTRA SONOGRAPHIC EVALUATION OF THE ANTERIOR CHEST WALL IN SPONDYLOARTHRITIS: A PROSPECTIVE STUDY

Verhoeven F., Guillot X., Godfrin-Valnet M., Prati C., Wendling D.
Rheumatology, CHRU, Besançon, France

Aim. Anterior chest wall (ACW) involvement is a characteristic feature of spondyloarthritis (SpA), even in early stages, but its paraclinic exploration is not standardized. The aim of this study was to evaluate prevalence and type of ultrasonic (US) ACW involvement in SpA, and to look for factors associated to this involvement.
Methods. This prospective monocentric study included consecutive SpA (ASAS criteria) patients and a control group (healthy subjects, discal sciatica). Clinical (pain, swelling) and US evaluation (synovitis, joint effusion, erosion, joint space narrowing, ankylosis, power Doppler activity) were performed on manubrio sternal and sternoclavicular joints. The main characteristics of SpA were recorded (disease duration, biologic features, BASDAI, ASDAS, radiographic and extra articular involvement). Patients were compared to controls (C).
Results. 131 SpA and 49 control patients (same age and sex ratio) were included. Clinical and US ACW involvement was found respectively in 36 and 39% of SpA and 10 and 15 % of controls (p<0.01). US findings were: synovitis (9 SpA vs 2 C), joint space narrowing (12 vs 0), erosions (34 vs 0), manubrio sternalankylosis (24 vs 3), power Doppler activity (12 vs 2). US involvement in SpA is associated to smoking (p<0.05), history of ACW pain (p<0.05), to radiographic changes of sacro iliac joint (p=0.05), to age (45 vs 41 y, p=0.004), disease duration (14.9 vs 11.1 y, p=0.04) and presence of inflammatory bowel disease (p=0.03). US involvement is not associated to HLA-B27, enthesitis, psoriasis or uveitis, whereas clinical ACW involvement is associated with higher BASDAI (47 vs 32; p=0.0009) and ASADAS (2.9 vs 2.2; p=0.006). There is only a weak correlation between clinical and US involvement of ACW in these patients and controls.
Conclusion. US involvement of ACW is frequent in SpA, associated to disease duration, smoking and bowel involvement.

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ULTRASONOGRAPHIC EVALUATION OF FEMORAL CARTILAGE THICKNESS IN PATIENTS WITH PSORIATIC ARTHRITIS

Batmaz I.[1], Sariyildiz M.A.[1], Can I.[2], Karkucak M.[2], Serdar Ö.F.[2], Yazmalar L.[1], Çapkin E.[2], Nas K.[1]
[1]Division of Rheumatology, Dept. of Physical Medicine and Rehabilitation, Medical School, Dicle University, Diyarbakir; [2]Karadeniz Technical University Medical School, Dept. of Physical Medicine and Rehabilitation, Trabzon, Turkey

Aim. To evaluate femoral cartilage thickness in patients with psoriatic arthritis (PsA) using ultrasonography.
Patients and Methods. Thirty-three patients (24 female, 9 male) with a diagnosis of PsA and 31 age-, sex- and body mass index-matched healthy subjects were enrolled. Demographic and clinical characteristics of the patients including disease duration, morning stiffness and medications were recorded. The femoral cartilage thicknesses of both knees were measured with a 7-12 MHz linear probe while subjects' knees were held in maximum flexion. Three mid-point measurements were taken from both knees (lateral femoral condyle, intercondylar area and medial femoral condyle).
Results. Compared with those of the controls, cartilage thicknesses were similar between PsA patients and healthy control subjects. However, there were significant correlations between cartilage thickness measurements and the Maastricht Ankylosing Spondylitis Enthesitis Score, Bath AS functional index and Bath AS disease activity index scores.
Conclusion. We show that femoral cartilage thickness is similar when PsA patients are compared to healthy controls. The femoral cartilage thickness in patients with PsA may be associated with the disease activity, functional inadequacy, and enthesopathy scores.

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ASSOCIATION BETWEEN SPONDYLOARTHRITIS FEATURES AND MRI FINDINGS IN PATIENTS WITH PERSISTENT LOW BACK PAIN

Arnbak B.[1,2], Jurik A.G.[2,3], Hørslev-Petersen K.[2,4], Hendricks O.[2,4], Hermansen L.T.[2,4], Loft A.G.[5], Østergaard M.[6], Pedersen S.J.[6], Zejden A.[3], Egund N.[3], Holst R.[2], Manniche C.[1,2], Jensen T.S.[1,2]
[1]Research Dept., Spine Centre of Southern Denmark, Hospital Lillebaelt, Middelfart; [2]Institute of Regional Health Research, University of Southern Denmark, Odense; [3]Dept. of Radiology, Aarhus University Hospital, Aarhus; [4]King Christian 10th Hospital for Rheumatic Diseases, Graasten; [5]Dept. of Rheumatology, Vejle Hospital, Hospital Lillebaelt, Vejle; [6]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark

Introduction and Aim. This study was based on the assumption that clinical and MRI finding which are strongly associated with the spondyloarthritis (SpA) disease entity, also are associated with each other. Therefore the objectives were to explore the prevalence of clinical SpA features and MRI findings and the association between these two domains.
Methods. The study sample included patients aged 18-40 years with persistent low back pain, referred to a public Spine Centre. The prevalence of and associations between clinical SpA features (incl. HLA-B27and CRP) and MRI of the entire spine and sacroiliac joints (SIJ) were estimated and analysed.
Results. Of the 1020 patients included in the study, 52% had ≥1 clinical SpA feature. The three most common SpA features were; inflammatory back pain, good response to NSAID and family disposition (15-17% each). SIJ bone marrow oedema (BMO) occurred in 21%. Although several SpA features, incl. HLA-B27, were positively associated with MRI findings at the SIJ (OR ranging from 1.1-9.0), the three most common clinical SpA features were not. Several SIJ and spinal MRI findings, incl. severe SIJ BMO (sum-scores ≥3) and SIJ erosions, were associated with positive HLA-B27 (OR ranging from 3.1-24.5). Slight BMO (sum-score of 1) was, however, not associated with any SpA features.
Conclusions. The high prevalence of both clinical SpA features and MRI findings and the lack of consistent associations between the two domains, indicate a need for further investigation of the diagnostic utility of SpA features and the minimum requirements of BMO for defining sacroiliitis.

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EVALUATING HIP JOINTS AND ENTHESES WITH POWER DOPPLER ULTRASOUND IN PATIENTS WITH ANKYLOSING SPONDYLITIS BEFORE AND AFTER 6 MONTHS OF TNF-α BLOCKING THERAPY IN DAILY CLINICAL PRACTICE

Wink F.R.[1,2], Bruijn G.A.W.[3], van der Veer E.[4], Bootsma H.[1], Brouwer E.[1], Arends S.[1,2], Spoorenberg A.[1,2]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen; [2]Rheumatology, Medical Center Leeuwarden; [3]Rheumatology, MC Groep Hospitals, Lelystad; [4]Laboratory Medicine, University Medical Center Groningen, The Netherlands

Introduction. Hip and entheseal involvement are characteristic extra-spinal manifestations of ankylosing spondylitis (AS). Standardized power Doppler ultrasound (PDUS) of hip joints and entheses can be of additional value in assessing inflammation.
Aim. To evaluate inflammatory PDUS lesions of hip joints and entheses in patients with AS before and after 6 months of tumor necrosis factor-alpha (TNF-α) blocking therapy in daily clinical practice.
Methods. Between November 2004 en October 2008, consecutive outpatients from the Groningen Leeuwarden AS (GLAS) cohort with available PDUS examination before and after 6 months of TNF-α blocking therapy were included. All patients fulfilled the modified New York criteria for AS. PDUS was performed of the hip joints and 9 bilateral entheses.
Results. Mean age of the 85 included AS patients was 43 years (SD±10.5), median symptom duration 17 years (range 2-49), 73% were male, 85% HLA-B27 positive and 26% had reported hip involvement.
At baseline, 21% of patients showed ≥1 inflammatory lesion of the hip joints, which decreased significantly to 7% after 6 months of TNF-α blocking therapy (p<0.05). In addition, the percentage of patients with positive PD signal of the hip joints decreased significantly from 16% to 6% (p<0.05).
81% of patients showed ≥1 inflammatory entheseal lesion at baseline. No significant difference could be found after 6 months (74%, p=0.29). Corresponding, no significant change was observed in patients with positive PD signal of the entheses (71% vs. 61%, p=0.17).
Conclusion. This prospective observational cohort study in AS patients before and after 6 months of TNF-α blocking therapy shows inflammatory PDUS hip and entheseal lesions in a substantial percentage of patients. The observed inflammatory PDUS lesions, including positive PD signal, of hip joints decreased significantly after TNF-α blocking therapy.
Acknowledgement. The GLAS cohort was supported by an unrestricted grant from Pfizer. Pfizer had no role in the design, conduct, interpretation, or publication of this study.

Table I. Clinical assessments of disease activity and enthesitis, and PDUS examination of the hip joints and entheses in AS patients before and after 6 months of anti-TNF treatment.

	Baseline	T=6 months	p-value
BASDAI	5.8 (0.8-9.0)	2.6 (0.0-7.4)	0.000
ASDAS	3.8 (1.7-5.3)	1.8 (0.6-4.0)	0.000
CRP	15 (2-99)	3 (2-38)	0.000
MASES	2 (0-12)	1 (0-9)	0.000
≥1 inflammatory lesion hip joints	18 (21%)	6 (7%)	0.012
≥1 positive PD signal hip joints	14 (16%)	5 (6%)	0.049
≥1 inflammatory lesion entheses	69 (81%)	63 (74%)	0.286
≥1 positive PD signal entheses	60 (71%)	52 (61%)	0.169

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CLINICAL AND IMAGING DIFFERENCES BETWEEN FAMILIAL AND SPORADIC EARLY AXIAL SPONDYLOARTHRITIS: ESPERANZA COHORT

Almodóvar R.[1], Zarco P.[1], Brito E.[2], Rosas J.[3], Muñoz-Fernández S.[4], Navarro-Compán V.[5] and ESPERANZA GROUP
[1]Unidad Reumatología, Hospital Universitario Fundación Alcorcón, Madrid; [2]Hospital Universitario Ramon y Cajal, Madrid; [3]Hospital Marina Baixa, Alicante; [4]Hospital Universitario Infanta Sofía, Madrid; [5]Hospital Universitario La Paz, Madrid, Spain

Background. At present, there are few studies on how genetic factors may influence phenotypic expression in familial and sporadic early axial spondyloarthritis (axSpA). To help physicians better understand SpA, our group decided to analyse potential differences.
Objective. To evaluate the existence of clinical and imaging differences between familial versus sporadic early axial spondyloarthritis.
Methods. Baseline data from ESPERANZA program (<45 years old, symptoms duration 3-24 months and with inflammatory back pain or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was used for a descriptive analysis. Patients fulfilling the ASAS classification criteria for axial SpA were included. Socio-demographic and disease characteristics, activity indices (ESR, CRP, BASDAI, BASFI), metrology (BASMI), quality of life (ASQoL) and imaging (BASRI and sacroiliitis on MRI -ASAS criteria-) were compared between patients with familial and sporadic SpA. Familial axial SpA was defined according to the ASAS/ESSG criteria definition as presence in first or second-degree relatives of any of the following: ankylosing spondylitis, psoriasis, uveitis, reactive arthritis, inflammatory bowel disease.
Analysis. Chi square was used to compare rates and Student-t test to analyze continuous variables.
Results. A total of 291 patients were included: 190 (65%) with sporadic and 101 (35%) with familial axial SpA. Sixty six % were male, with mean (SD) age 32 (7) years and disease duration of 13 (6.7) months. Statistically significant differences were found between both groups for the following parameters: age at symptom onset (29.4 ± 9.2 vs 31.5±10 years; p<0.05) presence of HLA B27 (83% vs 71%; p=0.02), BASMI (1.2± 13 vs 1.6 1.2; p=0.03) and presence of sacroiliitis on MRI (36% vs 47%; p=0.01). There were no significant differences in the others parameters.
Conclusion. Familial early axial SpA is related to manifestation of disease symptoms at a younger age, more frequency of positive HLA-B27 and higher spinal mobility while sporadic axial SpA is associated with the presence of sacroiliitis on MRI.
Acknowledgement. Esperanza Program has been supported by an unrestricted grant from Pfizer".

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THE SWEDISH EARLY PSORIATIC ARTHRITIS (SwePsA) REGISTRY 5-YEAR FOLLOW-UP: SLOW RADIOGRAPHIC PROGRESSION WITH HIGHEST SCORES IN MALE FEET AND PATIENTS WITH BASELINE X-RAY ABNORMALITIES

Theander E.[1], Husmark T.[2], Lindqvist U.[3], Larsson P.T.[4], Teleman A.[5], Alenius G.M.[6], Geijer M.[7]
Depts. of Rheumatology Malmö[1], Falun[2], Uppsala[3], Stockholm[4], Spenshult[5], Umeå[6] and Radiology Lund[7], Sweden

Aim. Description of early X-ray findings in psoriatic arthritis (PsA) patients from the SwePsA registry using the Wassenberg score, evaluation of progression of structural damage, analysis of correlations to clinical disease parameters and identification of predictors of progressive radiographic joint disease.
Methods. For 112 early (symptom duration max 24 months at baseline) SwePsA patients radiographs of hands and/or feet from the 5-year follow-up and at least one further investigation (baseline or 2-year) were available and scored according to Wassenberg. Radiographs were performed in symptomatic patients/joints at baseline and repeated during follow-up. Reading (MG) in chronological order was centralized. Clinical data were collected according to the SwePsA protocol.
Results. Mean age of the 67 women and 45 men was 47.1 (SD15.1) years, slightly higher in women. Baseline DAS28 and DAPSA were 3.7/21.4, HAQ 0.84 and PASI 2.9. The total radiographic score was 0 in 61% at baseline and 29% at 5-year follow-up. Only 15 (13%) had a score >10 at follow-up. In contrast to higher clinical disease activity in women, men had higher radiographic scores both in total (baseline: 3.95vs1.37, 5-year: 7.79vs3.37, p=0.017/0.034), erosion (baseline: 1.53vs0.37, 5-year: 3.41vs0.86, p=0.044/0.051) and proliferation (baseline: 2.42vs1.00, 5-year: 4.62vs2.56, p=0.031/0.041), mainly in the feet

(baseline: 0.93vs0.13, 5-year: 2.45vs0.84, p=0.007/0.028). Five-year scores were significantly associated with swollen joint counts, but not with HAQ, DAS28/DAPSA, tender joint counts, symptom duration or smoking. The only predictors of high Wassenberg score at follow-up were swollen joint count and an elevated score at baseline. None of the 15 patients with the highest scores/progress had received TNF-blockers.
Discussion/Conclusions. Radiographic progression in early PsA is slow in general, most prevalent in male feet and predicted by swollen joint count and baseline radiographic findings. Thus scoring of hand and feet X-rays at baseline cannot be substituted by clinical signs, especially not in men.

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THE DISTRIBUTION OF INFLAMMATION IN THE ANTERIOR AND POSTERIOR SPINAL STRUCTURES IN ACTIVE AS AND THE EFFECT OF TNF-α-BLOCKADE

Baraliakos X.[1], Hermann K.G.[2], Xu S.[3], Hsu B.[3], Braun J.[1]
[1]Rheumazentrum Ruhrgebiet, Herne, Germany; [2]Radiology, Charité Berlin, Germany; [3]Janssen R&D, Spring House, USA

Aim. Using data from GO-RAISE, we analysed in detail the distribution and course of inflammatory lesions in different spinal sites before and after treatment with golimumab in patients with active AS.
Methods. Complete MRIs at baseline, 3 months (placebo-controlled phase) and 2 years (open-label extension) were available from 98 active AS patients and evaluated by 2 blinded readers for presence/absence of inflammation in the cervical [CS], thoracic [TS] and lumbar [LS] spine, single vertebral units [VUs] and in the zygoapophyseal joints [ZAJ]. Improvement in inflammation was defined as any decrease in MRI score from baseline to year 2 of the study.
Results. Overall, inflamed VU and ZAJ lesions were seen in 81.6% and 31.6% patients, respectively, while 22.4% of VUs/ZAJs had baseline inflammation with mean number of lesions/patient of 6.7 for VUs and 3.6 for ZAJs. ZAJ inflammation without VU inflammation was present in 43 (0.97%) of all VUs and in 19 (20.9%) of patients. In detail, 7.2% of VU+ZAJ lesions were found in the CS, 27.9% in the TS and 27.9% in the LS. VU inflammation was detected more frequently in the anterior (23.5%) than in the posterior (8.5%) part of the LS. This difference was not observed in CS and TS. The most frequently inflamed segment in the CS was C7/T1, in the TS T8/9-T11/12, while in the LS there was an even distribution. After 3 months of golimumab treatment, the percentage of inflamed VUs/ZAJs decreased by 2.7%/0.7% in CS, 17.3%/3.6% in TS and 17.6%/2.7% in LS, while almost no change was seen under PBO. The decreased VU/ZAJ involvement afforded by golimumab treatment was sustained through 2 years.
Conclusions. This analysis confirms the predominance of inflammatory spinal lesions at the lower TS and LS. While ZAJ inflammation was evident in a substantial number of patients it was uncommon for it to occur in isolation in a non-inflamed VU.

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SPINAL MOBILITY IN THE CERVICAL AND THE LUMBAR SPINE CORRELATES WITH MRI FINDINGS IN AS–RESULTS FROM GO-RAISE

Baraliakos X.[1], Hermann K.G.[2], Xu S.[3], Hsu B.[3], Braun J.[1]
[1]Rheumazentrum Ruhrgebiet, Herne; [2]Radiology, Charité Berlin, Germany; [3]Janssen R&D, Spring House, USA

Aim. Using data from GO-RAISE, we analysed the relationship between single components of BASMI and MRI scores of the corresponding spinal segments in AS.
Methods. MRI and spinal mobility data were available for 91 pts from GO-RAISE. The MRI scores for active (ASspiMRI-a) and chronic changes (ASspiMRI-c) of the cervical (CS) and lumbar (LS) spine were compared to BASMI values for the cervical (cervical rotation (CR) and tragus-to-wall (TTW)) and the lumbar (lumbar flexion (LF) and lateral lumbar flexion (LLF)) spine using the linear definition. Spearman correlation coefficients were calculated for baseline scores and changes in BASMI and ASspiMRI-a and -c of patients treated with golimumab or placebo after 14 weeks and after 2 years of golimumab therapy. Subanalyses were performed with regard to age.
Results. At baseline, ASspiMRI-a scores of the CS correlated with TTW (r=0.31, p=0.003) and CR (r=0.32, p=0.002) measurements, while ASspiMRI-a scores of the LS correlated with LF and LLF scores (both r=0.41, p<0.0001). In addition, ASspiMRI-c scores of the CS correlated with TTW (r=0.46) and CR (r=0.45), both p<0.0001, while ASspiMRI-c scores of the LS correlated with LF (r=0.34, p=0.001) and LLF scores (r=0.41, p<0.0001). ASspiMRI-a scores correlated better in patients <40 years (TTW: r=0.31, p=0.04, LLF: r=0.42, p=0.005), while ASspiMRI-c scores correlated better in patients >40 years (TTW: r=0.35, p=0.015, LLF: r=0.48, p<0.001). No correlations were found in change scores.
Conclusion. Our data confirm that both inflammation and structural changes contribute to impairments of spinal mobility. In addition, we demonstrate significant correlations of MRI findings with detailed spinal mobility measures before anti-TNF treatment. Inflammatory changes had greater impact on spinal mobility in younger patients, while structural changes had more influence on spinal mobility in older patients. The lower correlation of the observed changes in MRI scores and spinal mobility may be due to the different mixture of active and chronic changes in individual patients.

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TREATMENT EFFECT OF USTEKINUMAB ON FATIGUE IN PATIENTS WITH PSORIATIC ARTHRITIS: RESULTS FROM PSUMMIT 2

Ritchlin C.[1], Rahman P.[2], Puig L.[3], Gottlieb A.B.[4], Kavanaugh A.[5], McInnes I.B.[6], Li S.[7], Wang Y.[7], Ganguly R.[8], Mendelsohn A.M.[7], Han C.[8], on behalf of the PSUMMIT 2 Study Group
[1]University of Rochester, Rochester, NY, USA; [2]Memorial University, NL, Canada; [3]Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Tufts Medical Center, Boston, MA; [5]University of California-San Diego, CA, USA; [6]University of Glasgow, Glasgow, Scotland; [7]Janssen Research & Development, LLC, Spring House, PA; [8]Janssen Global Service LLC, Malvern PA, USA

Aim. To assess the treatment effect of ustekinumab (UST) on fatigue from PSUMMIT 2.
Methods. Adult patients with active PsA despite DMARD (N=132)&/or previous treatment with biologics (N=180) were randomized to UST45mg, 90mg, or PBO at wks0, 4,&q12wks through wk40. PBO-treated patients crossed over to UST45mg at wks24, 28&q12wks through wk40. Fatigue was measured using FACIT-Fatigue, 0-52& the vitality scales of SF-36 health survey questionnaire (SF-36VT, 0-100). High scores indicate low severity in fatigue. Clinically meaningful improvement was defined as ≥4 point increase in FACIT-Fatigue or ≥3point increase in SF-36VT score from baseline. Disease activity was measured by DAS28, & physical function was measured using HAQ.
Results. At baseline, patients had a mean FACIT-Fatigue score of 25.8, & a mean SF-36VT score of 36.9,significantly below values of the U.S. normal population (50), indicating severe fatigue. Both FACIT-Fatigue&SF-36VT scores were significantly correlated with DAS28 (r=0.42, 0.38,) & HAQ (r=0.62,0.51) at baseline, & the improvements in FACIT-Fatigue&SF-36VT scores were significantly correlated with improvement in DAS28 (r=0.45,0.43) & improvement in HAQ scores (r=0.43,0.41) at wk24. At wk24, patients who received UST achieved statistically significantly greater improvement in FACIT-Fatigue score (4.35vs0.86, p=0.002) & in SF-36VT score (3.87vs0.67, p=0.004) vs PBO. Compared to PBO, a greater proportion of UST-treated patients achieved a clinically meaningful improvement in FACIT-Fatigue (49%vs25.5%) or SF-36VT (45%vs29.9%) (all p<0.01). No significant differences were observed between the UST45&90mg groups. The treatment effect on fatigue was consistent across biologically-&DMARD-experienced patients & maintained through wk52. Patients who were randomized to PBO & switched to active treatment at wk24 achieved comparable improvement at wk52.
Conclusion. UST therapy significantly reduces the symptom of fatigue in patients with active PsA. Clinically meaningful improvement in fatigue was observed within 3 doses of UST therapy.

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VEGF AND CRP SERUM LEVELS LACK PREDICTIVE VALUE FOR RADIOGRAPHIC AND MRI OUTCOMES IN PATIENTS WITH ACTIVE AS TREATED WITH THE TNF-INHIBITOR GOLIMUMAB

Baraliakos X.[1], Hermann K.G.[2], Xu S.[3], Hsu B.[3,] Braun J.[1]
[1]Rheumazentrum Ruhrgebiet, Herne; [2]Radiology, Charité Berlin, Germany; [3]Janssen R&D, Spring House, USA

Aim. Using data from GO-RAISE, we analyzed correlations between serum VEGF and CRP levels, radiographic progression and inflammation as detected by MRI.
Methods. 98 patients with active AS received golimumab or placebo up to wk16/24 and then golimumab up to 2y. All had sera, lateral spinal radiographs at baseline, wk104, and wk208 scored by the mSASSS and spinal MRIs at baseline, wk14, and wk104 scored with the ASspiMRI-a by two blinded readers. The relationship between VEGF or CRP levels and both mSASSS and MRI-a score was assessed by Spearman correlation analyses and logistic regression analyses were conducted to assess if VEGF levels conferred an increased risk of syndesmophyte formation from baseline to wk104 or wk208.
Results. CRP serum levels correlated with mSASSS scores at baseline, but not with radiographic progression or changes in MRI-a scores. No significant correlations were observed between VEGF serum levels and mSASSS at any time point. Logistic regression analyses failed to show an increased risk of changes towards syndesmophyte formation at wk104 and wk208 associated with VEGF (odds ratio, range: 0.990-1.006, all p=n.s). While a good correlation was observed between changes in ASspiMRI-a and VEGF level at wk14 (p=0.0008), the analysis showed that baseline and wk14 VEGF levels were not predictive of MRI-a scores including change scores at wk104.
Conclusion. CRP serum levels correlated with baseline mSASSS scores but did not predict radiographic progression or remaining spinal inflammation after anti-TNF treatment. Similarly, both VEGF and CRP serum levels at baseline were not predictive of either radiographic progression or spinal inflammation in these anti-TNF treated patients. Overall, our data suggest that suppression of VEGF and CRP is not sufficient to halt new bone formation in AS.

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SERUM BIOMARKERS ASSOCIATED WITH CHANGES IN ASDAS AND MRI FOLLOWING TREATMENT OF AS WITH GOLIMUMAB

Inman R.D.[1], Baraliakos X.[2], Hermann K.G.[3], Braun J.[2], Deodhar A.[4], van der Heijde D.F.M.[5], Xu S.[6], Hsu B.[6]
[1]University of Toronto, Toronto, Canada; [2]Rheumazentrum Ruhrgebiet, Herne; [3]Charité Hospital, Berlin, Germany; [4]Oregon Health Science University, Portland, USA; [5]Leiden University Medical Center, Leiden, The Netherlands; [6]Janssen R&D LLC, Spring House, USA

Aim. Using data from GO-RAISE, patients with active AS, had correlations analysed between multiple serum biomarkers & inflammation as detected by MRI&ASDAS.
Methods. Patients with moderately to severely active AS were randomized to SC GLM 50mg, 100mg, or PBO q4wks. PBO-treated patients crossed over to receive GLM at wk16 or 24. Spinal MRIs in the sagittal plane were acquired using 1.5T scanners with T1&STIR sequences at BL&wk14. 98 patients were scored for activity (ASspiMRI-a) & structural (ASspiMRI-c) scores. Radiographs & MRIs were assessed by 2 readers who were blinded to treatment & image time order. Mean scores were used for analyses. Sera were collected from 140 patients at BL&wk14 for analysis of markers by ELISA &/or using a multiplex platform (Rules Based Medicine). Spearman correlation analyses with Bonferoni p-value adjustment & logistic regression were conducted to assess the relationship between 76 serum biomarker levels &, ASDAS using C-reactive protein (ASDAS), ASspiMRI-a, or MRI-c score at various time points.
Results. Baseline ASDAS showed significant correlations with serum biomarkers for inflammation (IL-6, ICAM-1, haptoglobin, amyloid P)& lipid metabolism (Complement C3). BL IL-6 or TIMP-1 correlated with the reduction of ASspiMRI-a at wk14 in GLM-treated patients. Wk4 change in IL-6 & C3 also showed correlation with change in ASspiMRI-a at wk14. Development of new fatty degeneration in the spine at wk14 correlated with BL biomarkers involved in lipid metabolism (leptin, C3)& tissue remodeling (TIMP-1). Previously described predictors such as insulin, MMP-3, VEGF, or bone resorption markers did not have significant correlations with clinical or imaging outcomes.
Conclusion. This analysis suggests that serum biomarkers IL-6, TIMP-1, &C3 may be linked to a reduction in spinal inflammation in AS patients following GLM treatment. ICAM-1, haptoglobin & amyloid P correlate with BL disease activity & may implicate novel roles for these factors in AS-related inflammation.

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EFFICACY AND SAFETY OF USTEKINUMAB IN PSA PATIENTS WITH SPONDYLITIS AND PERIPHERAL JOINT INVOLVEMENT: RESULTS FROM A PHASE 3, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Kavanaugh A.[1], Puig L.[2], Gottlieb A.B.[3], Ritchlin C.[4], You Y.[5], Wang Y.[5], Mendelsohn A.M.[5], Song M.[5], Rahman P.[6], McInnes I.B.[7], on behalf of the PSUMMIT I Study Group
[1]University of California-San Diego, CA, USA; [2]Universitat Autònoma de Barcelona, Barcelona, Spain; [3]Tufts Medical Center, Boston, MA; [4]University of Rochester, Rochester, NY; [5]Janssen R&D, LLC, Spring House, PA, USA; [6]Memorial University, NL, Canada; [7]Universityof Glasgow, Glasgow, Scotland

Aim. To evaluate ustekinumab (UST) in sub-group of PsA patients with physician diagnosed spondylitis & peripheral joint involvement.
Methods. Adult PsA patients (n=615) with active disease despite DMARD&/or NSAIDs were randomized to UST45mg, 90mg or PBO at wks 0,4, & q12wks. Patients treated with prior anti-TNF agents were excluded. Stable MTX was permitted but not mandated. At wk16, patients with <5% improvement in TJC&SJC entered blinded early escape (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). PBO-treated patients crossed over to UST45mg at wk24. Patients received q12wks dosing to wk88, final efficacy evaluation at wk100&safety at wk108. Patients with spondylitis & peripheral joint involvement, also completed BASDAI assessments at wks12&24.
Results. 186 randomized patients (70PBO, 116UST combined) had spondylitis with peripheral joint involvement at baseline (BL); mean BL characteristics were similar to overall population (age 45.6yrs, weight 82.8kg, PsA duration 6.3yrs, SJC/TJC 14.3/24.1, HAQ-DI 1.3; BASDAI 6.5 (for spondylitis patients only). Mean BL scores among patients with dactylitis (n=100), enthesitis (148), & skin disease (147) were 8.3,5.6, &PASI14.2, respectively. At wk24, greater proportions of combined UST45/90mg treated patients had improvements in dactylitis/enthesitis, HAQ-DI&ACR20/50/70 responses than PBO. Clinical improvements were generally maintained through wk100.A significantly higher proportion of UST-treated patients achieved improved responses for BASDAI20/50/70 vs PBO at wk24(54.1%/27.9%/14.4% vs 26.2%/13.1%/0.0% for UST combined vs PBO, respectively). Peripheral structural damage assessed by total vdH-S mean change from BL also showed improvement for UST vs PBO at wk24. Of the 135 patients with ≥3%BSA involvement & spondylitis with peripheral arthritis at BL, PASI75 were maintained through wk100. During the PBO-controlled period, proportion of patients with AEs were comparable between PBO & combined UST-treated groups (AEs 32.9% vs 24.1%;SAEs 1.4% vs 0.9%; discontinuations due to AEs 2.9% vs 0.9%;serious infections 14.3% vs 7.8%). Through 2yrs,safety observations were consistent with the overall PsA population.
Conclusion. In this post-hoc sub-group analysis, UST significantly improved signs & symptoms, & demonstrated improvements in BASDAI & peripheral radiographic progression vs PBO through wk24; efficacy was maintained through wk100. UST was well-tolerated with safety similar to overall study population.

P154

DO BONE MARROW EDEMA LESIONS IN THE SACROILIAC JOINT CHANGE INTO FATTY LESIONS OVER A 1-YEAR PERIOD IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS OR POSSIBLE SPONDYLOARTHRITIS

Bakker P.A.C., van den Berg R., de Hooge M.S.M., van Gaalen F.A., Reijnierse M., Huizinga T., van der Heijde D.M.F.M.
Rheumatology, LUMC, Leiden, The Netherlands

Background. Bone marrow edema (BME) lesions in the sacroiliac-joints (SIJ) may change into fatty lesions (FL) over time. FL are regarded as the first structural changes as a consequence of inflammation but are sometimes also found in healthy-controls.[1,2]
Objectives. To investigate whether SIJ BME-lesions change into FL over 1-year time in patients with axial SpondyloArthritis (axSpA) or possible SpA and to evaluate the volatility of both lesions general.
Methods. Patients in the SPACE)-cohort (back pain: ≥ 3 months, ≤2 years, onset < 45 years) with (suspicion of) axSpA underwent MRI-SIJ at baseline and 1-year follow-up (n=76). MRI-SIs were scored on the presence of BME and FL in 4 quadrants (Q) per SIJ, independently by 2 well-calibrated readers, blinded for time sequence and patient characteristics. Lesions were defined as presence of 1 lesion on ≥2 consecutive slices or if >1 lesion was seen on a single slice. For the 2 readers individually, scores of baseline and 1-year were compared on quadrant level. Scores in all Qs were summed up (Q=608 in total).
Results. At baseline, 39/76 (51%) patients were classified as axSpA (ASAS axSpA criteria); 37/76 (41%) as possible SpA. BME or FL (any time point) was found in 27/76 (36%) and 20/76 (26%) patients respectively (1,2). In both readers, FL newly occurred in 8/76 patients (11%) over 1-year time; in 3 patients, a transition of BME to fat occurred; FL disappeared in 2/76 (3%) patients.
Conclusions. About 1/3 of patients showed BME/FL in the SIJ at any time point. There was not much change in site and/or type of lesions over 1-year. FL occurred more frequently de novo than in quadrants with previous BME. Moreover, FL can also resolve over time.

Reference

1. CHIOWCHANWISAWAKIT ARD 2010; 69: 262 2. *Song ARD* 2011; 70: 1257.

Table. Volatility of BME and fatty lesions in the SIJs over 1 year time.

Reader 1		1 year			
		no lesions	BME	FAT	BME & FAT
Baseline	no lesions	519	10	5	1
	BME	14	17	3	3
	FAT	0	1	20	1
	BME & FAT	0	1	6	7
Reader 2		1 year			
		no lesions	BME	FAT	BME & FAT
Baseline	no lesions	524	10	7	1
	BME	18	10	2	1
	FAT	5	0	9	1
	BME & FAT	5	1	6	8

8 quadrants per patient (n=76); 608 quadrants in total.

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CLINICAL SIGNIFICANCE FOR INFLAMMATORY LESIONS ON FACET JOINTS OF THE APINE USING NOVEL ANKYLOSING SPONDYLITIS ACTIVITY OF FACET JOINT (ASAFACET) SCORING SYSTEM

Lee S.[1], Lee J.Y.[1], Kim S.K.[2], Kim T.H.[3]
[1]Dept. of Radiology, Hanyang University Hospital for Rheumatic Diseases, Seoul; [2]Dept. of Internal Medicine, Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu; [3]Dept. of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea

Objective. The involvement of the facet joint is a crucial feature in ankylosing spondylitis (AS). The aim of this study is to validate novel magnetic resonance imaging (MRI) scoring system for inflammatory lesions in the facet joint and to clarify clinical significance of inflammation in the facet joint in AS.
Methods. Total 53 AS patients (male = 45, 84.9%) were reviewed for assessment of active inflammatory lesions with bone marrow edema in the facet joints at corresponding 23 disco-vertebral units (DVU) from C2 to S1 levels, which was scored from 0 to 2 points for both sides at each lesion and leading to maximum score of 92. The reliability of the Ankylosing Spondylitis Activity of Facet joint (ASAFacet) were tested using intra-class correlation coefficients (ICC) and Bland-Altman plots.
Results. The ICC values for ASASFact scores were 0.923 (95% CI 0.851 - 0.958) for inter-observer and 0.941 (95% CI 0.873 - 0.969) for intra-observer reliability. The inflammatory lesions for facet joints was evenly distributed from C2 to S1 levels, whereas spinal body lesions were more frequently in thoracic spine. ASAFacet scores were closely related with ESR and CRP levels, but not BASDAI and BASFI. Patients with peripheral arthritis had a lower ASAFacet scores in comparison to those without peripheral arthritis, suggesting possibility for less severe damage of the facet joints.
Conclusion. ASAFacet scoring method is reliable and valid MRI activity index for on the facet joint. This study proposes that recognition for acute lesion of facet joint might be helpful to understand clinical outcome and disease progression in AS.

P156

VALIDATION OF THE NEW CONCEPT OF BACKFILL ON MRI: A DISTINCT REPARATIVE TISSUE THAT FOLLOWS RESOLUTION OF INFLAMMATION AT SITES OF SACROILIAC JOINT EROSION

Maksymowych W.P.[1], Pedersen S.J.[3], Wichuk S.[1], Chiowchanwisawakit P.[4], Østergaard M.[3], Weber U.[1], Lambert R.G.[2]
[1]Medicine and [2]Radiology, University of Alberta, Canada; [3]Copenhagen Center for Arthritis Research, University of Copenhagen, Denmark; [4]Medicine, Mahidol University, Thailand

Introduction. We hypothesized that resolution of inflammatory lesions in erosions of sacroiliac joints (SIJ) is followed by development of a new tissue, which on T1W MRI has high signal intensity resembling fat metaplasia in bone marrow. We have called this type of fat lesion "Backfill" (BF). We aimed to demonstrate that BF can be reliably detected and that resolution of inflammation and reduction of erosion are both independently associated with its development.
Methods. BF, erosion, and fat metaplasia were scored with the SPARCC MRI SIJ Structural Score using T1W MRI. Four readers assessed baseline and 2 year scans from 20 patients (exercise 1) and then 45 patients after calibration (exercise 2). Inter-observer reliability was assessed by intra-class correlation coefficient (ICC). Two readers independently scored 147 pairs of scans (baseline, 2 years) from a prospective cohort of patients with SpA on either NSAID (n=69) or anti-TNF (n=78) therapies. SIJ inflammation was scored independently using the SPARCC MRI SIJ method. Predictors of new BF were analyzed by multivariate regression adjusted for patient demographics, treatment, baseline and 2-year change in inflammation and damage scores.
Results. ICC for detection of Backfill in exercises 1 and 2 were 0.86/0.66 for status scores and 0.55/0.56 for 2-year change scores. Development of new Backfill correlated significantly with reduction in SPARCC SIJ score for inflammation (r=-0.50, p<0.0001), reduction of SSS erosion score (r=-0.47, p<0.0001), and development of new fat metaplasia (r=0.29, p=0.003).
Multivariate regression revealed the following as independent predictors of new Backfill: change in SPARCC SIJ inflammation (β=-0.10, p=0.003), 2-year change in SSS erosion (β=-0.39, p<0.0001), baseline backfill SSS score (β=-0.32, p<0.0001).
Conclusions: Backfill is an MRI feature of SpA that can be reliably detected and its development is associated with the resolution of inflammation and reduction of erosion.

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THE SPONDYLOARTHRITIS RESEARCH CONSORTIUM OF CANADA MRI SACROILIAC JOINT STRUCTURAL SCORE: RELIABLE DETECTION OF STRUCTURAL PROGRESSION EVEN OVER ONE YEAR

Maksymowych W.P.[1], Wichuk S.[1], Chiowchanwisawakit P.[3], Lambert R.G.[2], Pedersen S.J.[4]
[1]Medicine and [2]Radiology, University of Alberta, Canada; [3]Medicine, Mahidol University, Thailand; [4]Copenhagen Center for Arthritis Research, University of Copenhagen, Denmark

Introduction. There has been limited validation of MRI-based scores for structural lesions in the sacroiliac joints (SIJ) but it is unclear whether change in structural progression can be reliably detected, especially over a time frame shorter than 2 years. We aimed to assess the reliability of a new MRI-based scoring method for detecting change in SIJ structural damage.
Methods. The SPARCC SIJ Structural Score (SSS) method is based on T1WSE MRI and scores fat and erosions in SIJ quadrants (scoring range 0-40 for each) and backfill and ankylosis in SIJ halves (scoring range 0-20 for each) on 5 consecutive slices through the cartilaginous portion of the joint. We conducted 3 validation exercises with 2-4 readers according to the OMERACT filter on baseline and either 2-year or 1 year scans from 147 patients with SpA assessed blinded to time point. Inter-observer reliability was assessed by intra-class correlation coefficient (ICC3,1). The smallest detectable change (SDC) was calculated using the Bland-Altman 80% levels of agreement.
Results. For status scores, reliability for ankylosis was very good-excellent (ICC=0.79-0.98), good for fat metaplasia (ICC=0.71-0.78), moderate/good for erosion (ICC=0.58-0.65), and fair/good for backfill (ICC=0.35-0.66). Mean change scores at 1 year were 0.73, -0.63, -0.03, 0.58 and percentage of patients with change >0 were 63%, 90%, 85%, 53% for fat, erosion, backfill and ankylosis, respectively. Despite the variability and small degree of change in scores at 1 year, SDC was comparably low for structural lesion scores at 5-7% of the scoring range with the exception of backfill (14%). Fair to good reliability by ICC analysis (ICC=0.61, 0.54, 0.42, 0.47 for fat, erosion, backfill, ankylosis, respectively) was also observed for 1-year change in all SSS scores.
Conclusion. The SPARCC MRI SSS method is a reliable scoring method for detecting structural progression in the SIJ, especially ankylosis.

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DIFFUSING WEIGHT MAGNETIC RESONANCE IMAGING MAY SUGGEST THE TREATMENT STRATEGY IN ANKYLOSING SPONDYLITIS

Sang Yeob L., Jae Ho B., Sung Won L., Won Tae C.
Dong--A university, Pusan, South Korea

Background. With the advanced MRI techniques, pathologic features can be detected at an early stage and quantitatively evaluated, resulting in the advantages of early diagnosis and prompt treatment. This study aimed to determine the value of diffusion-weighted MR imaging (DWI) in determined of ankylosing spondylitis (AS) treatment strategy and assess the role of quantitative MRI in the evaluation of AS treatment outcome.
Methods. 18 patients with the diagnosis of early AS were included in this study. Disease activity was measured according to clinical instruments and laboratory tests. For each patient, both inflamed sacroiliac (S-I) joint lesion was checked quantitatively at first diagnosis by diffusion-weighted imaging (DWI) measuring the apparent diffusion coefficient (ADC) and by dynamic contrast-enhanced imaging (DCEI) with evaluation of the enhancement factor (f_{enh}) and enhancement gradient (g_{enh}). All patients were revaluated by pelvis computer tomography (CT) for bone change in S-I joint, after two year.
Results. Clinical and quantitative MRI parameters diminished significantly with regression of the inflammatory activity. Median ADC values in AS patients were $(1.118\pm0.122) \times 10^{-3}$ mm^2/s in S-I joint. The high ADC ($>1.118\pm0.122) \times 10^{-3}$ mm^2/s, f_{enh} (>1.65) and g_{enh} (2.09 %/S) were associated severe disease activity and early administration of biologics ($p<0.05$). In each individual, the high ADC, f_{enh} and g_{enh} of S-I joint lesion was associated more severe localized pain than the other S-I joint, despite treatment ($p<0.05$). Paradoxically, because of high ADC, f_{enh}, g_{enh} and high disease activity, early administration of biologics group had minimal bone change of S-I joint, compared to only NSAIDs used group in pelvis CT finding.
Conclusion. Diffusion-weighted imaging and DCEI were shown to be effective in quantifying changes in inflammation in S-I joint at the diagnosis of AS, and could therefore be convenient for assessing treatment strategy. To the best of our knowledge this is the first time DWI was used to evaluate the treatment strategy and treatment outcome of AS.

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CORRELATION BETWEEN CLINICAL AND MRI DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS

MacKay J.W., Aboelmagd S., Gaffney J.K.
Dept. of Rheumatology, Norfolk & Norwich University Hospital, Norwich, UK

Introduction. Thresholds for biologic treatment in axial spondyloarthritis (aSpA) are traditionally defined using clinical disease activity scores (DAS). For example, in the UK a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of >4 is required for eligibility for biologics. Alternative, magnetic resonance (MR) imaging based DAS are available. The correlation between clinical and MR DAS has not been fully assessed outside of clinical trials. The aims of this study were to evaluate the correlation between clinical and MR DAS in a typical aSpA outpatient population, and to determine whether there was a difference in MR DAS in individuals with high (BASDAI >4) and low (BASDAI ≤4) clinical DAS.
Methods. Participants meeting diagnostic criteria for axial SpA presenting for MR of the whole spine and sacroiliac joints as part of ongoing management were included. Completion of BASDAI, Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and ASDAS-ESR questionnaires was performed at time of MR examination. MR images were scored by two independent observers using the Spondyloarthritis Research Consortium of Canada (SPARCC) MR DAS. Correlation between clinical and MR DAS was assessed using scatter plots and Pearson correlation coefficients. Differences in MR DAS in participants with high and low clinical DAS were assessed using an unpaired Student *t*-test.
Results. 40 participants completed the study. There were weak, non-significant correlations between total SPARCC score and BASDAI (r=0.18, p=0.26), ASDAS-ESR (r=0.31, p=0.07) and ASDAS-CRP (r=0.31, p=0.05). There was no significant difference in the SPARCC score of participants with BASDAI ≤4 compared to BASDAI >4 (p=0.14). Inter-observer intraclass correlation coefficient (ICC) for the total SPARCC score was 0.91 (95% confidence interval 0.84 – 0.95) indicating near perfect agreement.
Conclusion. There was no correlation between clinical and MR DAS, and no significant difference in MR DAS in participants with high and low clinical DAS. MR DAS are reliable and may more accurately reflect burden of inflammation than clinical DAS. This challenges the use of clinical DAS as a threshold for biologic treatment.

P160

PERFORMANCE OF HYBRID 18F-FLUORIDE PET/MRI OF THE SACROILIAC JOINTS AND THE SPINE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

Baraliakos X., Buchbender C., Ostendorf B., Ruhlmann V., Heusch P., Miese F., Beiderwellen K., Schneider M., Antoch G., Braun J.
Rheumazentrum Herne, Germany

Introduction/Aim. To examine whether inflammatory or chronic changes assessed by magnetic resonance imaging (MRI) in sacroiliac joints (SIJ) and spine of patients with active ankylosing spondylitis (AS) are associated with osteoblastic activity, which is assessed 18F-Fluoride uptake (18F-F) in positron emission tomography/MRI (PET/MRI).
Methods. Thirteen AS patients (mean age 37.8±11.4 years, BASDAI>4, no anti-TNF treatment) underwent 3-Tesla integrated whole-spine- and SIJ-PET/MRI. Two independent readers recorded pathologic changes related to vertebral- (VQ) or SIJ-quadrants (SQ). Final scores based on agreement.
Results. A total of 104 SQs and 1,196 VQs were examined. In the SIJ, bone marrow edema (BME) was seen in 44.2%, fat degeneration (FD) in 42.3% and 18F-F in 46.2% SQs. BME alone was associated with 18F-F in 78.6% and FD alone in only 7.7% SQs, while the combination BME/FD was associated with 18F-F in 72.2% SQs. In contrast, erosions, sclerosis, and ankylosis alone were rarely associated with 18F-F.
In the spine, BME alone was seen in 9.9%, FD in 18.2% and 18F-F in 5.4% VQs. BME alone was associated with 18F-F in 14.3% and FD alone in 8.7% VQs, while the combination BME/FD was associated with 18F-F in 40.6% VQs. Overall, 18F-F alone was found in 25% of all positive SQs and VQs.
Conclusion. In this first study on hybrid 18F-F-PET/MRI of active AS patients we show that rather BME than chronic changes is associated with osteoblastic activity. The combination of BME and FD showed the highest 18F-F uptake, confirming previous finding that this is the strongest predictor of future syndesmophyte formation.

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LYMPHATIC ENDOTHELIAL PROGENITOR CELLS AND VASCULAR ENDOTHELIAL GROWTH FACTOR-C IN SPONDYLOARTHRITIS AND CROHN'S DISEASE: TWO OVERLAPPING DISEASES?

Bandinelli F.[1], Milia A.F.[1], Lastraioli E.[1], Manetti M.[1], Fazi M.[2], Arcangeli A.[1], Matucci-Cerinic M.[1], Ibba-Manneschi L.[1]
[1]Dept. Experimental and Clinical Medicine, University of Florence, Florence; [2]Dept. Surgery and Translational Medicine, University of Florence, Florence, Italy

Background. The role of the lymphatic system in the connection between Spondyloarthritis (SpA) and Crohn's disease (CD) still remains to be elucidated.
Objective. To investigate the circulating levels of lymphatic endothelial progenitor cells (LEPCs) and vascular endothelial growth factor-C (VEGF-C) and their possible correlation with clinical indices in SpA, SpA associated with CD (SC) and CD.
Methods. Peripheral blood samples from SpA (n=36), SC (n=20), CD (n=28) patients and 20 age- and sex-matched healthy controls were collected and used for quantification of circulating LEPCs and VEGF-C. LEPCs were identified by FACS using FITC-CD34, APC-CD133 and PE-VEGFR-3 antibodies, while serum VEGF-C was evaluated by ELISA. SpA patients were diagnosed with ASAS criteria. The possible correlations between LEPC levels and disease duration (< or >10 years; < or >20 years) and BASDAI for SpA or CDAI for CD were analyzed.
Results. LEPCs levels were significantly increased in SpA (p=0.0006) and SC (p=0.0058) patients compared with controls. In CD patients, LEPCs levels negatively correlated with disease duration (r=-0.4668), with lower levels in longstanding disease (>20 years, p=0.018), but were not different from controls. Both LEPCs and VEGF-C levels were independent of BASDAI and CDAI.
Conclusions. Basing on our observation, an active mobilization of lymphatic cell precursors was observed only for spondylitis involvement, independently of disease activity.

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AUTOPHAGY AND UNFOLDED PROTEIN RESPONSE: A FINE BALANCE THAT CAN INFLUENCE THE PATHOGENESIS OF ANKYLOSING SPONDYLITIS AND INFLAMMATORY BOWEL DISEASE

Haroon N.[1], Guggino G., Zhang Z., Yee K., Abdullah H., Alessandro R., Raimondo S., Triolo G., Ciccia F.
[1]University of Toronto, University Health Network, Toronto Western Research Institute, Toronto, Canada

Introduction. We have shown an increase in the unfolded protein response (UPR) with decreased ERAP1 or ERAP2 function in an *in vitro* system. Similarly UPR has been demonstrated to correlate with onset of disease in the HLA-B27 rat model. UPR has been difficult to demonstrate in the gut of AS patients but autophagy is upregulated. ERAP2 is associated with both AS and inflammatory bowel disease (IBD). Here we explore the moderating effect of autophagy on UPR.
Methods. Lamina Propria Mononuclear cells (LPMC) were isolated from terminal ileal biopsies of 10 AS patients. Autophagy was suppressed with 2 agents anisomycin and 3-MA. In parallel an in vitro system was established with C1R-B27 cells (B-lymphoblastoid cells with stable HLA-B27 expression) and the presence of autophagy in these cells were established with electron microscopy as well as by transfecting these cells with LC3-RFP followed by confocal microscopy. Autophagy was suppressed in C1R-B27 cells using 3-MA.
In both LPMC and C1R B27 cells, suppression of autophagy was demonstrated by RT-PCR of appropriate markers. Changes in MHC-I free heavy chain (FHC) expression were tested by HC10 staining and flow cytometry. Changes in UPR following inhibition were tested by XBP1 splicing assay and RT-PCR for BiP, CHOP, PERK, GADD34 and PDIA6.
Results. Electron and confocal microscopy demonstrated autophagy in C1R-B27 cells. Autophagy was in a dynamic state in the C1R cells as demonstrated by changes with rapamycin a stimulator of autophagy. Significant suppression of autophagy was achieved in both LPMCs and C1R-B27 cells. Following autophagy suppression there was significant increase in FHC expression in both C1R cells and LPMCs. I parallel we demonstrated increase in UPR markers in both LPMCs and C1R cells.
Conclusions. Autophagy and UPR regulate each other and perturbations of this fine balance can influence the pathogenesis of AS and IBD. Enhanced autophagy could mask the UPR responses in the gut of AS patients.

P163

MICROSCOPIC GUT INFLAMMATION IN SPA IS A PROGNOSTIC FACTOR FOR INITIATION OF ANTI-TNF THERAPY IN DAILY PRACTICE

Cypers H., Varkas G., Van Praet L., Van den Bosch F., Elewaut D.
Dept. of Rheumatology, Ghent University Hospital, Ghent, Belgium

Introduction. Microscopic gut inflammation is present in about 50% of patients with spondyloarthritis (SpA). Two types of inflammation are distinguished: an acute type resembling infectious enterocolitis, and a chronic type, with features of early Crohn's disease. Microscopic gut inflammation in SpA is associated with a risk of evolution to Crohn's disease and to ankylosing spondylitis (AS). However, we had so far no information on the impact of gut inflammation on therapeutic decision making in SpA.
Aim. To assess the association between microscopic gut inflammation in SpA, and the need for biologic therapy.
Methods. Sixty-three patients from the Ghent Inflammatory Arthritis and spoNdylitis cohorT (GIANT) with at least 18 months of clinical follow-up were included. The GIANT is a prospective observational cohort study, following patients with newly diagnosed axial or peripheral SpA, classified according to the ASAS criteria. Patients underwent an ileocolonoscopy at baseline to assess the presence of microscopic gut inflammation and were then followed every 6 months. None of the patients were on anti-TNF treatment at time of inclusion in the cohort. The decision to start anti-TNF therapy was made by the treating rheumatologist, who was unaware of gut histology.
Results. Gut histology was normal in 34 patients (54,0%), whereas microscopic gut inflammation was found in 29 (46,0%)(acute/chronic). After 18 months of follow up 25 (39,7%) patients had started anti-TNF therapy because of persistent high disease activity despite use of ≥2 NSAIDs. Only 9 out of 34 (26,5%) patients with normal gut histology had started anti-TNF therapy. In patients with gut inflammation at baseline, however, a significantly higher proportion (16/29 *i.e.* 55,2%; p=0,038) had started anti-TNF treatment, and this was irrespective of the type of inflammation. Higher CRP value and ASDAS at baseline were associated with initiation of anti-TNF therapy as well, but this is probably influenced by current reimbursement criteria. BASDAI at baseline was not significantly linked with start-up of anti-TNF therapy. There was no significant difference between axial or peripheral SpA, nor between AS and nr-axSpA.
Discussion. SpA patients with microscopic gut inflammation, an elevated CRP or an elevated ASDAS at baseline more rapidly needed anti-TNF therapy in daily clinical practice. As we previously could not demonstrate a link between CRP and microscopic gut inflammation, we anticipate that gut inflammation might be an independent prognostic factor for anti-TNF initiation.
Conclusion. This is the first analysis linking microscopic gut inflammation in SpA with therapeutic implications in daily clinical practice. These findings provide yet another argument for the hypothesis that gut inflammation drives disease severity in SpA.

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VALIDATION OF THE ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE (ASDAS) AND EFFECTIVENESS OF INFLIXIMAB IN THE TREATMENT OF ANKYLOSING SPONDYLITIS OVER 4 YEARS

Rahman P.[1], Choquette D.[3], Khraishi M.[1], Bensen W.G.[3], Shaikh S.A.[3], Sholter D.[4], Sheriff M.[5], Rampakakis E.[6], Sampalis J.S.[6], Nantel F.[7], Otawa S.[7], Lehman A.J.[7], Shawi M.[7]
[1]Memorial University of Newfoundland, St. John's, NL; [2]Institut de Rhumatologie de Montréal, Montreal, QC; [3]McMaster University, Hamilton, ON; [4]University of Alberta, Edmonton, AB; [5]Nanaimo Regional General Hospital, Nanaimo, BC; [6]JSS Medical Research, Montreal, QC; [7]Janssen Inc., Toronto, ON, Canada

Introduction. The objective of this study was to assess in routine clinical practice the 4-year outcomes in patients with AS treated with infliximab and the performance of ASDAS, a new disease activity measure in AS.
Methods. BioTRAC is an ongoing, prospective registry of rheumatology patients initiating treatment with infliximab. Descriptive statistics were produced at baseline and over four years. Within-group changes were assessed with the paired Student's t-test. Correlations with ASDAS were assessed with Pearson correlation coefficient or Spearman's rho.
Results. 230 AS patients enrolled between 2005 and 2012 were included, with a mean age of 45.7yrs and mean disease duration of 10.0yrs. At the time of enrollment, mean (SD) patient parameters were: CRP: 16.9(20.2) mg/L, ESR: 25.8(20.2) mm/hr, morning stiffness: 74.6(40.2) minutes, HAQ-DI: 1.20(0.61), MDGA: 6.6(1.9), BASDAI: 6.4(2.1), BASFI: 6.1(2.5), and ASDAS: 3.8(1.0).

Significant improvements (p<0.01) were observed in all outcome parameters over 48 months.
Similar significant changes were observed in ASDAS, BASDAI, and BASFI over time. A strong positive linear correlation between ASDAS and BASDAI (r=0.85; p<0.001) and BASFI (r=0.76; p<0.001) was observed. The correlation of MDGA was strong with ASDAS (rho=0.73; p<0.001) and BASDAI (rho=0.70; p<0.001) and moderate with BASFI (rho=0.64; p<0.001).
By 12, 24, 36, and 48 months 37%/49%/47%/50%, achieved ASDAS major improvement (Δ≥2.0), respectively. The proportion of patients with very high disease activity (ASDAS>3.5) decreased from 62.4% to 6.9% at 48 months.
Conclusions. The results of this study demonstrate that treatment with infliximab over four years is effective in reducing symptom severity and improving outcomes. The data confirmed the validity and sensitivity to change of the ASDAS score.

P165

INTRAARTICULAR INJECTIONS OF SI JOINT ARE EFFECTIVE IN AS PATIENTS OBJECTIVE

Lee S.W., Lee S., Kim T.H.
Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Ankylosing spondylitis is chronic inflammatory disease which involves axial skeleton. NSAIDs are drug of choice and biologics are strongly recommended in case of NSAIDs failure. But some AS patients have intermittent, migratory pain and inflammatory pain could last several days or weeks. Intraarticular injections of sacroiliac joints are recommended in these cases. The goal of this study was to analyze the effectiveness of a fluoroscopy-guided intraarticular corticosteroid injection for the treatment of sacroiliac joint pain in patients with AS.
Material and Methods. Between March 2012 and May 2014, a total of 43 fluorosopy-guided intraarticular corticosteroid injections in the sacroiliac joints were performed in 41 patients with ankylosing spondylitis (29 males, 12 females; mean age 31.5 years, range 12 to 66 years). The mixture of triamcinolone acetonide 40mg and normal saline 0.5 mL was injected under fluoroscopic guidance.
Results. The mean disease duration before injection was 27.1 months (range 0 to 151 months) and the mean follow-up after injection was 11.7 months (range 0 to 26 months). The mean BASDAI score before injection was 5.81 (range 2.3 to 8.5) and the mean BASDAI score after injection was 5.03 (range 1.0 to 9.2). No initiation of biologic agents and additional intervention was required in 28 out of 41 patients (68.3%). 2 out of 41 patients (4.9%) needed a second injection. 2 patients already was on biologic agents before injection, 11 patients newly started biologic agents after injection due to their high disease activity and lack of effectiveness of injection. There was neither discontinuity nor change of biologic agents. There was no bilateral injection and no complication associated with the procedure. There was no significant difference between dose of medications which is prescribed before and after injection.
Conclusion. When AS patients complain of abrupt and severe pain in their sacroiliac joint, rheumatologists can consider fluoroscopy-guided intraarticular corticosteroid injection as one of treatment options instead of starting biologic agents or dose escalation of medications.

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COMPARISONS OF RADIOGRAPHIC PROGRESSION OF ANKYLOSING SPONDYLITIS BETWEEN TREATMENT WITH TNF ANTAGONIST, CONTINUOUS TREATMENT WITH NSAID, AND ON DEMAND TREATMENT OF NSAID

Min H.K., Kang J.Y., Koh J.H., Jung S.M., Lee J., Kwok S.K., Ju J.J., Kim W.U., Park S.H.
Division of Rheumatology, Dept. of Internal Medicine, Seoul St. Mary's Hospital, Seoul, South Korea

Aim. We investigated radiographic progression of ankylosing spondylitis (AS) patients treated with TNF antagonist, continuous nonsteroidal anti-inflammatory drug (NSAID), and on demand treatment of NSAID.
Patients and Methods. This retrospective single-center study included 41 Korean AS patients who fulfilled the 1984 Modified New York criteria for AS or 2009 ASAS criteria for classification of spondyloarthritis from January 2006 to June 2014. Patients who had been checked lateral cervical and lumbar radiographs at baseline, after 4 years, and 8 years were included. Radiologic progressions were measured by calculating modified Stokes AS spinal score (mSASSS) and number of syndesmophytes. Oneway analysis of variance and Kruskal-wallis test were used for assessing comparisons.
Results. Patients in TNF antagonist (n=14), continuous NSAID (n=12), and on demand NSAID (n=15) did not show difference in baseline characteristics and radiologic status (mSASSS score and number of syndesmophyte). Laboratory datas of ESR were higher in TNF antagonist group when compared with continuous NSAID group and on demand NSAID group (TNF antagonist vs continuous NSAID; 41.36±32.696 vs 9.33±7.750, p=0.002, TNF antagonist vs on demand NSAID; 41.36±32.696 vs 16.67±17.381, p=0.013). Radiographic progressions measured by mSASSS and number of syndesmophytes were differed significantly between TNF antagonist group and continuous NSAID group at 8 years: 9.29±6.219 mSASSS change in TNF antagonist group versus 4.58±2.151 in continuous NSAID group (p=0.040), 2.79±2.940 syndesmophyte change in TNF antagonist group versus 0.50±0.674 in continuous NSAID group (p=0.038).
Conclusion. In our study, continuous NSAID treatment group showed less radiographic progressions of AS than TNF antagonist treatment group. Continuous NSAID usage may have superior effect on blocking the progression of new bone formation in AS, hence physicians may consider continuous NSAID treatment regardless of patient's symptoms.

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CLINICAL RESPONSE AND REMISSION IN PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS AFTER THREE YEARS OF ADALIMUMAB THERAPY

van der Heijde D.[1], Sieper J.[2], Baeten D.[3], Maksymowych W.[4], Xia Y.[5], Anderson J.[5], Pangan A.[5]
[1]Leiden University Medical Center, Leiden, The Netherlands; [2]Charité Universitätsmedizin Berlin, Berlin, Germany; [3]AMC/University of Amsterdam, Amsterdam, The Netherlands; [4]University of Alberta, Edmonton, Canada; [5]AbbVie, North Chicago, USA

Aim. To evaluate Year-3 long-term response/remission and durability of adalimumab response in patients with non-radiographic axial SpA (nr-axSpA).
Methods. ABILITY-1 was a phase-3, randomized, controlled trial in patients with nr-axSpA and inadequate response, intolerance, or contraindication to NSAIDs. A 12-week double-blind period of adalimumab every-other-week or placebo was followed by open-label adalimumab treatment. *Post hoc* analysis evaluated Year-3 efficacy/safety for the overall population and an MRI+/elevated CRP sub-population, patients with a positive baseline MRI (SPARCC score ≥2, SI joints or spine) or elevated baseline CRP. Remission was defined by ASDAS inactive-disease (ASDAS<1.3) or ASAS partial-remission.
Results. 122/185 (66%) of patients enrolled and 97/142 (68%) in the MRI+/elevated CRP sub-population had Year-3 data. Clinical responses and remission rates were sustained between Years 2–3. Through 412.2 patient-years (PYs) of adalimumab exposure, serious infection rate was 2.4 events/100-PYs, including 1 case of disseminated TB. There were 2 deaths – 1 suicide and another due to opiate toxicity. No malignancies were reported.
Conclusions. Almost half of the patients remaining on adalimumab therapy were in remission at study completion, measured by ASAS PR or ASDAS ID. Results were similar between the two study populations.

Table.

	Overall Population				MRI+/elevated CRP Sub-population			
	Year 2		Year 3		Year 2		Year 3	
%	NRI N=185	Observed Data N=138	NRI N=185	Observed Data N=122	NRI N=185	Observed Data N=107	NRI N=185	Observed Data N=97
ASAS20	61	81	55	83	62	82	58	86
ASAS40	48	64	44	66	50	66	47	69
ASAS-PR	28	39[a]	28	43[d]	32	44[f]	32	47[i]
BASDAI50	49	65	46	70	52	69	49	72
ASDAS-CII	49	69[b]	44	69[e]	56	77[g]	48	73[j]
ASDAS-MI	27	38[b]	25	40[e]	30	41[g]	27	42[j]
ASDAS-ID	34	46[c]	30	46[d]	36	49[h]	32	47[k]

[a]N:135; [b]N: 131; [c]N:136; [d]N: 120; [e]N: 118; [f]N: 104; [g]N: 103; [h]N: 105; [i]N: 96; [j]N: 93;[k]N: 95.

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NSAID USE IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH AND WITHOUT TNF-α BLOCKING THERAPY DURING 2-YEAR FOLLOW-UP

Carbo M.J.[1], Arends S.[1,2], Brouwer E.[1], Bos R.[2], Efde M.[2], Leijsma M.K.[1], Bootsma H.[1], van der Veer E.[3], Spoorenberg A.[1]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen; [2]Rheumatology, Medical Center Leeuwarden; [3]Laboratory Medicine, University Medical Center Groningen, The Netherlands

Introduction. Little is known about concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) during tumor necrosis factor-alpha (TNF-α) blocking therapy in patients with ankylosing spondylitis (AS).
Aim. To evaluate NSAID use in AS patients with and without TNF-α blocking therapy during 2-year follow-up in daily clinical practice.
Methods. This analysis is part of the GLAS cohort, a prospective observational cohort study. All patients fulfilled the modified New York criteria for AS (>90%) or the ASAS criteria for axial spondyloarthritis. Follow-up was performed according to a fixed protocol. The recently developed ASAS-NSAID index was calculated. Generalized estimating equations were used to compare NSAID use between patients with and without TNF-α blocking therapy during the first 2 years of follow-up.
Results. Of the 407 included patients, 66% were male, 75% HLA-B27 positive, mean age was 43 years (SD±12.6), and median symptom duration 15 years (range 1-59). These patient characteristics were comparable between patients with (n=270) and without (n=137) TNF-α blocking therapy. As expected, patients who started TNF-α blocking therapy had significantly higher disease activity at baseline. Disease activity was comparable between both groups after 6 to 24 months.
Of the 270 patients who started TNF-α blocking therapy, 79% used NSAIDs at baseline. This proportion decreased significantly during follow-up to 42% at 6 months and remained stable until 24 months. Of the 137 patients without TNF-α blocking therapy, 74% used NSAIDs at baseline and this proportion remained stable over time (77% at 24 months). The course of NSAID use over time was significantly different between patients with and without TNF-α blocking therapy (p<0.001). Comparable results were found for the ASAS-NSAID index.
Conclusion. In AS patients with TNF-α blocking therapy, concomitant NSAID use decreased significantly over time, whereas NSAID use remained stable in patients without TNF-α blocking therapy.
Acknowledgement. The GLAS cohort was supported by an unrestricted grant from Pfizer. Pfizer had no role in the design, conduct, interpretation, or publication of this study.

Table I. NSAID use over time in AS patients with (n=270) and without (n=137) TNF-α blocking therapy.

	Baseline	1.5 mo	3 mo	6 mo	12 mo	18 mo	24 mo
Patients with TNF-α blockers							
NSAID use	79% 207/261	58% 130/223	48% 111/231	42% 101/238	40% 93/232	36% 72/199	38% 81/211
ASAS-NSAID score	65 (17-100)	33 (0-67)	0 (0-50)	0 (0-50)	0 (0-50)	0 (0-25)	0 (0-50)
Patients without TNF-α blockers							
NSAID use	74% 94/127	-	-	78% 83/107	81% 90/111	81% 39/48	77% 44/57
ASAS-NSAID score	50 (0-100)	-	-	50 (5-100)	50 (5-100)	50 (0-73)	50 (0-100)

Results are presented as percentage and number of patients for NSAID use or median (interquartile range) for ASAS-NSAID score.

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SPINAL RADIOGRAPHIC PROGRESSION DURING LONG-TERM TNF-α BLOCKING THERAPY IN PATIENTS WITH ANKYLOSING SPONDYLITIS: RESULTS FROM THE GLAS COHORT

Maas F.[1], Spoorenberg A.[1,2], Brouwer E.[1], Bos R.[2], Efde M.[2], Chaudhry R.N.[1], Veeger N.J.G.M.[3], Bootsma H.[1], van der Veer E.[4], Arends S.[1,2]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen; [2]Rheumatology, Medical Center Leeuwarden; [3]Epidemiology, University Medical Center Groningen; [4]Laboratory Medicine, University Medical Center Groningen, The Netherlands

Objective. To prospectively investigate spinal radiographic progression up to 6 years of TNF-α blocking therapy in patients with ankylosing spondylitis (AS) in daily clinical practice.
Methods. Between November 2004 and December 2008, consecutive AS patients from the Groningen Leeuwarden AS (GLAS) cohort were included. Patients had available cervical and lumbar radiographs before start of TNF-α blocking therapy and after 2, 4, and/or 6 years of follow-up. Spinal radiographic progression was assessed by two independent readers using the modified Stoke AS Spine Score (mSASSS). TNF-α blocker compliance was based on the total duration of exposure to TNF-α blocking therapy. Generalized estimating equations were used to analyze spinal radiographic progression over time within subjects.
Results. In total, 105 AS patients were included: mean age 42±11 years, median symptom duration 16 years (range 1-47), 73% male, 82% HLA-B27 positive, and median baseline mSASSS 12 (range 0-70). Of the 105 patients, 62 (59%) had ≥1 syndesmophyte at baseline. These patients were significantly older, had longer symptom duration, and were more frequently male.
At group level, linear spinal radiographic progression was found with a mean progression rate of 1.32 mSASSS units every 2 years. Significantly more radiographic progression was found in patients with versus without syndesmophytes at baseline (mean 2.08 vs. 0.52 mSASSS units every 2 years, p<0.001). There was no correlation between radiographic progression and compliance to TNF-α blocking therapy (Spearman's rho <0.2).
Conclusion. This prospective longitudinal observational cohort study shows linear spinal radiographic progression at group level in AS patients who used up to 6 years of TNF-α blocking therapy in daily clinical practice. Patients with ≥1 syndesmophyte at baseline have a 4-fold higher progression rate compared to patients without syndesmophytes.
Acknowledgement. The GLAS cohort was supported by an unrestricted grant from Pfizer. Pfizer had no role in the design, conduct, interpretation, or publication of this study.

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DEVELOPMENT OF NEW RADIOGRAPHIC VERTEBRAL FRACTURES IN PATIENTS WITH ANKYLOSING SPONDYLITIS DURING 4 YEARS OF TNF-α BLOCKING THERAPY

Maas F.[1], Spoorenberg A.[1,2],Brouwer E.[1], Bos R.[2], Chaudhry R.N.[1], Wink F.[2], Bootsma H.[1], van der Veer E.[3], Arends S.[1,2]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen; [2]Rheumatology, Medical Center Leeuwarden; [3]Laboratory Medicine, University Medical Center Groningen, The Netherlands

Objectives. To determine the prevalence of radiographic vertebral fractures in patients with ankylosing spondylitis (AS) before start of TNF-α blocking therapy and to investigate the incidence of vertebral fractures after 4 years of follow-up.
Methods. Consecutive AS patients from the Groningen Leeuwarden AS (GLAS) cohort with available thoracic and lumbar radiographs at baseline and after 4 years of TNF-α blocking therapy were included. Vertebral fractures were assessed by two independent readers using the Genant method and were defined as ≥20% reduction in vertebral height (grade 1 (mild), 20-25% reduction; grade 2 (moderate), 25-40% reduction; grade 3 (severe), >40% reduction). Bone mineral density (BMD) was measured with DXA.
Results. 105 AS patients were included: 72% male, mean age 42±11 years, median symptom duration 16 years (range 1-47), and 83% HLA-B27 positive. In 27 (26%) of 105 patients, vertebral fractures were observed at baseline (average 1.7 fractures per patient). These patients were significantly older, had larger occiput-to-wall distance, and more spinal radiographic damage.
After 4 years of follow-up, 21 (20%) patients had new vertebral fractures. Most fractures were mild and occurred in the thoracic spine. Older age, higher BASFI, low lumbar spine BMD, use of anti-osteoporotic treatment, and presence of moderate vertebral fractures at baseline were significantly associated with the development of new fractures. Lumbar spine and hip BMD increased significantly during treatment. Patients with new vertebral fractures showed significantly less

improvement in lumbar spine BMD than patients without new fractures (median change in Z-score 0.4 vs. 0.8).
Conclusion. The prevalence of radiographic vertebral fractures was 26% in AS patients with active disease before start of TNF-α blocking therapy. Although a significant increase in BMD was found, 20% of patients developed new vertebral fractures during 4 years of TNF-α blocking therapy.
Acknowledgement. The GLAS cohort was supported by an unrestricted grant from Pfizer. Pfizer had no role in the design, conduct, interpretation, or publication of this study.

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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN AXIAL SPONDYLOARTHRITIS: A COCHRANE REVIEW

Kroon F.[1], van der Burg L.[1], Ramiro S.[2], Landewé R.[2], Buchbinder R.[3], van der Heijde D.[1]
[1]Rheumatology, Leiden University Medical Center, Leiden; [2]Rheumatology, Amsterdam Rheumatology Center, Amsterdam, The Netherlands; [3]Rheumatology, Cabrini Hospital, Malvern, Australia

Aim. We performed a Cochrane systematic review to assess the efficacy and safety of NSAIDs in axial SpA.
Methods. All published randomised controlled trials of NSAIDs in patients with axial SpA were included up to April 2014, without language restrictions. The comparisons were traditional NSAIDs versus placebo, COX-2 NSAIDs versus placebo, traditional NSAIDs versus COX-2 NSAIDs, NSAIDs in low versus high dose and NSAIDs versus NSAIDs. Multiple efficacy outcomes were analysed (e.g. pain, BASDAI, CRP, ASAS responses, among others).
Results. We found 41 studies, of which 31 studies (n=5317) could be included in quantitative data-analysis, with a duration of 2 to 26 weeks (median 12 weeks). In 5 RCTs (n=1165), comparing conventional NSAIDs versus placebo (duration 2 to 12 weeks), there was a consistent significant effect in all efficacy variables. There were not significantly more (serious or any) adverse events or withdrawals due to adverse events, except for more gastrointestinal adverse events in patients taking NSAIDs. We found similar results in the comparison COX-2 versus placebo. When comparing conventional NSAIDs to coxibs we found no difference in either efficacy or safety. In general we found no clear dose-effect on efficacy or safety. When comparing different NSAIDs to each other, no consistent difference in efficacy could be determined. However, 11 studies (n=1135) showed that indomethacin resulted in more adverse events than other NSAIDs, in particular neurological adverse events (9 studies, n=963), although there were not more withdrawals due to adverse events.
Conclusion. This Cochrane review shows good efficacy and safety of conventional NSAIDs and coxibs for the treatment of axial SpA in short term clinical trials with similar results across various drugs. We found no comparative studies for safety on the long term, and for a full safety profile in SpA one depends on studies in other rheumatic diseases or non-comparative cohort studies.

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LOW DOSAGE AND SHORT TERM PROGRAMMED RELEASED PREDNISONE TREATMENT OF SPONDYLITIS PATIENTS IS MORE EFFECTIVE IN ESTABLISHED AND VERY ACTIVE DISEASE AND IN ASSOCIATION WITH DMARDS

Bandinelli F.[1], Scazzariello F.[1], Pimenta da Fonseca E.[2], Piemonte G.[1], Benelli L.[1], Guidi F.[1], De Luca R.[1], Guiducci S.[1], Santiago M.B.[2], Matucci Cerinic M.[1]
[1]Division of Rheumatology, Dept. Experimental and Clinical Medicine, University of Florence, Italy; [2]Service of Rheumatology, Hospital Santa Isabel, Bahia, Brazil

Introduction. Low dose prednisone administered at night during the maximal peak of IL-6 and TNF-α seemed to be efficacious on early morning arthritis symptoms.
Aim. To Investigate the clinical efficacy of low dosage of modified released prednisone (MRP) (lodotra® 5 mg –Mundipharma Pharmaceuticals-) administered at 10 p.m, in Spondylitis (SpA) patients, naive of steroids, evaluated at three months, shared in different subgroups: early (<1 year) vs established disease, high (BASDAI>4/10) vs low active SpA, association with DMARDs vs monotherapy.
Material and Methods. 50 SpA patients diagnosed with ASAS criteria (19 male and 31 female, mean age and duration of disease 55 and 5,8 years, respectively) were treated with lodotra® 5 mg consecutively for three months. BASDAI (0-10), fatigue NRS (0-10), axial pain NRS (0-10), peripheral pain NRS (0-10), morning stiffness NRS (0-10) and duration (minutes) were compared between baseline and follow up.
Results. The MRP efficacy was significantly higher in established disease (BASDAI p=0,0002, fatigue p=0,0010, axial pain p=0,0177, peripheral pain p=0,0001, stiffness NRS p=0,0010 and duration p<0,0001) than in early SpA (morning stiffness NRS p=0,004 and duration p=0,003). In active SpA (fatigue p=0,0066, peripheral pain p=0,0008, stiffness NRS p=0,0025 and duration p=0, 0002) was significantly more efficient than in low active SpA (only in fatigue p=0,02 and stiffness NRS p=0,0208 and duration p=0,0002). In patients treated with association DMARDs-MRP, the results were more significant (BASDAI p=0,0014, fatigue NRS p=0,0089, axial pain NRS =0,0472, peripheral pain p=0,0103, stiffness NRS p=0,0159 and duration p=0,0003) than in monotherapy (only fatigue p=0,0255 and stiffness NRS p=0,0056 and duration p=0,0028).
Conclusions. In naive SpA patients, low dosage MRP treatment might reduce disease activity, pain, fatigue and morning stiffness, overall in established and active SpA and when DMARDs were associated.

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LONG-TERM EVALUATION OF NT-ProBNP LEVELS IN ANKYLOSING SPONDYLITIS PATIENTS UNDER TNF BLOCKERS

Russo D.T., Moraes J.C.B., Saad C.G.S., Ribeiro A.C.M., Schainberg C.G., Sampaio-Barros P.D., Gonçalves C.R., Bonfa E.
Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Introduction/Aim. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a strong marker of cardiovascular risk with recent evidence that inflammation control reduces its levels in ankylosing spondylitis (AS) patients under TNF blockers in short-term evaluation. There are no data regarding long-term NT-proBNP assessment in AS patients using TNF blockers. Therefore, we evaluated NT-proBNP in AS patients pre- and post- long-term TNF blockage therapy to determine if this association between NT-proBNP levels and inflammatory parameters persists in long-term follow-up.
Patients and Methods. Forty-eight consecutive AS patients without previous/current cardiovascular disease or systolic myocardial dysfunction, who were eligible to anti-TNF therapy, were prospectively enrolled. All patients received TNF blockers (infliximab, adalimumab and etanercept) and they were evaluated for circulating NT-proBNP levels, clinical and laboratory parameters of disease activity including BASDAI, ASDAS, ESR and CRP, traditional cardiovascular risk factors including blood pressure, body mass index, waist circumference and dyslipidemia and treatment data at baseline (BL), 12 (12M) and 24 months after (24M). Statistical analysis used significance level of 0.05.
Results. At BL, all patients had active AS, NT-proBNP levels had a median (IQR) of 23.5 (8-53.7) pg/ml and 6.2% were high in spite of no systolic alteration. Multiple linear regression analysis revealed that this peptide, at BL, was independently correlated with ESR (p=0.003) and pulse pressure (p=0.025). After 12M and 24M, all disease parameters improved and NT-proBNP levels were significantly reduced [19 (5-38) pg/mL and 14 (5-35) pg/mL respectively, p=0.011]. Patients that persist with high/very high disease activity after 24M also have higher NT-proBNP levels compared to patients with inactive or moderate active disease. No clinical cardiovascular event was observed during follow-up.
Conclusions. The reduction of NT-proBNP levels in AS patients treated with anti-TNF therapy persists in long-term evaluation and it appears to reflect an improvement in inflammatory status.
(ClinicalTrials.govnumber:NCT01072058).

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ARE PATIENTS WITH AS WILLING TO PAY FOR TREATMENT WITH INFLIXIMAB?

Webers C.[1], Essers I.[1], Van Tubergen A.[1], Braun J.[2], Heldmann F.[2], Baraliakos X.[2], Boonen A.[1]
[1]MUMC/CAPHRI, Maastricht, The Netherlands; [2]Rheumazentrum Ruhrgebiet, Herne, Germany

Introduction. In view of the increasing pressure of biological on healthcare budgets, it is worthwhile to assess the value of biologicals for patients using health economic outcomes. A Willingness To Pay (WTP) represents the patients' preference for health as a consequence of treatment in monetary terms.
Aim. To investigate the WTP of patients with AS for a treatment with infliximab and explore factors associated with WTP.
Methods. Data were used from the EASIC open label extension study of ASSERT and included 96 European patients with AS who received treatment with infliximab. Demographics, clinical data (including BASDAI, BASFI, BASMI, BAS-G and ASAS20 response) and data on WTP were collected at baseline of EASIC. WTP was assessed with a hypothetical question whether the patient would be willing to pay for beneficial effects they experience from the infliximab treatment and, if so, what amount the patient would be willing to pay per dose of infliximab. To investigate factors associated with WTP, a series of models were explored using a zero inflated negative binomial regression (ZINB) technique.
Results. Eighty-five patients completed the WTP. Average age was 39.6 years, 67 patients (78.8%) were male and 62 (72.9%) patients had achieved an ASAS20 response. Sixty-three patients (74.1%) were willing to pay for treatment with infliximab. The mean (median) [Interquartile Range (IQR)] amount they were willing to pay was 274.6 (100) [50-200] euro per dose. In the willing-to-pay group, significantly more patients had an ASAS20 response (79.4% vs 54.5%, *p*-value=0.02) In the multivariable ZINB analysis, ASAS20 response status was invariably associated with WTP as well as with the amount patients are willing to pay, while age was only associated with the amount patients were willing to pay.
Conclusion. 74% of patients with AS are willing to pay an out of pocket contribution for treatment with infliximab. Treatment response contributes to the preparedness as well as to the amount patients are willing to pay.

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ALLOGENEIC MESENCHYMAL STEM CELL TRANSPLANTATION IN REFRACTORY ANKYLOSING SPONDYLITIS: 24 WEEKS EXPERIENCE

Yang M.[1], Lv Q.[1], Li Q.[1], Wu X.[1], Xiang P.[2], Chen X.[2], Gu J.[1]
[1]Dept. of Rheumatology, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong; [2]Center for Stem Cell Biology and Tissue Engineering, Sun Yat-Sen University, Guangzhou, Guangdong, China

Aim. This study aimed to determine the efficacy and safety of allogeneic mesenchymal stem cells transplantation (MSCT) in refractory ankylosing spondylitis (AS).
Patients and Methods. Forty-two patients with persistently active AS who were refractory to standard treatment over 6 months were enrolled. Allogeneic mesenchymal stem cells were harvested and infused intravenously. They were divided into two groups randomly. Twenty patients received 1×10^5 cells/kg and twenty-two patients received 1×10^6 cells/kg at week0, week4, week 8, week 12. Patients were treated with regular doses of NSAIDS at the same time. Primary outcomes were ASAS 20, ASAS partial remission (ASAS PR), as well as transplantation related adverse events. Secondary outcomes included CRP and ESR, total back pain visual analog scale (VAS), nocturnal pain VAS, patient's global assessment of pain VAS, patient's global assessment of disease activity VAS, bath ankylosing spondylitis disease activity index (BASDAI), bath ankylosing spondylitis functional index (BASFI), bath ankylosing spondylitis global score (BAS-G), health assessment questionnaire for the spondylarthropathies (HAQ-S), ankylosing spondylitis quality of life (ASQoL).
Results. During the 24 weeks follow up, the overall rate of ASAS20 was 72.7% and 21.6% patients achieved ASAS PR. Low-dose treatment group had better outcomes. All patients had no recurrence and no transplantation related adverse event was observed. Disease activity declined as revealed by significant changes in BASDAI and BAS-G score, levels of CRP, ESR, and all VAS scores at week16. Improvement of functional ability and quality of life were revealed by BASFI, HAQ-S, ASQoL. Two treatment groups had similar reactions.
Conclusions. Allogeneic MSCT resulted in the achieving of response, partial remission and improvement in disease activity and functional ability in refractory AS patients. No transplantation-related adverse event was observed. Allogeneic MSCT is a safe treatment in refractory AS patients and the effectiveness needs to be clarified.

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DO PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS AND ANKYLOSING SPONDYLITIS RESPOND SIMILARLY WELL TO NSAIDS?

Baraliakos X., Kiltz U., Heldmann F., Braun J.
Rheumazentrum Herne, Germany

Introduction/Aim. Patients classified as axial spondyloarthritis may have AS or nr-axSpA. After an unsatisfactory response to at least 2 NSAIDs within 4 weeks, TNF-inhibitors are to be considered. However, it is unknown whether nr-axSpA and AS patients respond similarly well to NSAIDs and how many patients will be candidates for TNF-inhibitors.
Methods. Consecutive axSpA patients (n=50 nr-axSpA and n=50 AS) were prospectively included if BASDAI was ≥4, had not yet received the maximally approved NSAID dose and had not been treated with TNF-inhibitors. After inclusion the maximal dose of at least one NSAID was administered over 4wks. MRIs of the SIJ (STIR/T1 sequences) were scored by the Berlin score. Data were collected before (BL) and after 1 and 4 weeks of treatment.
Results. Significant differences between nr-axSpA vs. AS, respectively, were found in mean CRP (0.6±0.9 vs. 1.2±1.1 mg/dl) and MRI scores (3.1±3.0 vs. 6.7±5.4) ($p<0.001$) but not other baseline characteristics. After week-1 and week-4, both groups showed similarly increased NSAID-index and similar NSAID responses: at weeks 1 and 4, ASAS20% response was found in 40% (21% nr-axSpA and 19% AS) and in 52% patients (23% nr-axSpA and 29% AS), while ASAS partial remission was found only in 10% (4% nr-axSpA and 6% AS) and in 16% patients (7% nr-axSpA and 9% AS), respectively. However, 49% and 44% of all patients still had a BASDAI≥4 at weeks 1 and 4, and similar results were found for an ASDAS-CRP cut-off of ≥2.1, with 37% and 33% achieving this at weeks 1 and 4 (no differences between nr-axSpA and AS). There were almost no changes observed on CRP levels and MRI scores after 4 weeks.
Conclusions. Patients with nr-axSpA and AS show similar response rates to NSAID treatment. Although there was some improvement of ASAS response rates, 40-50% of patients with axSpA still showed BASDAI levels >4 after 4 weeks of intensive NSAID therapy and could be considered eligible for anti-TNF treatment. Bone marrow edema on MRI and CRP levels were not influenced by continuous NSAID treatment.

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DIFFERENT PERFORMANCE OF THE ASDAS AND BASDAI IN PATIENTS WITH AXSPA TREATED WITH NSAIDS – RESULTS FROM A PROSPECTIVE STUDY

Baraliakos X., Kiltz U., Heldmann F., Braun J.
Rheumazentrum Herne, Germany

Introduction/Aim. The ASAS/EULAR recommendations have established NSAIDs as first treatment choice for the management of axSpA. BASDAI and ASDAS are routinely used to assess disease activity in axSpA. A direct comparison between ASDAS and BASDAI in axSpA patients treated with NSAIDs has not been performed to date. In a prospective study, we compared the performance of BASDAI and ASDAS to identify candidates for anti-TNF therapy after 4 weeks of full-dose NSAID treatment.
Methods. Consecutive patients (n=50 nr-axSpA and n=50 AS) were prospectively included if BASDAI was ≥4, had not yet received the maximally approved NSAID dose and had not been treated with TNF-inhibitors. After inclusion the maximal dose of ≥1 NSAID was administered over 4 weeks. BASDAI and ASDAS were collected before (BL) and after 1 and 4 weeks of treatment.
Results. At BL, an ASDAS >2.1 was found in only 74% and 76% of AS and nr-axSpA patients, respectively. There was significant overall decrease at both timepoints in ASDAS (BL: 2.5±0.6, 1wk: 1.9±0.8, 4wk: 1.6±0.8) and BASDAI (BL: 5.8±1.3 1wk: 4.0±2.1 4wk: 3.8±2.1). At weeks 1 and 4, BASDAI<4 was found in 50% and 58% of AS and 52% and 54% of nr-axSpA patients, while an ASDAS<2.1 in 58% and 68% of AS and 68% and 66% of nr-axSpA patients, respectively. However, at week 4 a BASDAI ≥4 was still present in 44% axSpA patients but only 34% of them had an ASDAS <2.1. On the other hand, 33% had an ASDAS ≥2.1 and 12% of them had a BASDAI<4. This difference was similar in AS and nr-axSpA patients.
Conclusions. After 4 weeks of continuous NSAID treatment about 40% of axSpA patients were still eligible for anti-TNF therapy according to BASDAI levels. There is need to find out whether BASDAI or ASDAS are better cut-offs to initiate anti-TNF therapy, since there was quite some discrepancy, again in both groups, AS and nr-axSpA.

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PREDICTORS OF REMISSION IN AXIAL SPONDYLOARTHRITIS PATIENTS TREATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Furtado C.[1], Fernandes S.[1], Rodrigues A.M.[3], Martins F.M.[2], Miranda Rosa C.[1], Pereira da Silva J.A.[1], Vieira-Sousa E.[1]
[1]Rheumatology Dept., Hospital de Santa Maria, Lisbon; [2]Portuguese Society of Rheumatology, Lisbon; [3]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal

Introduction. First-line therapy for axial spondyloarthritis (axSpA) has not yet changed in the biologic era, and non-steroidal anti-inflammatory drugs (NSAIDs) are still considered the cornerstone treatment. The aim of this work was to identify predictors of remission in axSpA patients, treated exclusively with NSAIDs.
Patients and Methods. AxSpA patients treated exclusively with NSAIDs, registered at the Rheumatic Diseases Portuguese Register - Reuma.pt, were included. Demographic and clinical parameters of disease activity as well as NSAIDs therapy [category (nonselective versus selective), dose, duration, regime (continuous versus on-demand)] were analyzed. Ankylosing spondylitis disease activity score (ASDAS) inactive disease, at the last visit, was defined as remission (primary outcome).
Results. 50 patients fulfilling the Assessment in Spondyloarthritis (ASAS) classification criteria for axial SpA were included. This cohort had a mean age of 48.5±14.2 years, a mean disease duration of 20.7±13.4 years and a mean follow up of 19.5±17.3 months, with female predominance (58%). Peripheral involvement was documented in 22%, uveitis in 22% and enthesitis in 28% of patients. 60% were HLAB27 positive. The mean BASDAI (2.8±2.1; 2.2±1.7) BASFI (2.7±2.4; 2.6±2.4), CRP (0.7±1.0; 6±0.7mg/dl) and ASDAS (2.0±1.0; 1.7±0.9) on baseline and last available visits, respectively. All patients were exclusively treated with NSAIDs, approximately half on demand (52%) and 20% at maximum recommended doses. On the last visit 36% of patients showed inactive disease. On univariate analysis male gender, disease duration and baseline ASDAS were negatively associated with ASDAS inactive disease. On a multivariate analysis ASDAS at baseline was the only independent predictor of ASDAS inactive disease. The covariate considered were gender, age, disease duration, presence of sacroiliitis, HLAB27 and NSAIDs dose.
Conclusions. ASDAS at baseline was the only independent predictor of remission in axSpA patients treated exclusively with NSAIDs.

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OBSERVATIONAL STUDY OF SWITCHING ANTI-TNF AGENTS IN ANKYLOSING SPONDYLITIS: EFFECTIVENESS AND PREDICTORS

Saad C.G.S., Shimabuco A.Y., Ribeiro A.C.M., Moraes J.C.B., Sampaio-Barros P.D., Goldenstein-Schainberg C., Gonçalves C., Bonfa E.
Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, Brazil

Introduction/Aim. Anti-TNF agents are efficacious in the treatment of ankylosing spondylitis (AS). Sometimes switching to another may be useful due to lack of efficacy, side effects and loss of efficacy over time. The aim of this study was to analyze switching of anti-TNF in AS patients in a routine clinical care center.
Methods. Data from 117 AS anti-TNF naïve patients from an ongoing longitudinal observational study between June 2004 and August 2013 were included. Demographic and clinical parameters, disease activity and treatment responses were analyzed to characterize switching of TNF blockage.
Results. Of 117 included, 48 patients (41%) switched to a second and later 13 (11%) to a third anti-TNF. We excluded for the switch analysis patients that stopped any anti-TNF treatment course before 24 weeks. At baseline, compared to non-switchers, switchers had higher ASQoL (p=0.03) and were less previously treated with sulphasalazine (p=0.04). No difference was found in demographic data, disease duration or disease activity at baseline (p>0.05). The analysis of the same parameters at the time of second anti-TNF switch, a higher BASDAI (p=0.01) was observed in the group of patients that switched for the third anti-TNF treatment. The last visit of all patients that remained receiving biologic treatment showed that non-switchers achieved lower BASDAI (p=0.02), BASFI (p=0.02), ASQoL (p=0.04), ASDAS-CRP (p=0.001) and ASDAS-ESR (p=0.02) when compared to switchers. ASDAS remission at the final assessment was achieved more by no-switchers patients (62% vs. 35, p=0.02). The drug survival of the last anti-TNF treatment was similar in the three groups (p=0.24).
Conclusion. This study confirms that switching to a second or even a third anti-TNF can be effective and useful in AS, although overall effectiveness seems to be lower in switchers' patients.

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USTEKINUMAB EFFECTIVELY REDUCES ACTIVE INFLAMMATION AS DETECTED BY MAGNETIC RESONANCE IMAGING IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: RESULTS OF A 28-WEEK, PROSPECTIVE, OPEN-LABEL, PROOF-OF-CONCEPT STUDY (TOPAS)

Poddubnyy D.[1], Hermann K.G.[1], Callhoff J.[2], Listing J.[2], Sieper J.[1]
[1]Charité Universitätsmedizin Berlin; [2]German Rheumatism Research Center, Berlin, Germany

Introduction/Aim. The purpose of the current work was to investigate the impact of ustekinumab on active inflammation and post-inflammatory structural changes in the sacroiliac joints (SIJ) and in the spine as detected by magnetic resonance imaging in the TOPAS study.
Materials and Methods. In the TOPAS study, ustekinumab in a dose of 90 mg was administered subcutaneously at baseline, week 4 and week 16 in 20 patients with active AS. MRI of the SIJ and of the spine (STIR and T1-weighted sequences) was performed at baseline and at week 24. Images were scored according to the Berlin scoring systems for active inflammation and for chronic changes independently by two trained readers in a concealed and randomly selected order, blinded for all clinical data.
Results. Complete MRI sets (baseline and follow-up) were available in 17 patients (13 ASAS40 responders and 4 non-responders; in 3 ASAS40 non-responders no follow-up MRIs were available). There was a significant reduction of active inflammation on MRI at week 24 as compared to baseline both in the SIJ (osteitis change score -2.2±3.8 corresponding to 41% reduction) and in the spine (osteitis change score -1.2±2.3 corresponding to 31% reduction) – table. Reduction of active inflammation after 24 weeks was more prominent and statistically significant in patients with clinical response (ASAS40): osteitis change score in the SIJ was -3.1±3.8 in responders as compared to +0.6±1.3 in non-responders, p=0.015; similarly, osteitis change score in the spine was -1.9±1.9 in responders as compared to +1.0±2.4 in non-responders, p=0.023. There were no substantial changes in the scores for post-inflammatory lesions including fatty lesions in the entire group – table.
Conclusions. Ustekinumab effectively reduced active inflammation in the axial skeleton as detected by MRI in patients with AS after 24 weeks of treatment. There was a clear correlation between clinical and MRI responses. Higher level of active inflammation at baseline was associated with good clinical response.

Table. Changes in MRI scores over 24 weeks in patients with active AS (n=17) treated with ustekinumab.

Parameter	Baseline	Week 24	p-value
SIJ osteitis score (0-24)	5.4±4.9	3.2±3.4	0.026
SIJ fatty lesion score (0-24)	11.9±7.1	12.2±7.2	0.2
SIJ erosion score (0-6)	4.0±2.4	4.1±2.3	0.3
SIJ sclerosis score (0-2)	1.2±0.6	1.2±0.6	1.0
SIJ ankylosis score (0-2)	0.4±0.8	0.4±0.8	0.3
Spine osteitis score (0-69)	4.1±3.6	2.8±3.0	0.041
Spine fatty lesion score (0-69)	5.9±4.8	6.2±4.3	0.2
Spine erosion score (0-46)	0.5±1.1	0.5±1.1	1.0
Spine bone proliferation score (0-69)	2.6±5.9	2.7±5.8	0.3

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INFLIXIMAB INDUCED SUBACUTE CUTANEUS LUPUS-LIKE SYNDROME IN PATIENT WITH ANKYLOSING SPONDYLITIS

Dai K., Holc I.
University Clinical Center, Maribor, Slovenia

Background. A TNF alpha antagonist-induced lupus-like syndrome (TAILS) has been reported with the use of adalimumab, etanercept, golimumab and most frequently, infliximab, in patients with rheumatic diseases, including ankylosing spondylitis.
Materials and Methods. We present a 42-year-old Caucasian man with ankylosing spondylitis who presented with a malar rash nine months after the initiation of infliximab therapy. His skin biopsy was consistent with systemic lupus erythematousus. Laboratory investigation revealed a positive serum anti-nuclear antibody (ANA, H+, 1: 640 titer) and a positive anti- double-stranded (ds) DNA antibody(1: 320 titer). Anti-Sjoegren's syndrome A (SSA)/Ro, anti-Sjoegren's syndrome B (SSB)/La, anti-ribonuclear protein (RNP) and anti-Smith (SM) antibodies were negative. Anti-histone antibodies were not tested.
Topical corticosteroid ointment was applied twice daily to the lesions of the face. Infliximab was discontinued. Patient was subsequently transitioned to adalimumab, which successfully controlled his ankylosing spondylitis for more than four years now without recurrence of lupus symptoms and with the disappearance of ANA antibody.
Results. Treatment of TAILS can include discontinuation of the offending drug, corticosteroids, immunosuppressives, and hydroxychloroquine sulfate. However, there are only few case reports of ankylosing spondylitis patients with TAILS who have continued therapy with an alternative TNF alpha antagonist without recurrence of lupus symptoms.
Conclusions. Ankylosing spondylitis patients who develop TAILS after treatment with one TNF alpha antagonist can be successfully treated with an alternative TNF alpha antagonist.

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INFLUENCE OF TNF BLOCKER ON RADIOGRAPHIC DAMAGE IN ANKYLOSING SPONDYLITIS: OSKAR DATA

Kim T.J.[1], Joo K.B.[2], Lee S.[2], Shin J.H.[3], Kim T.H.[3]
[1]Dept. of Rheumatology, Chonnam National University Hospital; [2]Dept. of Radiology; [3]Dept. of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, South Korea

Aim. To evaluate the influence of tumor necrosis factor (TNF) blocker on radiographic damage in ankylosing spondylitis (AS).
Methods. A total of 598 AS patients from the Observation Study of Korean spondyloArthropathy Registry (OSKAR) data were recruited for this study. The subjects were stratified in relation to the using state of TNF blocker. We evaluated collected clinical and radiographic parameters at two different time points. Then we compared radiographic progression between groups. Univariable and multivariable regression analyses were done after adjusting for potential confounding factors.
Results. 45.3% (271 patients) had received TNF blockers. The mean mSASSS unit (SEM) at baseline was not significantly different between groups (TNF blocker naïve 16.40±0.88 vs TNF blocker user 19.16±1.12, p=0.054). Patients treated with TNF blockers had a higher CRP level (2.52±0.19 vs 1.59±0.10, p<0.01) and longer disease duration (11.70±0.45 vs 8.40±0.37, p<0.01) at baseline. On simple analysis, the TNF blocker naïve patients had less radiographic progression than those with TNF blocker (2.21±0.54 vs 4.48±0.80, p=0.020). However, after adjustment for multiple comparisons by the Bonferroni correction, the radiographic progression between groups was no significant difference (OR 0.87, [95% CI 0.42-1.81], p=0.71). Furthermore, we stratified groups according to the proportion of disease duration exposed to TNF inhibitor (0%, <25%, 25-50 %, ≥50). On simple analysis, there was a significant difference in the rate of progression in patients who continued the medication for ≥50% of their disease duration as compared to the naive patients (7.53±1.41 vs 2.21±0.54, p=0.028). However, there was no difference of radiographic progression between groups (7.61±1.99 vs 2.83±0.79, p=0.18)
Conclusion. Treatment with TNF inhibitors has no influence on radiographic progression in AS.

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