Seventh International Congress on Spondyloarthropathies

October 7-9, 2010
Gent, Belgium

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Abstracts

Opening Talks

INV 1

PLASTICITY OF TH 17 T CELLS: IMPLICATIONS FOR HUMAN DISEASE

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CD4+ T cells are critical for host defense but are also major drivers of immune-mediated disease. It has long been apparent that these T cells specialize to become distinct subsets and produce restricted patterns of cytokines, which are tailored to combat various microbial pathogens. Recently though, many new fates for CD4+ T cells have become apparent. In addition to the classical Th1 and Th2 subsets, regulatory T cells and Th17 cells are now recognized as important players in the pathogenesis of autoimmunity. In addition though, cells that produce IL-9, IL-21 (follicular helper T cells) and IL-22 have also been recognized. Although classically viewed as distinct lineages, recent work calls into question whether helper CD4+ T cell subsets are more appropriately viewed as terminally differentiated cells or flexible stages in development. The transcriptional and epigenetic factors that contribute to helper CD4+ T cell commitment and plasticity will be discussed, as will the therapeutic implications.

INV 2

ABNORMAL BONE FORMATION IN ANKYLOSING SPONDYLITIS: WHAT CAN WE LEARN FROM ACVR1 AND FIBRODYSPLASIA OSSIFICANS PROGRESSIVA?

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Ankylosing spondylitis (AS) is a complex disorder with a contribution from in excess of a dozen genes. Most research to date has concentrated on the inflammatory component of the condition, latterly on the important contribution apparently coming from the Th17 lymphocyte pathway. However, it is clear that factors causing abnormal bone formation are also highly relevant albeit rather poorly understood. There are even suggestions that aggressive control of inflammation using anti TNF drugs may not have quite the expected effect on suppressing enthesopathic new bone formation in AS that might have been predicted. In this review we review the physiological regulation of bone formation and resorption and describe some of the rare genetic disorders that cause uncoupling of these processes, resulting in a range of phenotypes with excess bone or osteopenia. One of these, fibrodysplasia ossificans progressiva (FOP), provides an interesting example of how knowledge of the underlying genetic abnormality has informed new treatment approaches, with potentially important implications for our approach to the spondyloarthropathies. FOP is an autosomal dominant disorder with a particularly nasty phenotype, which is fortunately very rare (~1 in a million live births). It is characterized by episodic inflammation and abnormal ossification of the muscles and related soft tissues that may eventually lead to a statuesque appearance in the affected individual. Study of FOP has generated insights into the ways in which abnormal bone formation may be initiated but also prospects for how this may potentially be rectified using small molecule inhibitors of anabolic bone pathways. FOP can be diagnosed at birth by the developmental patterning defects that are apparent in the abnormally short, monophalangic great toes and failure of development of the zygoapophyseal joints in the cervical spine. Subsequently, throughout childhood and adolescence, recurrent episodes of myositis occur, leading to the progressive formation of an "exoskeleton" as new bone forms in the inflamed muscles and associated soft tissues. By the end of the second decade the affected individual is typically severely disabled with movement of the spine and proximal joints greatly restricted by new bone bridging the joints. A global effort in 2006 led to the mapping of the mutant locus in 5 families to a region on chromosome 2 (2q23-24) containing the candidate gene *ACVR1*, (activin A type 1 receptor), a receptor for bone morphogenetic protein (BMP). Subsequent analysis of the structure/ function relationships of the protein have given realistic possibilities of developing new forms of treatment for FOP and important lessons for other disorders including AS about how knowledge of the genetic basis of the disease can potentially be translated into therapies. ACVR1 is a type I BMP receptor which belongs to the extensive TGF-β superfamily. Mutations in ACVR1 result in aberrant signaling and the symptomatic dysregulation of bone growth in FOP. The receptor consists of an extracellular ligand-binding domain coupled via a transmembrane region to an internal kinase domain.

Type I receptors work in a concerted activation cycle along with type II receptors to transduce extracellular signals across the cell membrane. Upon activation, the receptor complex triggers an intracellular signaling cascade, via downstream SMADs, that ultimately results in the regulation of target genes. In recent years, advances have been made in understanding the function of this class of receptors with the aid of crystallographic studies. The structural aspects of the internal domains of ACVR1 have been elucidated in high resolution. This structure provides an opportunity to correlate specific gene mutations in individual FOP patients, and their resulting protein changes, to alterations in receptor structure and function. Aside from the common *ACVR1* mutation that affects about 90% of individuals with FOP (617g→a), a number of other mutations have been reported in FOP, all within the *ACVR1* gene. Intriguingly, these mutations cluster at various sites of functional importance. These mutations can be mapped to the structure of ACVR1 in an attempt to determine their likely outcome regarding altered signaling. By applying this analysis, regions such as the *GS regulatory loop* of ACVR1 are crucially implicated in having abnormal functionality in FOP. These mutations can be related to differences in the severity of FOP as exemplified by various individual case studies.

Armed with the structural knowledge and functional implications of ACVR1 mutations, it has proved possible to screen libraries of potential inhibitors to identify new classes of targeted drugs for therapeutic applications. The compound, dorsomorphin, was identified in this way, paving the way for the use of this or other related compounds in clinical trials. This paradigm may also be applied to the study of complex diseases with a polygenic component, like AS, potentially generating an array of new targets for pharmacologic manipulation.

Invited Lectures

INV 3

THE RELATIONSHIP BETWEEN VERTEBRAL INFLAMMATION AND SYNDESMOPHYTES IN ANKYLOSING SPONDYLITIS

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Demonstration of an association between inflammation and spinal ankylosis has been challenging, despite such a link seeming intuitive as ankylosis is only observed in spinal locations that are also sites of inflammation. Until the advent of MRI prospective study was not possible due to inaccessibility of tissue. Recent prospective studies that have noninvasively assessed spinal inflammation using MRI generally support a link between inflammation and ankylosis. MRI allows direct visualization of inflammation at vertebral corners as detected by increased free water signal on the STIR sequence.
Four reports have now described an association between the presence of bone edema at vertebral corners on MRI and the subsequent development of syndesmophytes at the corresponding vertebral corners on plain radiography after 2 years of follow-up. These reports focused on patients who were recruited to trials of anti-TNF therapy, but one report also described similar findings in an observational cohort of patients receiving both anti-TNF and standard therapies. All reports have also highlighted the development of new syndesmophytes where both the baseline plain radiograph and the baseline MRI show a completely normal vertebra. It is important to point out that this 'normal' appearance at baseline does not exclude the presence of inflammation, as MRI has limited sensitivity for detection of spinal inflammation that is clearly evident on histopathology. There are also crucial methodological challenges to this approach. Plain radiographic assessment is limited to the anterior corners of the cervical and lumbar spine. Because inflammatory lesions at vertebral corners are often small and/or demonstrate only a slight alteration in signal intensity on STIR sequences, reliable assessment of lesions in the cervical spine is particularly difficult due to the small size of the vertebrae when the spine is depicted in two halves, cervico-thoracic and thoraco-lumbar, as is now standard for imaging protocols in SpA. In addition, phase encoding artefact constitutes a significant limitation to the reliable assessment of lesions in the anterior vertebral corners of the lumbar spine. Specifically, MRI is subject to physiological motion artefact so that flowing blood in the inferior vena cava and the abdominal aorta may cause spurious signal that mimics anterior vertebral corner inflammatory lesions in the lumbar spine. Consequently, the focus on the assessment of lesions that are concordantly detected by two readers assessing MRI scans independently is a methodologically essential requirement of studies using MRI to detect these lesions. Follow-up MRI evaluation in two independent studies has also shown that inflammatory lesions which completely resolve on follow-up MRI after anti-TNF therapy are more prone to develop into syndesmophytes as compared to persistent inflammatory lesions. This appears contradictory with data from phase III trials of anti-TNF therapy which have not demonstrated any overall difference in radiographic progression as compared to historical controls receiving standard therapy. Lesions in AS evolve from early inflammatory lesions with features of subchondral marrow inflammation followed by reparative processes that may become autonomous and excessive leading to new bone formation. Lesions at all these stages of evolution are often present simultaneously in the individual patient with established AS who is characteristic of patients recruited to phase III trials of anti-TNF therapy. It may be possible that very early inflammatory lesions resolve completely without any sequelae if anti-TNF therapy is introduced before new bone formation becomes largely autonomous. On the other hand, once a lesion has become more advanced and crossed a certain "threshold" of maturation, introduction of anti-TNF may alleviate inflammation but may promote new bone formation. For an individual patient the overall development of new bone during anti-TNF therapy may therefore depend on the balance between the number of early and more mature inflammatory lesions. An example of a more advanced inflammatory lesion on MRI is the "dimorphic" vertebral corner inflammatory lesions where the inflammatory signal at the vertebral corner on the STIR sequence does not itself extend all the way to the corner as in a typical "Romanus" inflammatory lesion but surrounds an area of decreased signal intensity which, on T1 weighted images, may be due to fat infiltration or bone sclerosis. Clinical trials of anti-TNF agents in early SpA together with prospective MRI studies will therefore allow more detailed testing of this hypothesis as a major priority for the research agenda in SpA.

INV 4

THE WNT PATHWAY AND STRUCTURAL REMODELING IN SPONDYLARTHRITIS

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Two major pathophysiological processes dominate the clinical picture of ankylosing spondylitis: One is the inflammation of distinct anatomical structures of the spine and the other is bony overgrowth.
Syndesmophyte formation and ankylosis preferentially affect those sites of the skeleton, which are also affected by inflammation. The spatial association between inflammatory changes in the spine and bony overgrowth is however by far not complete and much less pronounced than in rheumatoid arthritis. Although the prerequisites for induction of bone overgrowth remain to be identified, inflammation and appropriate resolution of inflammation appear to be important triggers to induce this mesenchymal tissue response. In contrast to rheumatoid arthritis, where bone changes are considered as „damage", the structural changes in ankylosing spondylitis are more considered a tissue response than damage. Aside prostaglandins, transforming growth factor beta and bone morphogenic proteins, Wnt proteins are currently considered as the key effector molecules of bony overgrowth. Wnt molecules stimulate the differentiation of osteoblasts and also facilitate endochondral bone formation, which involves the formation of hypertrophic chondrocytes, which are then transformed into bone and a bony spur. Natural inhibitors of these Wnt proteins can block bone formation by antagonizing the anabolic function of Wnt proteins. Dickkopf (Dkk)-1 as well as sclerostin are potent inhibitors of the Wnt pathway which competitively inhibit the assembly of Wnt proteins with their receptors and co-receptors. Expression of Dkk-1 and sclerostin as well as their serum concentrations are tightly linked, partly because Dkk-1 induces sclerostin expression. In ankylosing spondylitis the expression of Dkk-1 and sclerostin is low, which facilitates bone formation. Indeed those patients with the lowest levels of Dkk-1 and sclerostin show the most enhanced progression of bony overgrowth. Experimentally, blockade of Dkk-1 as well as sclerostin leads to bony overgrowth and ankylosis of joints, particularly also of the axial joints. This process is mediated by endochondral ossification. The factors leading a down regulation of Dkk-1 and sclerostin in ankylosing spondylitis are poorly defined but may not be identical to classical proinflammatory cytokines such as TNF as they typically increase the expression of these molecules. Nonetheless, analysis of he expression of Wnt antagonists may not only help to identify those patients at high risk for bone overgrowth but may also substantially increase our knowledge on the pathomechanism of bone formation in ankylosing spondylitis.

INV 5

BMPS AND ABERRANT BONE FORMATION IN SPONDYLOARTHRITIS

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Bone morphogenetic proteins (BMPs) are members of the transforming growth factor beta superfamily and have pleiotropic effects on different cells. Different BMPs can induce a cascade of ectopic endochondral bone formation. We have demonstrated that BMP signaling is activated in different types of human chronic arthritis, including the spondyloarthritides. Moreover, in a mouse model of peripheral joint ankylosis, inhibition of BMP signaling prevents and treats the development of new cartilage and bone formation. Activation of the BMP – Smad signaling cascade is associated with early chondrogenic differentiation of entheseal progenitor cells. Inhibition of the alternative p38 MAPK signaling system may result in increased severity of disease.
BMPs can also be linked to the development of an inflammatory cascade in the enthesis as they can upregulate different chemokines from mesenchymal cells types in vitro. In addition, BMP signaling is modulated by biomechanical stress and by proinflammatory cytokines such as TNF thereby generating a positive feedback loop that is likely involved in both new bone formation and chronic inflammation. BMP signaling has also been associated with genetic disorders characterized by new bone formation and joint ankylosis. In addition, recent studies suggest that some BMPs in the serum of patients with ankylosing spondylitis can be considered as biomarkers for severity of disease and structural damage.

INV 6

ULTRASONOGRAPHY FOR VISUALIZING THE ENTHESIS

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The importance of peripheral entheses involvement among spondylarthritis (SpA) manifestations has been emphasized by several authors and is best reflected by its inclusion as a classification criterion for SpA diagnosis. However, peripheral enthesitis is commonly mistaken for other pathologies and most certainly under diagnosed during the course of SpA (1). Over the last years, uyltrasonography (US) has been recognized as a highly sensitive and non invasive tool, especially to assess tendon and joint involvement. Several studies have described in grey-scale the US aspect of lower limbs enthesitis in SpA, revealing the high frequency of asymptomatic US abnormal findings (2,3). More recently the capacity of power Doppler to detect inflammation of musculoskeletal tissues such as synovial membrane was reported. Recently has been demonstrated that the use of power Doppler permits to distinguish between enthesis involvement in SpA patients and controls (affected by rheumatoid arthritis, degenerative spinal disease or healthy subjects) (4-7). The landmark of US enthesitis in SpA patients seems the presence of abnormal vascularization of entheses insertion, which is independent of disease phenotype (i.e. axial vs peripheral). Several scoring system have been published until now, some of them combined grey-scale and Doppler (PDUS) for grading lesions. It is also well established that the performance of power Doppler could be influenced by the examiner, the machine, and acoustical conditions involved in image processing. In order to answer to these problems, the OMERACT US task force created in 2004 has decided to focus their attention on obtaining an international consensus on definition and scoring enthesitis in SpA by using a recently developed stepwise approach (7). A complete overview of PDUS lesions, scoring system, application and future development will be discussed.

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INV 7

QUANTITATIVE MR IMAGING IN SPA

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Quantification of abnormalities in SpA using MRI has to date principally found application in the assessment of disease activity in clinical trials. Formal methods for quantifying disease activity in the sacroiliac joints can be generally categorized as being primarily based on either a global scheme that focuses on the single most severely affected semi-coronal image or on a more detailed method that scores several consecutive semicoronal images that depict the synovial portion of the sacroiliac joint.

The presence and extent of bone marrow edema in the synovial portion of the joint is the primary MRI feature that is scored. Anatomical orientation and interpretation of abnormalities is greatly facilitated by simultaneously viewing T1-weighted images whilst scoring edema on the STIR images. In the SPARCC method, each sacroiliac joint is divided into quadrants and the presence of marrow edema in each quadrant is scored on a dichotomous basis with additional weighting for intensity and depth. One method also scores inflammation in the joint space and the ligamentous portion of the joint. Most approaches require T1-weighted and STIR sequences although one method additionally requires Gd-augmentation. ASAS/OMERACT conducted a multi-reader exercise evaluating the different scoring methods for reliability and sensitivity to change according to the requirements of the OMERACT filter. Agreement between readers and sensitivity to change was somewhat better for the more detailed SPARCC scoring method. This approach to scoring inflammation in the sacroiliac joints is to date the only method shown to discriminate between treatment groups in a randomized placebo-controlled trial.

A significant effect of active treatment with adalimumab on sacroiliac joint inflammation was demonstrated despite the frequent presence of chronic changes in patients with long-standing disease.

Systematic evaluation of the sacroiliac joints and the use of an online training module (www.arthritisdoctor.ca) have been shown to enhance reliability. Several methods have recently been described for scoring chronic changes in the sacroiliac joints. Validation will be the subject of a forthcoming OMERACT/ASAS initiative. Two primary approaches have been validated for the quantification of the extent of inflammation in the spine for the purposes of evaluation of new therapeutics in clinical trials. Both are based on the assessment of a discovertebral unit (DVU) which represents the region between two imaginary lines drawn through the middle of two adjacent vertebrae. The first method, the ASspiMRI-a (AS spinal MRI activity) index, scores the severity of bone edema and erosions at each DVU according to a 0 to 6 scoring scheme with higher values being assigned to the presence of erosions. The score for edema is based on the total area involved in the DVU according to a <25%, 25-50%, and >50% grading scheme. The Berlin method does not score erosions but otherwise is the same as ASspiMRI-a. For both methods all 23 DVUs in the spine are scored in a single sagittal plane. This approach has been shown to be reproducible and to discriminate between treatment groups in trials of anti-TNF therapies. The second method, the SPARCC MRI spinal inflammation index, takes advantage of the ability of MRI to visualize lesions in three dimensions and scores a maximum of 6 of the most severely affected DVU for the purposes of clinical trials. Since inflammatory lesions observed on MRI are often asymmetrical there are theoretical advantages to using a scoring method that systematically assesses lesions in several dimensions.

The rationale for the choice of 6 affected DVU is based on data that shows that the mean number of affected DVU in patients with AS is 3.2. However, this method has also been validated for scoring all 23 DVU where discrimination appears comparable to a more limited assessment of 6DVU. In the SPARCC method each DVU is divided into quadrants with bone edema in each quadrant being scored on a dichotomous basis as being present or absent with additional weighting for intensity and depth.

Lesions in each affected DVU are scored in 3 consecutive sagittal slices so that the extent of the lesion can be defined in both the coronal and the sagittal planes and also in the lateral segments of the spine which may be important for assessing inflammation in the thoracic spine. Recent work has shown that a major portion of spinal inflammation in the thoracic spine occurs in the lateral segments involving the costovertebral and costotransverse joints. A validation exercise has been conducted by ASAS/OMERACT using multiple readers to determine which method performs best with respect to feasibility and ability to discriminate between active and control therapies. Both scoring methods demonstrated high responsiveness after administration of anti-TNFα therapies although the SPARCC method was consistently more reproducible, particularly when evaluated by neutral observers with limited experience in either method. One method has been reported for scoring chronic changes in the spine, the ASspi-MRI-c, which analyzes sclerosis, squaring, syndesmophytes, and fusion in all 23 DVU. Inter-reader reliability was poor. Furthermore, a comparative study showed that this approach offered no advantages over plain imaging in the detection and scoring of chronic lesions in the spine.

There are no comparative reports for CT imaging. Further study is necessary before any conclusions can be drawn regarding the value of MRI in quantification of chronic lesions.

INV 8

CURRENT STATUS AND FUTURE PROSPECTS FOR BIOLOGICS THERAPY OF SPA

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The treatment of spondyloarthritis has dramatically changed over the past 10 years by the introduction of TNF-blocking drugs. It is especially patients with ankylosing spondylitis (AS) that have benefited from these treatments. Lately we have seen trials with TNF-blocking agents in patients with SpA who do not (yet) meet the criteria for AS, and it looks as if such a policy is effective as well. But it is not only the treatment of SpA that has been changed. We have also seen important developments in the concept of SpA, in that SpA has been redefined. We now talk about axial SpA and peripheral SpA, and such a redefinition may have important implications for the application of biologics. Another interesting area with potential treatment implications is the current thinking about syndesmophyte formation. Against all odds, anti-TNF-therapy appeared not to inhibit the formation of syndesmophytes whilst clinical efficacy was beyond argumentation. We now start to learn about how syndesmophyte formation should be explained, and which processes play a role. The more we understand about syndesmophyte formation, the better we can target particular processes and potentially interfere. In this lecture I will discuss the current status of biologics therapy in SpA as well as a number of recent developments in the field of SpA with potential implications for the treatment of SpA.

INV 9

TREATMENT OF EARLY AXIAL SPONDYLOARTHRITIS INCLUDING ANKYLOSING SPONDYLITIS

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The ASAS classification critieria for axial spondyloarthritis (axSpA) and the modified New York criteria for ankylosing spondylitis (AS) are today the basis for most but not all clinical trials on the treatment of patients with SpA who have inflammatory or just chronic back pain as their predominant symptom.
Several years ago, two small open trials on undifferentiated SpA with both, patients with predominat axial or peripheral symptoms have reported favourable clinical results. Since some of the major trials have been performed before the new classification criteria have been published, different criteria have been used, other criteria sets have been used to include patients. Main differences between the trials are the age and disease duration of the patients, and whether a positive finding by magnetic resonance imaging (MRI) and HLA B27 are obligatory for inclusion. Other inclusion criteria are rather similar to the main AS trials. In the future the ASAS classification criteria will be used to obtain an approval for the indication 'axial SpA' by authorities. There are mainly three trials which need to be discussed in which the 3 biologics that were first approved for AS were tested in 'early' disease: adalimumab, infliximab and etanercept. According to the prediction models published age, disease duration, function and structural damage at baseline, C-reactive protein (CRP) and MRI results of AS patients predicts a major response to treatment. Thus, it was not surprising that all trials reported rather positive clinical ASAS and MRI responses. However, the by far best result reported so far is the partial remission rate of 56% after 16 weeks in the infliximab trial – the trial that most probably managed to include patients with a high likelihood to proceed to structural changes in the sacroiliac joints and the spine (AS). Indeed these patients had a mean age of 28 years, were HLA B27+ and had proven sacroiliac inflammation by MRI. Because of the design of the study we will not learn from further results whether it was possible to prevent structural damage to occur in this really early patient group. Since the mean age in the two other trials was > 30 years, we need to be reminded that not all patients with 'non-radiographic' axial (u)SpA will develop AS. Thus, there at least two subgroups among these early patients based on the potential to either develop structural changes rather rapidly within the next years (probably spreading later to the spine) or to have a comparatively benign course regarding damage and develop structural changes rather late (>10 years) or never. The latter may be especially relevant for female patients who are known to have a much lower likelihood to develop syndesmophytes and ankylosis. Taken together, the main challenge for clinical trials with biologic agents in the future is (i) to include very early axial SpA patients and (ii) to concentrate on the development of structural changes in the sacroiliac joints and the spine.

INV 10

LONG-TERM OUTCOME OF ANTI-TNF THERAPY

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Active ankylosing spondylitis patients have shown a very good efficacy when treated with TNF-blockers: a BASDAI 50 or an ASAS 40 response can be achieved in about 50% of patients. More and more long-term data have become available now up to 8-10 years from the extension phases of clinical trials and from registries. The drug survival rate is generally good with about 15% of patients discontinuing treatment every year. There is no single reason for drug discontinuation sticking out.
Treatment is stopped because of side effects, inefficacy, or low compliance of the patients. No new side effects, which differ from the first year of treatment, were observed over the years. In patients remaining on the drug even a small increase of improvement, including BASDAI, BASFI and BASMI, can be observed over the years. There is also a further reduction of the acute subchondral bone marrow inflammation as shown by MRI when patients are treated long-term. However, not all of the patients become completely free of inflammation on MRI. But TNF-blockers did not inhibit new bone formation in the spine, as seen by x-rays, over a 2 year treatment period. It remains to be seen whether such an effect occurs if patients are treated longer. If patients are treated with TNF-blockers the rate of uveitis flares is also reduced. Thus, long-term treatment has been shown to be quite effective and has been well tolerated.

INV 11

GUT INVOLVEMENT IN THE SPONDYLOARTHRITIDES

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The concept of Spondylarthritis (SpA) is the most classical and evident model of relationship between gut and joint inflammation. Reactive arthritis can occur after intestinal infections; peripheral arthritis will develop in 12-30% of patients suffering from Inflammatory Bowel Disease (IBD) (Crohn's disease (CD) and ulcerative colitis). On the other hand, subclinical histological gut inflammation was discovered in 52% of patients with Ankylosing Spondylitis (AS), but also in other diseases of the concept (psoriatic arthritis, juvenile SpA and undifferentiated SpA). A direct temporal relationship was detected between gut- and joint inflammation by performing repeated colonoscopy over time. Finally prospective studies revealed that 7% of the SpA patients will develop CD over time.
The strong linkage between gut and joint inflammation in SpA and the therapeutic response of TNF-blockade in Rheumatoid Arthritis (RA) and CD led to the use of these drugs in SpA. It is demonstrated that the TNF monoclonal antibodies (infliximab and adalinumab) are not only highly effective in the treatment of severe CD, but also in the treatment of all inflammatory features of the SpA concept (spondylitis, arthritis, enthesitis, dactylitis, uveitis, skin- and gut inflammation). In contrast the p75 soluble TNF receptor antagonist etanercept, highly effective for the locomotoric inflammation in SpA, has no effect in IBD and can even cause flares of gut inflammation in SpA patients.
The pathogenesis of the link between gut and joint inflammation in SpA has still to be unravelled. Increased intestinal permeability, facilitating interaction between bacteria and the immune system has been described in both AS and IBD. Recent studies demonstrated the high prevalence of subclinical intestinal inflammation in first-degree relatives of patients with AS, comparable to relatives of CD patients with comparable severity, suggesting a common genetic risk factor for development of subclinical intestinal inflammation.
An Icelandic genealogy database demonstrated that AS and IBD patients are significantly more related to each other than are randomly sampled control subjects, in terms of increased risk of either of both conditions developing in the third degree relatives, suggesting that one or more undiscovered genetic variants may underlie the risk of both diseases.
HLA B27 is not increased in the IBD population, however increased in IBD patients with AS (25-78%).
Having IBD and being HLA B27 positive seems to put the patient at risk for development of AS (odds ratio 15-25). Genetic variants of CARD15/NOD2 have been shown to increase the risk for CD.
Although the prevalence of CARD15 mutations in SpA patients was not different from controls, the prevalence of this mutation in SpA patients demonstrating chronic gut inflammation was not different from CD. CARD 15 mutations could be a predisposal factor for the development of CD in SpA patients.
This list of predisposing genes has been extended by newer genes such as IL23R. Hence, the IL23R gene on chromosome 1p31 was found to be associated with CD. Recently significant associations of IL23R were found with psoriasis, psoriatic arthritis, but also with AS independent of IBD status. IL23R gene polymorphism seems to be associated with all forms of the SpA concept confirming the genetic background of this concept. The integration of each of these genetic contributions into the inflammatory pathways that ultimately lead to the development of SpA remains to be unravelled.
Altogether, the findings indicate that SpA, and its link with gut inflammation, occurs as the result of genetically determined disturbed innate and adaptive immune responses.

INV 12

THE IMMUNOLOGICAL SIGNATURE OF SUB-CLINICAL INTESTINAL INFLAMMATION IN AS

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Sub-clinical gut inflammation, as well as a significant association with Crohn's disease (CD) has long been demonstrated in patients with Ankylosing Spondylitis (AS) (1). The pathogenesis of intestinal inflammation in AS however is not yet clearly understood. Both innate and adaptive immune response seem to be involved in pathogenesis of intestinal inflammation of AS patients.
The innate arm of the immune system provides an initial, rapid response to microbes through the production of pro-inflammatory cytokines such as IL-32, the activation of leukocyte-like epithelial cells, mainly Paneth cells (PC) and through the activation of autophagic pathways. IL-32 is constitutively expressed in epithelial cells of colon mucosa and IL-32 over-expression has been demonstrated in the inflamed colon mucosa of CD patients. In addition IL-32 synergizes with nucleotide

oligomerization domain (NOD) 1 and NOD2 ligands for IL-1β and IL-6 production. IL-32 is over-expressed at both m-RNA and protein levels in the subclinical inflamed ileal specimens of AS patients (personal observations), suggesting IL-32 as a key contributor in the pathogenesis of intestinal inflammation in AS.
PC alpha-defensins HD5 and HD6, that contribute to innate host defense against enteric pathogens, are up-regulated in the inflamed ileum of AS, suggesting that intestinal inflammation in AS is characterized by abnormal PC function in response to local environmental stimuli leading to an altered control of mucosal immune homeostasis (2). Process of autophagy is basically enhanced within the intestinal epithelium of AS and CD patients. Recent evidences indicate that autophagy, is selectively required for maintaining the integrity of the PC granule exocytosis pathway and regulates PC expression of adipocytokines. In addition ATG16L1, which gene product is part essential for autophagy, was identified as a CD susceptibility gene, strongly implying autophagy as an important biological pathway in the pathogenesis of intestinal inflammation. Furthermore active formation of autophagosomes, mainly modulated by the stimulation of NOD2 through muramyldipeptide, selectively occurs in PC in both physiological and pathological conditions (3).
Immune cells present in the intestinal lamina propria are required to balance immune tolerance of luminal microbiota with the need to defend against pathogens. Th1, Th17 and regulatory T cells (Treg), must be continually fine-tuned to maintain intestinal immune homeostasis. The interleukin-23 pathway through the control of Th17 cells, that are highly proinflammatory and induce severe autoimmunity, seems to be a fundamental player in the intestinal immune responses. We have demonstrated a strong and significant up-regulation of IL-23p19 transcripts in the terminal ileum in patients with AS and patients with CD (4). Consistent with the fundamental function of PC in regulating mucosal immunity, we identified resident PC as a pivotal source of IL-23 in physiologic and pathologic conditions strongly suggesting that IL-23 is a master regulator of gut mucosal immunity, and providing a pathophysiologic significance to the reported association between IL-23 receptor polymorphisms and intestinal inflammation.
Unlike CD, in AS patients, IL-23 was not associated with up-regulation of IL-17 and the IL-17–inducing cytokines IL-6 and IL-1β, indicating a role for IL-23 independent from Th17 in AS. Interestingly a significant up-regulation of TGF-β, without a concomitant over-expression of IL-1β and IL-6, was observed in the ileum of both AS and CD patients. The participation of TGF-b in the differentiation of Th17 cells places them in close relationship with $CD4^+CD25^{high}$ T_{reg} cells, as TGF-β, among its numerous properties, is also able to induces expression of FOXP3 in naïve antigen-stimulated T cells in the peripheral immune compartment, leading to cells with regulatory or suppressor function. The absence of a clear Th17 polarization, despite the high levels of IL-23 observed, could be related to a T_{reg}-mediated suppression in the gut of AS patients. $CD4^+CD25^{high}$ T cells were increased in the gut and in the peripheral blood of AS patients, with a concomitant significant intestinal increase of the T_{reg}-related transcripts (STAT-5, TGF-ß and IL-10) (5) suggesting that an active T_{reg} response, mainly dominated by IL-10 production, occurs in AS.
We don't know actually the exact mechanism by which a breakdown in immune regulatory networks, leads to chronic inflammatory diseases in the intestine of AS patients. We could hypothesize that in genetically prone subjects unknown infective stimuli could induce the production of pro-inflammatory cytokines, such as IL-6 or IL-1, down-regulating Treg response with the occurrence of active differentiation of pathogenic Th17 cells. In this context the high levels of IL-23 present in the gut of AS patients, could sustain the Th17 commitment, leading to the development of gut inflammation.

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INV 13

VASCULAR ADHESION PROTEIN -1: A TWO-FACED MOLECULE IN CONTROL OF LEUKOCYTE MIGRATION INTO SITES OF INFLAMMATION

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Leukocyte migration into sites of inflammation is a prerequisite for mounting an adequate inflammatory response. Blood-borne leukocytes enter tissues using a multi-step adhesion cascade. During this process the leukocytes first roll on endothelial cells, became activated, adhere to the endothelial cells in a shear resistant manner and finally transmigrate through the vessel wall. The adhesion cascade is regulated by several adhesion and activation molecules both on the leukocytes and endothelial cells.
Vascular adhesion protein-1 (VAP-1) is a unique adhesion molecule which has an intrinsic enzymatic activity. It is an amine oxidase expressed on the luminal surface of endothelial cells. VAP-1 oxidatively deaminates amines in a reaction which produces biologically active end products including hydrogen peroxide. VAP-1 supports leukocyte migration in multiple in vitro and in vivo models. In frozen section adhesion assays anti-VAP-1 antibodies inhibit binding of human leukocytes to vessels in gut and joint.
VAP-1 deficient mice show attenuated leukocyte infiltration and inflammatory responses in various models including arthritis and mucosal inflammation. The function of VAP-1 can be blocked both by monoclonal antibodies and enzyme inhibitors to alleviate inflammation. We have also shown that the enzymatic activity of VAP-1 induces other molecules involved in leukocyte-endothelial interactions. VAP-1 can be one molecule which is responsible for the aberrant binding of mucosal leukocytes into synovial vessels. The leukocyte counter-receptor for VAP-1 has been unknown for a long time.
Recently, we have found that two different Siglec molecules expressed on different leukocyte subpopulations can bind to VAP-1. VAP-1 thus provides a new paradigm of ecto-enzymatic control of leukocyte traffic. Targeting of VAP-1 by either function-blocking monoclonal antibodies or small molecule enzyme inhibitors may provide a new way of inhibiting inappropriate inflammation.

INV 14

MUCOSAL INFLAMMATION IN SPONDYLOARTHRITIS: PAST, PRESENT AND FUTURE

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The relationship between intestinal inflammation and spondyloarthritis is well established. However, almost 30 years after its discovery, the mechanisms linking gut and joints are still relatively poorly understood. In addition, the predilection sites as well as the initial events leading to inflammation are unclear. This is in part explained by the relatively limited availability of experimental model systems in which intestinal inflammation and joint inflammation coexist. One such a model is the TNFdARE mouse which combines ileal Crohn's like inflammation and axial and peripheral signs of spondyloarthritis. Using cell targeted strategies it was shown that several myeloid and lymphoid cells contribute to the production of the TNF load that induces spondyloarthritis in this model, yet the cell type responding to chronic TNF overexposure was found to be a mesenchymal cell. Thus, a stromal cell type is at least one of the main drivers of inflammation in spondyloarthritis. Furthermore, additional regulatory cell types are able to modulate TNF levels to dampen TNF driven inflammation in vivo; natural killer T cells being one such an example. More recently, we have focused on the initial sites and events of inflammation and observed a strikingly role for angiogenesis both in mice and men. Altogether, these observations provide new insights in the regulatory as well as the effector mechanisms of spondyloarthritis.

INV 15

THE GENETICS OF ERAP1 IN ANKYLOSING SPONDYLITIS

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Pronounced familial clustering of cases initially inspired the idea that ankylosing spondylitis (AS) was a genetic disorder. In 1973 this prompted the study of HLA genes in AS rather than RA, leading to the discovery of the association with HLA-B27. For many years the strength of this association (odds ratio~120) led many to believe that the genetic contribution to AS was mongenic, with an important environmental contribution accounting for the rest of population variance. Subsequent twin and other population-based studies strongly indicate the polygenic nature of AS, suggesting that individual susceptibility to disease is mainly genetically determined but that a relatively large number of genes may be involved. The full extent of this polygenic contribution to AS is only now being fully appreciated from the results of genome-wide association studies (GWAS).
In the early 21st century the Wellcome Trust Case Control Consortium was established to study the genetic component of common complex diseases (eg. Type 1 and Type 2 diabetes mellitus, inflammatory bowel disease, psychiatric disorders, hypertension, cardiovascular disease and rheumatoid arthritis). On the back of these extensive GWAS a smaller study employing 15,000 gene-targeted (coding) single nucleotide polymorhisms (SNP) was deployed in the examination of four other diseases (AS, breast cancer, multiple sclerosis and autoimmune thyroid disease). Around 3,000 of the SNPs used in this study were in the MHC, leaving a marker density for the rest of the genome of ~1 SNP for every 2.5 genes. Quite by chance *ERAP1* (endoplasmic reticulum associated peptidase 1) was over-represented in this scan with 5 SNPs and a further SNP in the neighbouring *LNPEP* locus. Outside the MHC, these 6 markers gave the strongest signal for association with AS, ranging between 10^{-4} and 10^{-6}. In contrast, the signal from the single coding SNP (rs11209026) in *IL23R*, a gene subsequently amply replicated in AS, was only weak ($p=1.7x10^{-3}$). Whereas there was a clear indication to follow up the finding with *IL23R* in view of its potential importance in inflammation the biological relevance of *ERAP1 to AS* was far less clear. It was therefore essential to replicate this finding in an independent data set to exclude a false positive result of the sort that potentially bedevils such analyses. Initial replication of the WTCCC result was achieved in a US data set through collaboration with the **T**riple **A** (Australo-Anglo-American) **S**pondyloarthritis **C**onsortium (TASC) with meta-analysis of the combined data set providing maximum evidence of association for rs30187 ($p=3.4x10^{-10}$). In parallel examination of the *IL23R* locus confirmed the association in AS with peak association for rs11209032 ($p=7.5x10^{-9}$). There was no clear cut primary association at *ERAP1* with any of the SNPs that were analysed in this study but this unequivocal replication of the association initiated a detailed investigation of the structure function relations of ERAP1 and its likely effects in AS. Subsequently we have undertaken extensive resequencing of the coding sequence, intron/exon boundaries and flanking regulatory regulatory sequences of *ERAP1* in 100 chromosomes from individuals with AS. A total of 34 variants were identified, including several rare coding variants. The multiple associations with AS were replicated in this study but using regression analysis we could not identify any primary associations with particular SNPs. Two rare variants of *ERAP1* were only found in the disease population, a finding of potential pathogenic relevance that should be replicated in other studies. We found a very strong correlation between the strength of association between AS and SNPs in *ERAP1* and apparent influence on *ERAP1* transcript abundance as previously reported in genome-wide studies of gene expression.
Modelling the individual mutations in ERAP1 on a theoretical molecular model based on homology with another member of the M1 aminopeptidase family, tricorn-interacting factor 3 which shares 25% homology with ERAP1, it became apparent that many of the variants that we observed were at sites considerably distant from the Zn active-site of ERAP1. However, one of the variants K528R is close to the putative substrate pocket and is known to be associated with a 40% reduction in catalytic activity. In order to refine our knowledge of the structure of ERAP1 full-length recombinant ERAP1 protein was expressed in insect cells using baculovirus transfection. Efficient expression was achieved and following extensive purification yields sufficient for crystallographic and functional studies of the wild type protein and 6 variants have been obtained. The structure of ERAP1 has now been solved at high resolution and we are investigating the effects of specific inhibitors on this structure. We are studying the effects of individual amino acid mutations on the catalytic activity of ERAP1 in vitro and in vivo. ERAP1 is a potentially multifunctional peptidase; it is alternatively known as aminopeptidase regulator of TNF receptor 1 (ARTS1). There has been considerable discussion about its primary mechanism of action in the pathogenesis of AS. Its potential role as a "sheddase" in facilitating the cleavage of cell surface cytokine receptors, such as TNFR1, has a siren attraction in a disease so strongly associated with the effects of TNF. However, the latest epistatic genetic analyses quite clearly indicate that its role is almost certainly in the MHC class I pathway of antigen presentation, where it facilitates the cleavage of small peptides to optimal length for binding to HLA class I molecules, such as HLA-B27. This observation is likely to have ramifications far beyond the spondyloarthropathies alone. By screening large libraries of peptidases we hope to find additional ligands with both inhibitory and enhancing actions on ERAP1 which at least in theory could form the basis of novel forms of treatment for AS and related conditions.

INV 16

THE ROLE OF ERAP1 IN THE BIOLOGY OF MHC CLASS I

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Abstract not available.

INV 17

PROGRESS IN STUDIES OF THE GENETICS OF ANKYLOSING SPONDYLITIS

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Genetic studies of AS have made rapid progress over the past 5 years, with associations with novel genes and genetic loci providing insights into the disease pathogenesis, stimulating much follow-up functional research and therapeutic development. In order to identify further genetic variants predisposing to AS, we performed a gwas of 1782 British and Australian cases fulfilling modified New York Criteria, and 5167 historical controls from the Wellcome Trust Case Control Consortium 2 (WTCCC2). The study was combined with existing results from the Australo-Anglo-American AS Consortium (TASC) consortium, and replication of the most significant findings performed in 2109 cases and 4410 controls from Australia, Britain, and the Canadian SPARCC consortium. As well as confirming known associations at *HLA*, *IL23R*, *ERAP1*, *KIF21B, 2p15* and *21q22,* we identified and subsequently replicated risk predisposing variants in *RUNX3* (combined $p=3.3 \times 10^{-12}$), *IL12B* ($p=1.8 \times 10^{-8}$), and *LTBR* ($p=4.5 \times 10^{-10}$), and found suggestive association at *ANTXR2* ($p=3.8 \times 10^{-7}$), *PTGER4* ($p=7.8 \times 10^{-8}$), *CARD9* ($p=1.2 \times 10^{-6}$), *TRADD* ($p=4.1 \times 10^{-6}$) and *TBKBP1-TBX21* ($p=5.9 \times 10^{-8}$).
Additionally, we identified a single SNP, rs4349859 near the gene *MICA*, which tagged HLA-B27 with near perfect sensitivity (98%) and specificity (99%) in 531 cases and 729 controls of Australian and British origin. These findings were confirmed in independent sets of Sardinian and Azorean cases, and show that whilst rs4349859 tagged the non-AS associated *HLA-B*2709* subtype, it did not tag the AS-associated *HLA-B*2707* subtype, indicating that rs4349859 is not AS causative, and further reducing the likelihood that a *B*27*-linked gene is responsible for the association of B27 with AS. This SNP is far cheaper and easier to genotype than *B*27*-itself, and can be used as an alternative to *B*27*-typing, at least in European populations. In most common diseases the proposed genetic model involves interaction between loci, but to date no convincing examples of such interaction have been demonstrated. In the current study however, we identified an interaction between *HLA-B*27* and variants within *ERAP1* in the WTCCC2 ($p=0.008$), TASC ($p=0.004$) and replication datasets ($p=0.004$).
Specifically, risk variants in *ERAP1* increased odds of disease in *HLA-B*27*-positive, but not *B*27*-negative, cases (combined interaction $p=1.4 \times 10^{-6}$). In contrast, *IL23R* was associated with disease in both *B*27*+ve and *B*27*-ve cases. This result indicates that *B*27*+ve and *B*27*-ve forms of disease have substantially different but overlapping aetiologies. Interestingly, in a separate WTCCC2 study, we have demonstrated that ERAP1 is associated with psoriasis, and that the association is restricted to cases carrying the HLA Class I protein HLA-Cw6. The findings support mechanisms of association of *B*27* and *ERAP1* with AS that involve peptide presentation, and that ERAP1 contributes to disease risk through its action in trimming peptides prior to loading into nascent HLA class I molecules, rather than by cleaving pro-inflammatory cytokine receptors on the cell membrane. Using *ERAP1* +/+ compared with -/- mice, we have confirmed that ERAP1 does not act as a cytokine receptor cleavase.
Many further genes are likely to be identified over the coming years. The International Genetics of Ankylosing Spondylitis Consortium will perform what will likely be the definitive SNP genotyping study of AS, involving over 10,000 cases and 20,000 healthy controls genotyped for 200,000 markers targeting immunogenetically relevant genes, in the next 12 months. This study will bring new findings including new genes, fine-mapping of known genes, data about the value of genetic risk prediction in different world populations, and even pharmacogenetic data regarding TNF-antagonist response and intolerance. This landmark study has been made possible by the collaborative spirit of the AS-researchers involved. These findings provide substantial material for the functional biology community to research, with the promise of early translation in both therapeutics and improved diagnostic tests.

INV 18

GENOME-WIDE ASSOCIATION SCAN IDENTIFIES TWELVE SUSCEPTIBILITY LOCI FOR PSORIASIS AND/OR PSORIATIC ARTHRITIS

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In an effort to identify psoriasis susceptibility genes, we carried out a collaborative genome-wide association study with support from the Genetic Association Information Network (GAIN). After initial follow-up genotyping of 20 SNPs showing strong evidence of association in the initial scan, we confirmed evidence of association at seven loci. Of these loci, three confirmed previous reports of association (at *HLA-C, IL12B, IL23R*) and four identified novel signals located near plausible candidate genes (*IL23A, IL4/IL13, TNFAIP3*, and *TNIP1*). While functional variants remain to be identified, we speculate that genetic variants at the *IL4/IL13* locus lead to Th2 hypofunction, contributing to the Th1 bias that is characteristic of psoriasis, while Th1-derived IFN-γ may support the survival and expansion of IL-17+ T-cells via its effects on APC-derived IL-23. *T*he proteins encoded by *TNFAIP3* and *TNIP1* interact with each other to regulate inflammatory signaling through the NF-kB axis. Recent follow-up studies have identified four additional novel regions of association, to be described at this meeting, which further emphasize the importance of these inflammatory pathways in psoriasis and psoriatic arthritis. Two of these novel loci are significantly more strongly associated with psoriatic arthritis than with purely cutaneous psoriasis. Finally, evidence for locus heterogeneity within the MHC in PsA will be presented.

INV 19

DEVELOPMENT AND APPLICATION OF ASAS CRITERIA FOR AXIAL SPA

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The concept of spondyloarthritides (or spondyloarthropathies, SpA) that comprises a group of interrelated disorders has been recognised since the early 1970's. While the European Spondyloarthropathy Study Group (ESSG) criteria and the Amor criteria have been developed to embrace the entire group of SpA, other criteria such as the modified New York criteria for ankylosing spondylitis (AS) focus on specific SpA subgroups. The modified New York criteria have been used widely in clinical studies on AS but are not applicable in early disease when the characteristic radiographic signs of sacroiliitis are not visible but active sacroiliitis is readily detectable by MRI. This led to the concept of axial SpA that includes patients with and without radiographic damage, and diagnostic algorithms to be applied in daily practice were developed. As imaging modality in early axial SpA magnetic resonance imaging (MRI) plays an important role. MRI of the sacroiliac joints can visualize active inflammation (sacroiliitis) in patients without yet readily detectable structural damage on radiographs. The diagnostic value for early axial SpA of other SpA parameters including clinical manifestations such as inflammatory back pain, enthesitis, arthritis or uveitis, and of HLA-B27 or elevated acute phase reactants has also been elaborated. Based on this reasoning and a limited number of paper patients judged by Assessment of SpondyloArthritis international Society (ASAS) experts, new candidate criteria for axial SpA were developed. These new classification criteria for axial SpA were tested, refined, and validated in a large international prospective ASAS study. In the new ASAS criteria for axial SpA, sacroiliitis on MRI has been given as much weight as sacroiliitis on radiographs, thereby also identifying patients with early axial SpA. The ASAS criteria for axial SpA are useful for application in clinical trials of axial SpA that include the non-radiographic (early) disease state and may help to establish a diagnosis in daily clinical practice.

INV 20

MEASURING DISEASE ACTIVITY – ASDAS?

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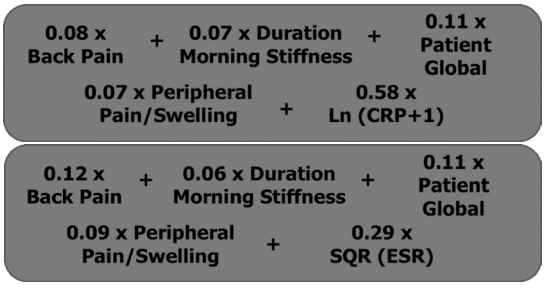
Need for a new disease activity index in AS: Since the concept of disease activity encompasses such a wide range of measures or concepts, many experts in the field think that we do not have an instrument available that appropriately reflects the level of disease activity in AS. Currently used single-variable parameters (eg. pain, stiffness, ESR, CRP, patient global assessment) or constructs/indices (eg. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index) do not satisfy because they cover only part of disease activity, lack face- and construct validity, are "too lenient", are not sensitive to change, or are either fully patient- or physician oriented. Only a disease activity index (score) can capture multiple important aspects of disease activity. Indices can be entirely expert-derived, including domains that have a high level of face validity. The BASDAI is an example of such an index developed by experts (including patients), consisting of 6 questions referring to fatigue, back pain, peripheral joint pain and swelling, enthesitis, and severity and duration of morning stiffness. The BASDAI is fully patient oriented and self-reported. These expert derived indices are widely accepted by clinicians, are easy to understand, but may not perform efficiently, due to variable-redundancy (the phenomenon that separate variables cover the same aspect of the disease (high correlation)).
Moreover, the various instruments are simply summed without taking the relative importance and dependency into account. Indices can also be statistically derived. The statistical process underlying the development of such indices assures an optimal collection of items, including item-weight if necessary, but complexity and lack of face validity may jeopardise the implementation in the clinical practice. The disease activity score (DAS) used in rheumatoid arthritis is a good example of an appropriate index, because it has shown to perform well in clinical research and it has been implemented and accepted in clinical practice even though the DAS algorithm is rather complex. In general, and referring to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative, an index should be truthful, discriminative and feasible. In a statistically derived index the single variables that are covering a part of the construct of disease activity without to much overlap with other variables are selected. So the statistically derived index selects the appropriate measures, but also gives the appropriate weight to each of the variables.
Development and validation of ASDAS: The development of the ASDAS consisted of several steps. First we selected the variables that are candidates to be included in a new index, variables that are considered to reflect disease activity. This was done by a Delphi exercise by the members of ASAS. In total 11 aspirant variables were selected. Thereafter we used data from a large database that had all these aspirant variables available to discriminate between patients with high and low disease activity.
Patients who were considered a candidate for the start with a TNF-blocker were regarded as having high disease activity and patients that could do without as having low disease activity. This resulted in four possible ASDAS scores. Further validation steps compared the performance of these four scores.
This was performed in several databases: the OASIS cohort, a prospective cohort of consecutive patients in rheumatology practices to study the natural course of the disease; the NOR-DMARD database, a longitudinal registry in Norway including all patients starting with a DMARD or a TNF-blocker; data from several placebo-controlled RCTs studying several TNF-blockers. All these data were presented to the ASAS membership and they selected the best performing ASDAS. The ASDAS including CRP is the preferred ASDAS; however if CRP is not available but ESR is, an alternative ASDAS including ESR can be used. The variables included in both ASDAS versions and the calculation of the ASDAS is presented below.

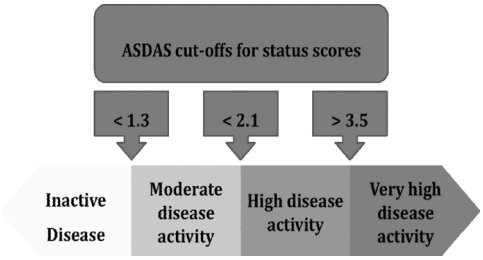


$ASDAS_{CRP}$ is the preferred ASDAS but the $ASDAS_{ESR}$ can be used in case CRP is not available. CRP in mg/l; all patient assessments on a 10 cm scale.

It is well known that the correlation between the patient and physician global assessment of disease activity in AS is poor. The ASDAS is the variable (comparing all single and combined scores) that correlates best with the physician global assessment of disease activity, and also shows the highest correlation to the patient global assessment of disease activity, at the same level as the BASDAI. In all the

tested databases the discrimination of the ASDAS was best in comparing patients with high versus low disease activity according to patient and according to physician. Comparing change over time, again the ASDAS was the best discriminating score in the comparison of DMARDs and TNF-blockers and in the comparison of placebo and TNF-blockers resulting in the highest t-scores. Also testing sensitivity to change by Guyatt's effect size was significantly better with the ASAS (2.4) as compare to the second best variable (physician global 1.8; BASDAI 1.5). As both a measure for acute phase reactants (CRP) and a measure for involvement of peripheral joints (BASDAI q3 on swelling and pain of peripheral joints) are included in the ASDAS, it was important to test if the ASDAS is still the best performing variable in patients with a normal CRP and without peripheral arthritis. This was confirmed for both situations: the discriminatory capacity of the ASDAS was similar in patients with normal versus elevated CRP and in patients with versus without peripheral arthritis.

Further to the validation of the ASDAS, cut-offs for defining a clinically important improvement, and a major improvement have been defined (1.1 and 2.0, respectively). Also definitions of various status scores have been selected. These are presented below.



Discussion: The ASDAS fulfils important aspects of the truth criterion of the OMERACT filter, as it reflects disease activity both from the patient and physician perspective, which are known to be inherently different. In addition, it is highly discriminatory in differentiating patients with different levels of disease activity and in differentiating patients with different levels of change. This latter aspect is very important in the assessment of treatment efficacy in clinical trials. Comparing the performance of the single components and the entire BASDAI, an important conclusion is that in the various settings a different measure was performing best. This underscores the importance of using an index, as a single measure or BASDAI are reflecting only a part of the entire construct of disease activity. Another major conclusion is that the BASDAI is frequently performing very similarly as one of the single components of the BASDAI. In particular, the back pain and the 2 morning stiffness questions (severity, duration), as well as the average of these two, perform very well. This may indicate a significant level of redundancy in the BASDAI: aggregated information is captured by only one question. This is especially the case if change is assessed. The ASDAS is a continuous measure, and as such comparable to the BASDAI or the DAS in RA. It can be used to discriminate between groups of patients, or over time after an intervention. The great advantage in comparison to a response measure such as the ASAS20 is that the ASDAS not only can provide information about improvement, but also about the actual disease activity state that has been reached. This is relevant in monitoring patients over time, where it is useful to follow the actually achieved disease activity state rather than being informed about improvement with reference to baseline (which can be more than 2 years ago).

Conclusion: In conclusion, we developed and validated an ASAS-endorsed ASDAS consisting of total back pain, duration of morning stiffness, the BASDAI question on peripheral joints, patient global assessment of disease activity and CRP. As an alternative the ASDAS with ESR, which consists of the same variables apart from the acute phase reactant, but with slightly different weighting, can be used if CRP is not available. However, it should be clearly understood that these ASDAS versions with CRP or with ESR are not interchangeable. One version should be used consistently within patients or within a study. The ASDAS is a highly discriminatory tool, clearly showing the advantage of the use of a well balanced index covering the same underlying construct without too much redundancy. Applying the ASDAS in comparison to the BASDAI as the primary outcome measure in RCTs gives the opportunity to reduce sample size with approximately 40% while preserving the same statistical power to detect a treatment effect. Definitions of two levels of improvement and various states of disease activity have been presented.

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INV 21

ENTHESITIS-RELATED ARTHRITIS: IS IT JUVENILE SPONDYLOARTHRITIS?

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Juvenile spondyloarthritis often begins as an undifferentiated disease with important differences in presentation compared to adult onset disease. Most notably, the perception is that there is a relative paucity of spinal involvement, with a greater frequency of hip arthritis and enthesitis in juvenile onset disease. Currently, classification of spondyloarthritis in children is approached very differently from adult disease. Using the International League of Associations for Rheumatology (ILAR) classification system for juvenile idiopathic arthritis (JIA), many children with spondyloarthritis will be classified as having enthesitis-related arthritis (ERA). However, co-existing psoriasis, or even a family history of psoriasis, will exclude patients from this category who would otherwise fit ERA criteria. Other co-existing conditions such as inflammatory bowel disease, and reactive arthritis, are not specifically addressed by the ILAR criteria. In addition, the ILAR system does not distinguish juvenile spondyloarthritis patients with axial disease, either in a pre-radiographic phase, or when criteria for ankylosing spondylitis are fulfilled. Resolution of these issues will enhance communication and patient transitioning between pediatric and adult rheumatologists, and facilitate research in the field, which will be particularly important as the early use of TNF inhibitors and other biologics in axial spondyloarthritis is evaluated.

Oral Presentations

O 1

GENE SILENCING OF ERAP1 AND ERAP2 DISPLAYS DIFFERENTIAL EFFECTS ON INTRACELLULAR FREE HEAVY CHAIN ACCUMULATION AND PEPTIDE PRESENTATION IN B27 SUBTYPES ASSOCIATED WITH AS COMPARED WITH SUBTYPES NOT AS-ASSOCIATED

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Introduction: HLA subtypes B*2704 and *2705 are associated with AS while *2706 and *2709 are not. We investigated the interaction of 2 novel AS associated genes ERAP1 and ERAP2 with HLA B*27 subtypes.
Methods: C1R cells stably transfected with the respective B*27 subtypes (B*2704, *2705, *2706 and *2709) were used. For gene silencing, two duplexes each of Stealth RNAi™ for ERAP1 and ERAP2 and a negative control (NC) siRNA were nucleofected. For flow cytometry, ME1, HC10, W6/32 and MARB4 antibodies were used respectively for intact B27, MHC-I free heavy chains (FHC), intact MHC-I and B27 presenting abnormally long peptides (B27_lp). For intracellular FHC (IFHC) HC10 was used after cell permeabilization. The change in MFI was calculated as a ratio of the MFI with specific siRNA to NC for each antibody. Western blot showed more than 80% suppression of ERAP with specific siRNAs but not with NC.
Results: Silencing of ERAP1/2 was associated with a significant increase in IFHC in B*2704 and *2705 cells compared to *2706 and *2709 cells (p=0.002). The median (IQR) increase in IFHC (ΔIFHC) in the B*2704 and *2705 cells was 2.5 (1.8, 4.2) compared to 1.3 (1.1, 1.5) in the *2706 and *2709 cells. There was no significant difference in the level of surface FHC, B27 or MHC-I expression. The median ΔB27_lp expression with ERAP1/2 silencing in B*2704 and *2705 cells was 1.2 (1.1, 1.4) and was significantly higher (p=0.03) than the median ΔB27_lp of 0.9 (0.8, 1.0) in *2706 and *2709 cells. There was no significant difference in the results whether ERAP1 or ERAP2 was suppressed.
Conclusion: ERAP1/2 silencing causes accumulation of more IFHC and higher B27_lp in AS-associated B*27 subtypes cells compared to non-associated subtypes. This is the first report suggesting that ERAP1/2 could be the missing link in the conundrum of B27 subtype specificity in AS.

O 2

BIOMECHANICAL STRETCH IS A KEY INITIATING EVENT IN THE DEVELOPMENT OF ENTHESITIS IN MURINE SPONDYLOARTHRITIS

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One of the hallmarks of spondyloarthritis (SpA), is the development of enthesitis, most typically of the Achilles tendon and plantar fascia. In this study, we investigated the initiating events leading towards enthesitis development in TNF$^{\Delta ARE}$ mice. These mice are characterized by an enhanced TNF mRNA stability, which in turn leads to the development of several features of SpA, including peripheral and axial arthritis, and Crohn´s like ileitis. One of the striking features of this model is the early appearance of tendinitis/enthesitis of the Achilles tendon. We subjected TNF$^{\Delta ARE}$ mice which had not yet developed signs of inflammation to tail suspension, a biomechanical unloading procedure, thereby prohibiting weight loading on hind paws for 7days. Western blotting was performed for phosphorylated Erk, one of the mitogen-activated protein kinases on cell lysates from Achilles tendon samples of tail suspended TNF$^{\Delta ARE}$ mice, versus mice that were allowed to walk for 15 minutes after a 7 days period of tail suspension. The effect of small molecular inhibitors of Erk and p38 on enthesitis development was evaluated. In addition, Achilles tendon fibroblasts from TNF$^{\Delta ARE}$ and control mice were subjected to cyclic stretch in a bioreactor, and cytokine and chemokine responses were measured in supernatant. Biomechanical unloading studies indicated that almost no inflammation of the Achilles tendon occurred in unloaded animals compared to weight bearing controls. By contrast, weight bearing front paws exhibited severe inflammation. As early as 15 minutes after initiation of weight bearing, phospho-Erk was upregulated compared to continuously unloaded conditions. Treatment of TNF$^{\Delta ARE}$ mice with small molecular inhibitors of Erk and p38 markedly reduced the extent of Achilles tendon enthesitis. Furthermore, several chemokines were differentially produced in supernatant from stretched TNF$^{\Delta ARE}$ fibroblasts versus controls.
Conclusion: These findings provide a novel proof that biomechanical stretch may activate pro-inflammatory signalling pathways, setting off a cascade of events, which in a genetically predisposed host may lead to enthesitis.

O 3

CONTINUED EFFICACY OF INFLIXIMAB IN THE TREATMENT OF HLA B27 POSITIVE VERY EARLY ANKYLOSING SPONDYLITIS FOLLOWING ITS DISCONTINUATION – CLINICAL AND IMAGING RESULTS OF THE 40 WEEK FOLLOW-UP STUDY OF A THREE MONTH, RANDOMISED, PLACEBO-CONTROLLED TRIAL

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Objective: Treatment of early inflammatory back pain with infliximab was shown to be efficacious during a 3 month trial. This report describes clinical and imaging outcomes following discontinuation.
Methods: All patients had received either infliximab or placebo for 3 months, discontinued treatment and were followed up to week 40 or clinical flare (BASDAI>4). MRI scans of the spine and SIJs were performed at baseline, week 16, and week 40 or clinical flare. MRIs were scored by 2 observers blinded to treatment group and order.
Results: In the placebo group, 17/19 patients (89.5%) had a high BASDAI (>4) between 12 and 40 weeks, compared to 12/19 (60.0%) in the infliximab group (Chi-square=4.44, p=0.035). Time to BASDAI>4 was shorter with placebo [median (IQR) 5.0 weeks (4.0 to 16.0)] than infliximab [20.0 (7.9 to 28.0), Log-rank Chi-square=5.77, p=0.016]. At endpoint (BASDAI>=4 or week 40), infliximab patients showed greater improvements in ASQoL (p=0.05), BASFI (p=0.033) and BASDAI (p=0.045). There was no difference in the changes in total MRI scores between placebo [-3.00 (-4.00 to -1.00)] and infliximab [-2.00 (-3.25 to 1.00), MWU=38.0, p=0.443] groups from baseline to endpoint. Considering grade>1 lesions, in the 10 patients who did not flare (8 infliximab treated, 2 placebo), there was only one grade >1 lesion at week 16 and no new lesions on follow-up scan. In the 11 patients who flared (6 infliximab 5 placebo) there were 8 grade>1 lesions at week 16 and 12 new lesions.
Conclusions: Infliximab treatment results in improvement in disease activity and quality of life in early AS, which is sustained on withdrawal. Fewer patients who had active therapy flared by week 40, and those who did not demonstrated no progression of grade>1 lesions on MRI. This raises the possibility that the "remission induction" approach could work in a sub set of early AS.

O 4

EROSIVE STRUCTURAL CHANGES AND THE IMPACT OF ANTI-TNFA THERAPY IN THE SPINE OF PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: Spinal inflammation, erosions and syndesmophytes are characteristic for ankylosing spondylitis (AS).
Objective: To study the course of erosions and their relationship to spinal inflammation by MRI in AS patients treated by anti-TNF.
Methods: T1 and STIR MRIs of patients with active AS at baseline (n=42), after 3 months (n=38) of anti-TNF or placebo, and after 2 years (n=21) of continuous anti-TNF therapy were analyzed based on vertebral units (VU) by the ASspiMRI-a (scores erosions) and its modification, the Berlin score (scores only inflammation).
Results: At baseline, 95% patients showed spinal inflammation and 73% patients active erosions, while active erosions were seen in 7.8% VUs.
After 3 months all inflammatory lesions (inflammation and active erosions) improved by 46% in the anti-TNF group (p=0.007) vs. 20.3% in the placebo group, while active erosions only improved by 21.4% in the anti-TNF group but worsened by 5.3% in the placebo group.
After 2 years, improvement was found for 66.7% for all inflammatory lesions (p<0.001), which corresponds to an improvement of 62.1% for inflammation only and an improvement of 80% for active erosions (both p<0.05). During the placebo-

controlled phase of the studies, both scoring systems showed similar ability for discrimination between treatments (56% and 52% improvement in the anti-TNF-group, no change in the placebo-group), while improvement of inflammation by 73% and 69% was seen after 2 years in the ASspiMRI-a and Berlin, respectively.
Conclusions: Active erosions occur in the majority of AS patients but in <10% of vertebrae and have no impact on the treatment outcome on spinal inflammation. After 2 years, inflammation is still present in 25% of patients. This may have an impact on future therapeutic strategies.

O 5

MULTIPLEX ASSAY OF A PANEL OF 58 BIOMARKERS IN ANKYLOSING SPONDYLITIS: IDENTIFICATION OF HIGH PRIORITY CANDIDATES FOR PREDICTION OF STRUCTURAL DAMAGE

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Background: Radiographic progression in ankylosing spondylitis (AS) requires 2 years before it can be reliably detected and prospective studies have consistently identified only baseline radiographic damage as an independent predictor. Prior reports suggest that biomarkers reflecting joint inflammation and bone turnover may be useful predictors.
Objective: To simultaneously analyze a large panel of serologic biomarkers reflecting pathophysiological processes in AS as predictors of radiographic progression.
Method: We used multiplexed sandwich immunoassays to simultaneously quantify a panel of 58 biomarkers. Serum was obtained at a single time point from 60 patients with AS and 60 age- and sex-matched controls. For subgroup analysis we defined rapid progressors (baseline mSASSS at least 10 units, progression over 2 years at least 5 units, at least one new syndesmophyte) and non-progressors (disease duration at baseline of at least 10 years, baseline mSASSS of less than 5 units, and no change in mSASSS over 2 years).
Results: A total of 23 biomarkers demonstrated significant differences between AS patients and controls, especially osteocalcin and Rantes (both $p<0.0001$). Ten biomarkers demonstrated significant differences from controls when analysis was stratified according to progressor phenotype: in the rapid progressor subgroup MMP-9, transforming growth factor alpha, and tumor necrosis factor alpha were significantly elevated compared to controls (all $p<0.0001$). Eotaxin, interferon alpha-2, and monocyte chemotactic protein-3 were significantly increased in the non-progressor subgroup. Three biomarkers, interleukin-17, interferon-gamma, and macrophage inhibitory protein-beta, demonstrated significantly increased levels in AS patients that were further increased in the rapid progressor subgroup. Six biomarkers were significantly increased only in male patients and particularly the rapid progressor subgroup, especially macrophage derived chemokine and CD40 ligand (both $p<0.0001$).
Conclusion: Multiplexed assay of an extensive panel of biomarkers reflecting pathophysiological processes implicated in AS has identified several biomarkers as high priority candidates for predictors of structural damage in AS.

O 6

IMPACT OF ANKYLOSING SPONDYLITIS-ASSOCIATED ERAP1 VARIANTS ON ITS AMINOPEPTIDASE ACTIVITY

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Introduction: The genetic association between *ERAP1* and ankylosing spondylitis (AS) was first reported in 2007 by the WTCCC. We have subsequently identified all AS-associated non-synonymous single nucleotide polymorphisms (nsSNPs). In the endoplasmic reticulum ERAP1 trims antigenic peptides 10-16 residues in length to 8-9 residues, the optimal length for binding MHC class I molecules. The aim of this study was to investigate the impact of AS-associated ERAP1 nsSNPs on its aminopeptidase activity.
Methods: Wild-type (WT) ERAP1 and ERAP1 containing individual AS-associated amino acid substitutions were expressed in insect cells using the baculovirus expression system. ERAP1 activity was studied using two different substrates. Initially we measured the fluorescent signal produced upon digestion of the substrate Leu-AMC. Subsequently we measured the rate at which ERAP1 cleaved the N-terminal tryptophan residue from three peptide substrates, also measured by a fluorescence method (Evnouchidou *et al*. 2008).
Results: The activity of the ERAP1 variant with the Lys528Arg substitution was ~3 fold lower than WT ERAP1 towards Leu-AMC ($p=0.00014$). Similarly the Arg725Gln substitution resulted in a ~35% reduction in activity ($p=0.0076$). In contrast, the Gln730Glu substitution increased ERAP1 activity towards Leu-AMC (~69%) compared to WT ($p=0.0061$). The ERAP1 substitutions Lys528Arg, Arg725Gln and Gln730Glu all had reduced activity towards the three peptides studied ($p<0.01$). The Lys528Arg substitution resulted in the largest decrease in activity (~40%) towards WRVYEKC^{DNP}ALK, the peptide trimmed at the greatest rate by WT ERAP1 ($p=0.0094$).
Conclusions: Specific ERAP1 variants appear to alter its activity towards a range of substrates.
Further *in vitro* and *in vivo* studies are required to investigate the activity of these ERAP1 variants.

O 7

INVESTIGATING THE ROLE OF ENDOPLASMIC RETICULUM AMINOPEPTIDASE-1 (ERAP1) IN ANKYLOSING SPONDYLITIS

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Background: Recent studies have shown that genetic variation within *ERAP1*, encoding endoplasmic reticulum aminopeptidase 1, is strongly associated with ankylosing spondylitis (AS).
Within the endoplasmic reticulum, ERAP1 is involved in the trimming of peptides to the optimal length for their presentation by major histocompatibility complex (MHC) class 1 proteins, such as HLA-B27 that is also associated with AS. Here, we investigate the differential activity of WT-ERAP1 and the ERAP1 mutant (Lys528Arg) that is strongly associated with AS.
Methods: The N-terminal-extended HLA-B27 Chlamydia peptide epitope (13-mer, QITANRELIQQEL) was incubated with WT-ERAP1 and with the K528R mutant in time course experiments at 37°C (Up to 6h). The reaction was stopped by the addition of 0.6% trifluoroacetic acid. After 15 min on ice, the precipitated protein was moved by centrifugation. Then the supernatants were analyzed on a Chipcube-coupled Agilent 6520 Q-TOF mass analyzer. For each time point, extracted ion chromatograms of the trimming intermediates were generated and integrated.
Results: The K528R mutant was able to degrade the 13-mer at a comparable rate to WT-ERAP1, but trimmed the 12-mer (ITANRELIQQEL) with reduced efficiency compared to the WT-ERAP1. The difference between WT-ERAP1 and the K528R mutant became more significant when it came to the11-mer (TANRELIQQEL): the K528R mutant seemed unable to further process the 11-mer while the WT-ERAP1 continued to cleave off N-terminal amino acids until it generated 8/9 mers.
Conclusions: WT-ERAP1 is able to trim the N-terminal extended HLA-B27 Chlamydia peptide more efficiently than the K528R ERAP1. The differences in activity between the K528R mutant ERAP1 and WT-ERAP1 may alter the array of B27-peptide complexes at the cell surface *in vivo*, which may be involved in the pathogenesis of AS.

O 8

IDENTIFICATION OF ANTI-TNF CANDIDATES BASED ON PREDICTED RESPONSE AND REMISSION IN ANKYLOSING SPONDYLITIS

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Purpose: To identify AS patients who are candidates for anti-tumor necrosis factor (anti-TNF) therapy.
Methods: ASSERT and GO-RAISE data were analyzed. Matrix models were

developed to predict probability for achieving response or remission from AS after initiating anti-TNF therapy or continuing conventional therapy. In the separate and combined datasets, univariate analyses identified possible baseline predictors for BASDAI50 at wk12 and ASAS partial remission at wk24.
Individual variables were explored using Spearman correlation analysis. Multivariate regression, ROC analysis, and Spearman correlation were used to select predictors for the final model. Logistic regression was used to calculate probable BASDAI50 response and ASAS partial remission state respective to combined predictors at baseline.
Results: 479 patients treated with anti-TNFs and 156 patients treated with placebo+conventional therapy (NSAIDs/DMARDs/corticosteroids) for AS were included. Predictors included: age, BASFI, enthesitis score, therapy (anti-TNF/conventional), CRP, and HLA-B27 genotype (+/-). Area under the ROC curve was 82%, 75%, & 77% for BASDI50 at week12 and 80%, 77%, & 78% for ASAS partial remission at wk24 for ASSERT, GO-RAISE, &combined data, respectively. After categorization of age (≤40 vs>40yrs), enthesitis score (0 vs>0), CRP (≤0.6, >0.6 ≤2.0, >2.0mg/dL) and BASFI (≤4.5, >4.5, ≤ 6.5, >6.5cm), AUC of combined dataset prediction model was 80% for BASDAI50 and 77% for ASAS partial remission, suggesting a good prediction model. A matrix model was developed to represent increasing proportion of BASDAI50 response (range:1%–80%) and ASAS partial remission (range:0%–54%) respective to the characteristic at baseline. Only 2% of patients without BASDAI50 at week12 had ASAS partial remission at week 24.
Conclusions: Most AS patients with elevated disease activity and back pain respond to anti-TNFs while few respond to continued conventional therapy. Younger patients and patients without peripheral enthesitis receiving anti-TNFs demonstrate an improved response. CRP, functionality, and HLA-B27 measurements can help in assessing which patients will respond and subsequently achieve an improved disease state and who, therefore, might be better candidates for anti-TNFs.

O 9

KIR3DL2 INTERACTION WITH HLA-B27 PROMOTES THE SURVIVAL OF TH17 CELLS IN ANKYLOSING SPONDYLITIS

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Background: Possession of HLA-B27 is strongly associated with development of the spondyloarthropathies including Ankylosing Spondylitis (AS). Genetic studies implicate IL-23 receptor in disease and this and other work suggests a role for CD4 T cells making IL-17 (Th17) in pathogenesis. Previously we have shown that KIR3DL2 is a ligand for B27 heavy chain homodimers ($B27_2$) but not classical beta-microglobulin-associated B27. We have also shown an increased frequency of activated KIR3DL2+expressing CD4 T cells in patients with ankylosing spondylitis (AS; Chan et al, Arthritis and Rheumatism (2005) 52. 1. 3586-3595). We asked whether KIR3DL2+expressing CD4 T cells could make IL17 and what role $B27_2$ KIR3DL2 interactions have in promoting the survival of this subset in AS.
Methods: IL17 production by peripheral blood mononuclear cells from 26 AS patients was compared with 6 HLA-B27+ and 18 HLA-B27- healthy controls, 10 rheumatoid arthritis (RA) and 10 ulcerative colitis (UC) patients by FACS analysis. CD4 T cells were labelled with CFSE and cultured *ex vivo* with HLAB27-expressing cells. Production of IL17, TNF-α and IFNγ by CD4 T and FACS-sorted KIR3DL2+ CD4 T cell lines was measured by FACS analysis and ELISA.
Results: 1) KIR3DL2+ CD4 T cells were enriched for IL17 production and accounted for the majority of the increase in production of IL17 by CD4 T cells in AS patients compared with controls**.** 2) Although they constituted a minority population of cells compared with KIR3DL2-CD4 T, KIR3DL2+ CD4 T expressed the majority of IL23 receptor in AS patients. 3) KIR3DL2+ Th17 were enriched in the synovial fluid of spondyloarthritis patients compared to peripheral blood and were stimulated to produce IL17, TNF-α and IFNγ by diverse stimuli including gram-negative bacteria. 4) KIR3DL2+ Th17 were expanded by co-culture with B27 dimer expressing antigen presenting cells (APCs).
Conclusion: Our data are consistent with the hypothesis that Th17 CD4 T cells play a role in Ankylosing Spondylitis, and for the first time link these cells with expression of HLA-B27. Ligation of KIR3DL2 by $B27_2$ could promote the expansion of Th17 in Ankylosing Spondylitis.
Acknowledgements:
Arthritis Research UK (SK, JG, JS), Medical Research Council (PB KMcH) and the Oxford NIHR Biomedical Research Centre (AR, PB), Thames Valley Comprehensive Local clinical Research network.

O 10

BOTH DKK-1 AND SOST ARE SUPPRESSED DURING LATE STAGE DISEASE DEVELOPMENT IN A MOUSE MODEL OF ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis (AS) targets the spine and pelvis progressing from initial inflammation to uncontrolled bone formation in affected joints frequently resulting in complete joint fusion.
Although the inflammatory stages can be controlled by anti-inflammatory drugs, very little is known about the progression to the uncontrolled bone formation and no therapies are available that can slow this progression. The proteoglycan-induced spondylitis model (PGISp) is a well-characterised mouse model of AS. Disease is induced by injections of a human proteoglycan extract with axial inflammation evident after 9-weeks in the spine and sacral-iliac joints resulting in intervertebral disc destruction which is then followed by massive ectopic cartilage formation that eventually ossifies resulting in ankylosis, as demonstrated by toluidine blue staining and immunohistochemistry for collagen type I and osteocalcin. We then investigated the role of two inhibitors of bone formation which act through the Wnt pathway, DKK-1 and SOST, and expression levels of both genes were significantly down-regulated in the spine and knee joints of PGISp mice with advanced disease. We then undertook an array study comparing joints from control and PGISp mice. Unsupervised clustering clearly delineated between control and PGISp mice with 2600 genes being significantly differentially expressed between the two groups with 125 genes upregulated >2-fold and 18 downregulated >2-fold. Interesting candidates included genes involved in inflammation, connective tissue matrix, immune-regulation and genes specifically involved in bone regulation including other members of the Wnt pathway. We have demonstrated that the PGISp mouse is a suitable model in which to study the progression from inflammation to bone formation in AS and we have confirmed the Wnt pathway as a possible mediator of this progression and identified a number of other genes involved in the process.

O 11

VALIDATION OF THE ASAS DEFINITION OF A POSITIVE MRI IN A COHORT OF PATIENTS WITH EARLY SPA FOLLOWED FOR EIGHT YEARS

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Background: The Assessment of SpondyloArthritis International Society (ASAS) has recently proposed a definition of a positive MRI for sacroiliitis according to consensus opinion. This is based on the finding of bone marrow edema (BME) on STIR in subchondral or periarticular bone marrow of the sacroiliac joint (SIJ). The MRI is considered positive for SpA if there are two BME lesions on the same coronal slice through the SIJ or if a single BME lesion is present on two consecutive slices. This proposal now requires validation, preferably in cohorts followed prospectively to assess the development of radiographic changes of sacroiliitis.
Objective: To compare the diagnostic utility of global assessment of MR scans versus the ASAS definition using a standardized approach to evaluation of the SIJ in an early SpA cohort followed over 8 years.
Method: Four rheumatologists, blinded to patient and diagnosis, independently assessed MRI scans (T1W and STIR) from 37 patients with SpA according to ESSG criteria (median symptom duration 24 weeks) of whom 13 developed radiographic sacroiliitis after 8 years, 11 controls with mechanical low back pain (mLBP), and 11 healthy controls. Semi-coronal slices through the SIJ were read systematically according to a standardized online training module. We recorded BME, fat infiltration, erosions, and ankylosis using an online data entry system with schematics of the SIJ divided into quadrants allowing the recording of these lesions (dichotomously yes/no) in each quadrant of each coronal slice. We considered the ASAS definition as being met when BME was recorded in 2 SIJ quadrants on the same slice or when a single lesion in one SIJ quadrant was present in 2 consecutive slices. Readers also answered the following question dichotomously (yes/no): This SIJ scan confirms the presence of SpA? Sensitivity, specificity, and likelihood ratios for individual and concordant data (at least 2 readers) were calculated according to clinical diagnosis at baseline and according to the development of radiographic sacroiliitis.
Results: MRI had high diagnostic utility for SpA according to global assessment by individual readers (mean for 4 readers (range) sensitivity/specificity: 66.9% (61.8-70.6)/94.4% (88.9-100), LR+ 11.9, LR- 0.2) as well as concordant data (sen-

sitivity/specificity: 67.6%/94.4%, LR+ 12.1, LR- 0.3). By comparison, sensitivity for SpA of the ASAS definition was higher but there was reduction in specificity with 11.1% of control scans (3 mLBP) meeting the ASAS definition so that diagnostic utility was lower than for global assessment. Diagnostic utility of baseline MRI for radiographic sacroiliitis after 8 years follow up was even higher: global assessment (sensitivity/specificity: 100%/94.4%, LR+17, LR- not calculable (nc), ASAS definition (sensitivity/specificity: 100%/88.9%, LR+ 9, LR- nc).

	Global Assessment				ASAS Definition			
	Sensitivity	Specificity	LR+	LR-	Sensitivity	Specificity	LR+	LR-
R1	70.6	94.4	12.6	0.3	70.6	88.9	6.4	0.3
R2	70.6	94.4	12.6	0.3	70.6	88.9	6.4	0.3
R3	64.7	88.9	5.8	0.3	82.4	77.8	3.7	0.2
R4	61.8	100	nc	0.3	58.8	100	nc	0.4
Concordant*	67.6	94.4	12.1	0.3	79.4	88.9	7.2	0.2

Conclusion: The diagnostic utility of the ASAS definition resembles global evaluation by expert readers, the principle limitation being the finding of BME in patients with mechanical back pain.

O 12

TARGETING MONOCYTE-EXPRESSED HLA-B27 HOMODIMERS IN ANKYLOSING SPONDYLITIS

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Background: Possession of HLA-B27 is strongly associated with development of Spondyloarthropathies including Ankylosing Spondylitis (AS). The mechanism by which HLA-B27 confers this susceptibility is unclear. HLA-B27 forms both heterotrimers (B27) associated with peptide and beta-2-microglobulin, and also heavy chain homodimers ($B27_2$). A pathogenic role for these homodimers has been proposed. However lack of a specific detection reagent has hampered elucidation of $B27_2$ expression. We generated an antibody to $B27_2$ using phage display technology, to investigate the role of homodimers in AS.
Methods: Phage display technology was used to generate monoclonal antibodies specific for $B27_2$. Biotinylated recombinant $B27_2$ complexes were used for positive selection and heterotrimeric B27 for negative selection of a phage fAb library. One clone selected for further characterisation, HD6, was then sub-cloned to generate a chimeric antibody comprising human fAb_2 and murine IgG1 Fc. ELISA was used to confirm its specificity for $B27_2$ complexes. For recognition of cell-expressed $B27_2$, the human B cell lines LBL721.220 (.220), C1R stably transfected with HLA-B27 or control HLAs, and AS patient and control peripheral blood mononuclear cells were used and results analysed by FACS. Inhibition of the interaction of $B27_2$ with the immunoreceptors KIR3DL1, KIR3DL2 and LILRB2 was determined using transfected and FACS-sorted cell lines.
Results: 1) HD6 specifically recognised recombinant $B27_2$ in ELISA, but not HLA-A2, B7 or B27 heterodimers. 2) HD6 bound in FACS to LBL721.220 cells transfected with HLA-B27, which express $B27_2$ cell surface homodimers, but not to LBL721.220 B7 or to B27 with Cys 67 mutated to serine (which do not express $B27_2$). 3) HD6 bound in FACS to peripheral blood monocytes from AS patients but not controls. 4) HD6 inhibited the interaction of $B27_2$ with the immunoreceptors KIR3DL1, KIR3DL2 and LILRB2.
Conclusions: A novel phage display-derived monoclonal antibody has been generated that recognises both recombinant and cell-expressed $B27_2$ by ELISA and FACS. HD6 stains monocytes of AS patients. HD6 will be a powerful tool to understand the role of $B27_2$ in the pathogenesis of SpA and may additionally have therapeutic potential.

O 13

EFFECTS OF ETANERCEPT VS. SULFASALAZINE ON ACUTE INFLAMMATORY LESIONS AS DETECTED BY WHOLE BODY MRI IN EARLY AXIAL SPONDYLOARTHRITIS – A 48 WEEK RANDOMIZED CONTROLLED TRIAL

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Purpose: To evaluate the potential of etanercept (ETA) versus sulfasalazine (SSZ) to reduce active inflammatory lesions on whole-body magnetic resonance imaging (wb-MRI) in active axial spondyloarthritis (SpA) of symptom duration of less than 5 years.
Methods: Patients were randomized to ETA (n=40) or SSZ (n=36) treatment over 48 weeks. All patients showed active inflammatory lesions (bone marrow edema) on wb-MRI in either the sacroiliac joints (SIJ) or the spine. Wb-MRIs were performed at weeks 0, 24 and 48 and were scored for active inflammatory lesions in SIJ, spine including posterior segments, peripheral enthesitis and synovitis by two radiologists, blinded for treatment arm and MRI time point. The primary endpoint was the reduction of active inflammatory lesions on wb-MRI.
Results: Patients' baseline characteristics were similar between both groups. At baseline, 95% of the patients showed active inflammatory lesions in the SIJ, 47% in the spine, but only 5% in the spine but not in the SIJ. In the ETA group, the reduction of the SIJ score (from 7.7 at baseline to 2.0 at week 48) was significantly (p=0.003) larger compared to the SSZ group (from 5.4 at baseline to 3.5 at week 48), similar to the reduction in the spine: 2.2 to 1.0 in the ETA group vs. 1.4 to 1.3 in the SSZ group between baseline and week 48, respectively (p=0.0024). Enthesitis improved also significantly (p=0.027) better in the ETA (26 sites at baseline to 11 sites at week 48) compared to the SSZ group (24 sites at baseline to 26 sites at week 48). Peripheral synovitis and inflammation on the posterior segments showed no significant difference between the two treatment groups.
50% of the patients reached ASAS clinical remission and 70% ASAS 40 response in the ETA group vs 19% and 31% in the SSZ group at week 48.
Conclusion: In patients with early axial SpA active inflammatory lesions detected by wb-MRI improved significantly better in ETA- versus SSZ-treated patients. This effect correlated with a good clinical response in the ETA group.

O 14

RADIOGRAPHIC PROGRESSION IN PATIENTS WITH ACTIVE NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS TREATED WITH ADALIMUMAB OVER 2 YEARS IN COMPARISON TO A HISTORICAL CONTROL GROUP

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Purpose: To evaluate the baseline radiographic changes and long-term effects of adalimumab on radiographic progression in patients with active axial spondyloarthritis (SpA) not yet fulfilling the modified New York Criteria who showed a good clinical response (1).
Methods: Radiographs of the SI-joints (SIJ), lateral cervical and lateral lumbar spine were obtained at baseline and at year 2 in patients treated with adalimumab. Results were compared with baseline and 2-year follow up radiographs from a historical cohort (GESPIC) of axial SpA patients naïve to TNF-antagonist therapy and matched for disease activity and gender. Radiographs from the GESPIC cohort and the adalimumab study were combined and read in 1 batch by 3 independent assessors (all blinded to origin of cohort and sequence) using the modified New York criteria for the SIJ and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).
Results: For the GESPIC cohort 13 radiographs of the SIJ, the cervical and lumbar spine were scored. Twelve pairs of radiographs of SIJ, 12 of cervical and 14 of lumbar spine were available from the adalimumab group. Patients in this analysis were 53 % male for the GESPIC cohort and 52% males for the adalimumab study with a mean age of approximately 43 years for the GESPIC group and 32 years for the adalimumab study. Baseline disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 5.5 (± 1.3) for the GESPIC patients and 4.8 (± 1,68) for the adalimumab group. The baseline mSASSS score for the cervical spine (SD)/ lumbar spine (SD) was 1.22 (1.94) and 0.80 (1.21) for the GESPIC cohort and 0.85 (0.79) and 0.76 (0.88) in the adalimumab patients. After two years follow up there was no clear change in the scores for both groups. The mean changes are listed in Table I.

Conclusions: Both in the intervention and in the non intervention group no significant radiographic changes in SI joints and spine could be observed for both groups after two years in patients with early non-radiographic axial SpA, which is different from patients with established AS (2-4). Longer follow ups are necessary to answer the question whether TNF-blockers can inhibit radiographic progression if axial SpA patients are treated early.

Table I. Mean Changes in the mSASSS and the sacroiliitis score* in patients with active axial Spondyloarthritis treated with adalimumab over two years in comparison to a historical cohort (GESPIC)

	Cervical Spine	Lumbar spine	SI-Joints
GESPIC	0.04	0.00	0.04
Adalimumab	0.01	0.25	0.03

(*according to the modified New York criteria).

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Poster Presentations

P 1

EXPRESSION PROFILING OF SYNOVIAL BIOPSIES REVEALS MMP-3 AS A LOCAL MARKER OF ANKYLOSING SPONDYLITIS

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Many expression profiling studies in ankylosing spondylitis (AS) have focused on peripheral blood due to ease of sample collection. Although such samples can generate an accurate profile for the activity of circulating immune cells they are less informative for disease-associated changes occurring at the joints. Specifically targeting the actual local sites of disease activity can generate valuable insights into cellular activity underlying the severe damage occurring in the joints in AS due to excessive bone formation. Currently little molecular detail is known about how the initial inflammatory stimulus "switches-on" the bone formation response. We obtained synovial biopsies from 8 seronegative spondylarthropy (SpA) and ankylosing spondylitis patients and compared their expression profiles to 7 samples from healthy controls and osteoarthritis (OA) patients. Using the Illumina microarray-based DASL protocol, specifically developed to allow analysis of degraded RNA obtained from archived FFPE-biopsies, we generated an expression profile that clearly delineated the AS/SpA patients from the Cont/OA samples. No differences were seen between the SpA and AS patients and between the OA and control samples. One of the genes most highly overexpressed in the AS/SpA samples was MMP-3 and we confirmed this overexpression using quantitative RT-PCR. To further confirm a possible role in local joint pathology we then validated the expression changes using immunohistochemistry, and showed significant numbers of MMP-3-positive cells in AS and SpA samples with neglible numbers of positive cells in OA and control samples. Previously MMP-3 has been well-characterised as a serum biomarker of SpA and it has been suggested that the circulating MMP-3 could originate from affected joints. We have demonstrated overexpression of MMP-3 in disease-site specific samples at both the RNA and protein level in SpA and AS tissues supporting MMP-3 playing a role in the local tissue pathology possibly contributing to the progression from inflammation to bone formation.

P 2

GENETIC STUDIES OF ANKYLOSING SPONDYLITIS IN KOREA CONFIRM ASSOCIATIONS WITH ERAP1 AND 2P15 REPORTED IN CAUCASIAN CASES

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Objective: Ankylosing spondylitis (AS) is a chronic disabling disorder and pathogenesis is not understood. Multiple genetic factors are thought to be important contributors to disease susceptibility and MHC, IL23R, ERAP1, 2p15 and 21q22 are known to be associated with AS. TASC investigators have recently reported additional genes associated with AS susceptibility including IL1R2, ANTXR2, and gene deserts at 2p15 and 21q22. We evaluated these new candidate genes in a large cohort of Korean AS cases.
Methods: A total of 1164 AS cases and 752 ethnically matched, healthy controls who are native Koreans were enrolled for this study. 8 SNPs were analyzed to define genetic association with Korean AS. The MassARRAY® system (Sequenom, San Diego, CA) was used to genotype each study participant in a two-well reaction designed using Assay Designer 3.1.
Results: Significant positive associations of AS with ERAP1 SNPs, rs27037 (p=1.31×10^{-4}) and rs27434 (p=4.59×10^{-6}), were observed. The SNP rs10865331 of gene desert at 2p15 also showed a significant association with AS (p=4.63×10^{-5}).
Conclusions: This is the first confirmation in a non-Caucasian population that genetic polymorphisms of rs27037, rs27434 and rs10865331 are associated with AS, implicating common pathogenetic mechanisms in Korean and Caucasian AS.

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P 3

FAMILIAL RISK OF ANKYLOSING SPONDYLITIS IN CHINA

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Background: Previous studies have suggested that genetic susceptibility may play an important role in the etiology of Ankylosing spondylitis (AS). However, nowadays, few large-scale studies have been conducted on familial risk of AS China.
Objective: In the era of genome-wide association studies, familial risks are used to estimate disease heritability and the likelihood of candidate-gene identification. This study was to investigate the familial of the blood relatives of AS patients.
Methods: One thousand four hundred and forty-nine patients with AS in China were enrolled and identified as probands in the study. A face-to-face investigation was performed and family histories of AS were observed in blood relatives of the patients, including first-degree relatives (FDRs), second-degree relatives (SDRs) and third-degree relatives (TDRs). To assess familial aggregation, we used standardized incidence ratios (SIRs) to measure the risk of AS for blood relatives and compared the observed number of cases with the number predicted by population-based frequencies in China. The prevalence of AS in Chinese Han population is 0.253%.
Results: A total of 2039 patients with AS, including 1637 (80.28%) male and 402 (19.72%) female, with an average age of 27.32±8.90 years were investigated in the study. Among all the patients, 636 (31.20%) patients had hip involved. and familial history of SpA were observed in 420 (20.60%) patients. The study showed that in all AS patients (including familial AS and sporadic AS), the SIR of developing AS in all blood relatives, first-degree relatives(FDRs), second-degree relatives(SDRs) and third-degree relatives(TDRs) were 3.65 (95% confidence interval 2.90-4.23; p= 0.000), 15.18 (95% CI 8.98-24.65; p= 0.000), 3.44 (95% CI 2.280-4.33; p=0.000), and 1.25 (95% CI 0.89-1.65; p=0.098) respectively. What's more, a significantly elevated risk for AS was observed in the relatives of familial AS, the SIR were: 17.31 (95% CI 11.70-25.02; p=0.000), 68.74 (95% CI 25.47-247.11; p=0.000), 16.49 (95% CI 8.14-29.15; p=0.000), and 5.92 (95% CI 3.36-10.02; p=0.000) in all blood relatives, FDRs, SDRs and TDRs respectively.
Conclusions: Comparing to population-based frequencies in Chinese Han population, the blood relatives of AS patients tend to have a significantly elevated risk for AS, especially in the FDRs and SDRs of the familial AS patients.

P 4

CARD9 IS A CANDIDATE GENE FOR THE CHROMOSOME 9 ASSOCIATION WITH ANKYLOSING SPONDYLITIS

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Background: Ankylosing spondylitis (AS) is polygenic with contributions from the genes HLA-*B*27*, *ERAP1* and *IL23R*. A recent genome-wide association screen (GWAS) identified associations (p~0.005) with two non-synonymous single nucleotide polymorphisms (nsSNPs), rs4077515 and rs3812571 in a region of chromosome 9q previously been linked to AS. These SNPs are in the adjacent genes caspase recruitment domain-containing protein 9 (*CARD9*) and small nuclear RNA-activating complex polypeptide 4 (*SNAPC4*).
Results: We replicated these associations in 730 AS patients compared with 2879 historic disease controls (rs4077515 p=4x10^{-4}, odds ratio (OR)=1.2, 95% confidence interval (CI)=1.1–1.4; rs3812571 p=3x10^{-4}, OR=1.2, 95% CI=1.1–1.4). Meta-analysis revealed strong associations of both SNPs with AS, rs4077515 p=5x10^{-6}, OR=1.2, 95% CI=1.1–1.3 and rs3812571 p=6x10^{-6}, OR=1.2, 95% CI=1.1–1.3. We then typed 1604 AS cases and 1020 controls for 13 tagging SNPs; 6 showed at least nominal association, of which 5 were in *CARD9*. We imputed genotypes for 13 additional SNPs but none was more strongly associated with AS than the tagging SNPs. Finally, interrogation of an mRNA expression database revealed that the SNPs most strongly associated with AS were those most associated with *CARD9* expression.
Conclusion: *CARD9* is a plausible candidate for AS given its central role in the innate immune response. The *CARD9* SNP rs10870077 is also associated inflammatory bowel disease (IBD). This SNP is independently associated with AS in our study as the association remains after removal of cases with IBD. A similar independent AS association has been found with the *IL23R* gene which is also associated with psoriasis and Crohn's disease. We propose that *CARD9* is the second gene to share an independent genetic association with both AS and IBD.

P 5

TNFR1 & ANKYLOSING SPONDYLITIS

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Background: TNFR1 is the primary TNF receptor that causes NK-kB activation leading to cell survival and pro-inflammatory signals. TNFRSF1A is an attractive candidate gene for AS, it showed marginal association in the TASC study, and its association with other inflammatory diseases such as inflammatory bowel disease strengthens the case for a role in AS.
Objectives: The aim of this study is to determine whether variations in TNFRSF1A are associated with susceptibility to AS.
Methods: 11 SNPs were genotyped in 1604 cases and 1019 controls. Cochrane-Armitage test of trend was used for case-control analysis (p<0.05). For haplotype analysis, $\chi 2$ test was used to determine statistically significant associations. Two SNPs were also genotyped in the TASC study (rs4149577 and rs4149578). Data for these SNPs were combined in a meta-analysis. TNFRSF1A was re-sequenced in 48 AS cases. One novel and two known SNPs were genotyped in the larger case-control population and tested for association with AS.
Results: No statistically significant associations between TNFRSF1A SNPs and AS were observed.
Meta analysis of data for rs4149578 showed nominal association (p=0.0067, OR~0.86, 95% CI 0.77-0.96). Data for rs4149577 were not combinable (Cochrane Q p=0.026). None of the 25 haplotypes tested reached statistical significance.
Conclusions: In the meta-analysis, magnitude and direction of the associations are in agreement for the two different studies with a very narrow confidence interval for the random effects pooled odds ratio for rs4149578. The power of this study was 75% which indicates that larger sample populations may be required to detect an association with TNFRSF1A SNPs.

P 6

A GENOME-WIDE SNP LINKAGE ANALYSIS SUGGESTS A SUSCEPTIBILITY LOCUS ON 6P21 FOR ANKYLOSING SPONDYLITIS AND RELATED WITH INFLAMMATORY BACK PAIN TRAIT

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Objectives: We aim to screen for ankylosing spondylitis (AS) disease and clinical traits susceptibility loci by using an affected-only linkage analysis based on SNPs in a genome-wide manner.
Subjects and Methods: Ten AS families of Cantonese origin were enrolled. Each DNA sample was genotyped by Illumina HuamHap 610-Quad SNP Chip. Data formatting and quality control of genome-wide SNP linkage analysis were using PLINK with exclusion criteria including minor allele frequency <0.01, SNP call rate <90%, and deviation from Hardy-Weinberg Equilibrium (p<0.001). One of each pair of SNPs was removed if there shared high LD with an r2 >0.3. The LD estimation was based on a Cantonese population with 980 healthy controls. An affected-only linkage analysis was executed using linkage analyses for disease and clinical traits. The customized allele frequencies were based on the 980 Cantonese controls. SNP genetic map positions were interpolated as their physical positions in megabyte. We validate the susceptibility genes by case-control association analysis in 386 sporadic cases and 977 unrelated healthy, and P values were corrected by Bonferroni method.
Result: 78 AS patients in ten families: mean age was 39.47±15.79 years, mean onset age was 22.69±9.62 years, male to female ratio was 1.6:1, dactylitis (5/78, 6.41%), hip joint involvement (9/78, 11.54%), peripheral arthritis (22/78, 28.21%), inflammatory back pain (69/78, 88.46%) and HLA-B27 (70/78, 89.74%). In addition, the age (mean age: 28.23±9.01) and gender (male to female ratio 328/58) of 386 sporadic cases were not significantly different compared with the 977 unrelated healthy (mean age: 47.51±11.61, male to female ratio: 713/264) controls in this association analysis.
The similar region were detected in disease (AS), IBP and HLA-B27 by the nonparametric and parametric linkage analysis respectively. And the identical susceptibility locus of these three traits ranged from 30177504 to 32154253 on 6p21, spanning above 19.8Mb region. In this susceptible locus, we detected 1538 SNPs in the same Infinium array (Illumina) between case and control in our association analysis data, P value corrected by Bonferroni method was 3.25E-05.
Conclusion: Genome-wide SNP linkage analysis in ten family with ankylosing spondylitis suggests a susceptibility locus on 6p21 for AS, and it also was the risk locus affecting IBP of AS patients.

P 7

THE CD3CD56 CELLS ARE ELEVATED IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Objective: The aim of this study was to investigate a systemic analysis of the immune cells in ankylosing spondylitis (AS) comparing to healthy controls.
Methods: Patients with AS (n=49) defined by the modified New York criteria, and healthy controls (n=51) were included in the experiments. Frequencies of immune cells were measured by flow cytometry. The following monoclonal antibodies (mAbs) and reagents were used in this study: The following monoclonal antibodies (mAbs) and reagents were used in this study: phycoerythrin (PE)-conjugated anti-CD56 mAb, fluorescein isothiocyanate (FITC)- or peridinin chlorophyll-*a* protein (PerCP)-conjugated anti-CD3 mAb, FITC-conjugated anti-CD4 mAb, allophycocyanin (APC)-conjugated anti-CD8 mAb, FITC-conjugated anti-CD14 mAb, APC-conjugated anti-CD19 mAb, PE-conjugated anti-6B11mAb (all from Becton Dickinson, San Diego, CA), and PE-conjugated anti-TCRVα24 mAb. Clinical parameters and radiographic damage score were also investigated simultaneously.
Results: Among 49 patients, the mean age (SD) was 36.5 (10.8), and the mean disease duration (SD) was 53.5 (50.0) months. 89.8% were men. There was no statistically significant difference in age and gender between AS and healthy controls. No significant associations were observed between clinical parameters of the AS and the number of immune cells. However, percentage and absolute number of CD3CD56 cells in peripheral blood mononuclear cells (PBMCs) were significantly higher in patients with AS compared with age- and sex- adjusted healthy controls (mean 2.36% Vs 0.9%, p=0.004; mean 65.3 cells/μl vs 19.7 cells/μl, p=0.006). No differences of the percentage or absolute number of other immune cell were observed between patients with AS and healthy controls.
Conclusions: Increased CD3CD56 cells may play a role in the pathogenesis in AS. Further studies are needed to evaluate the function of this cell.

P 8

FACTORS LEADING TO LOW QUALITY OF LIFE IN ANKYLOSING SPONDYLITIS (AS)

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Background: ASQoL is a specific quality of life instrument for AS. There are no studies about this index in patients with severe radiographic damage.
Methods: Seventy-four patients with AS (modified New York criteria) and severe radiographic score (BASRI-t ≥ 8) were prospectively analyzed. The clinical assessments included demographic data, metrology analysis of spine (modified Schober's, chest expansion, cervical rotation) and hip (intermaleolar distance). In addition, indexes of disease activity (BASDAI), physical function (BASFI), hip and shoulder pain or disability and visual analogical scale (VAS) for total spinal pain and patient overall assessment were performed. Quality of life was evaluated by ASQoL (0 to 18). Low quality of life was considered when ASQol >11. Means and standard deviations [Mean (SD)] were calculated for clinical variables and compared using the student's t-test. Categorical variables were analyzed with Fisher's test. Statistical significance was determined at p<0.05.
Results: Twenty-four (32%) patients had low quality of life. In spite of similar restriction of spine, hip mobility and radiological index (p>0.05), the group with low quality of life had statistical association with higher mean age [54 (11) vs. 45 (12) years p<0.001] and disease duration [29 (10) vs. 20 (9) years p<0.01], higher BASDAI [5.0 (2.0) vs. 2.8 (1.5) p<0.01], worse physical function [7.5 (1.4) vs. 4.4 (2.0) p<0.01], more shoulder involvement [83% vs. 18% p<0.01] and higher VAS for total spine pain [5.1 (2.8) vs. 3.2 (2.3)] and the overall assessment of the patient [8.0 (1.4) vs. 3.9 (2.6) <0.01]. No statistical association were found with education level, family income, race or work disability (p>0.05).
Conclusion: Low quality of life in severe long term AS is mostly determined by disease activity and physical dysfunction. Our results support that appropriate control of disease activity can improve quality of life in this subgroup of AS patients.

P 9

MAJOR DETERMINANTS OF WORK DISABILITY IN ANKYLOSING SPONDYLITIS

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Background: Although work disability in AS ranges from 9% to 41%, no previous studies have assessed metrology and radiographic indexes.
Methods: One hundred - twelve AS patients were included in a cross-sectional study and divided in two groups: work disability (WD) and working group (W). Demographic parameters and disease related indexes included: disease activity index (BASDAI), physical function index (BASFI), health-related quality of life (ASQoL), visual analogue scale (VAS), patient's assessment scale (AVG), hip disability and metrology parameters. Radiological examination of spine, sacroiliac and hip (BASRI-t) were performed. Inflammatory parameters were detected by C-Reactive Protein (CRP) and erythrocyte sedimentation rate (ESR) analysis. Means and standard deviations [mean (SD)] were calculated for clinical variables and compared using student's t-test. Categorical variables were analyzed by Fisher's test. Statistical significance was determined at p<0.05.
Results: A high prevalence of labor force withdrawal was noted in 64% patients. No significant differences among gender, race, BASDAI, CRP and ESR were observed. WD was related to higher mean age [48 (13) vs. 39 (10) years, p<0.01] and disease duration [22 (10) vs. 15 (9.7) years, p<0.01]. Furthermore, WD was associated to worse BASFI [5.4 (2.2) vs. 3.4 (2.5), p<0.01], worse BASRI-t [11.2 (3.7) vs. 8.3 (3.7), p<0.01] and more limitation at modified Schober's test measurement [2.2 (1.4) vs. 3.3 (1.4) cm, p<0.01] and intermaleolar distance [71 (24) vs. 91 (26) cm, p<0.01]. ASQol and AVG scores were higher in WD [8.4 (4.9) vs. 4.2 (4.4), p<0.01; and 5.8 (2.7) vs. 4 (3), p<0.01].
Conclusion: AS work disability is related to late-stage radiologic and functional impairment of the disease, in spite of inflammatory activity.

P 10

MAPPING MEASURES OF DISEASE TO THE EQ-5D IN PATIENTS WITH ANKYLOSING SPONDYLITIS: WHICH APPROACH AND WHICH INSTRUMENTS FIT BEST?

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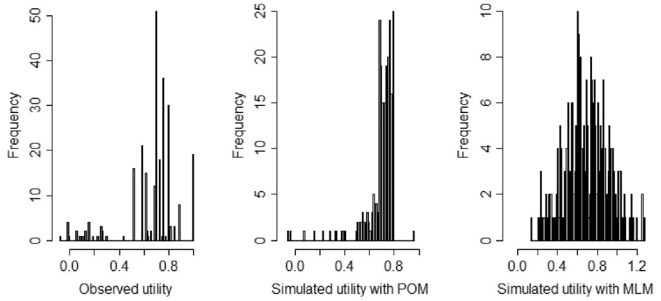
Introduction: In economic evaluations the long-term course of the diseases can be modelled in terms of not only disease status, but also health utility (HU). Since clinical studies that are frequently used to parameterize the economic models do not give HU data, mapping specific disease status measures to HU has become increasingly popular. In ankylosing spondylitis (AS), no studies have been conducted on the methodological approach to estimate the association between possible explanatory variables and HU.
Objectives: To investigate (1) which statistical approach is the most relevant for analyzing the relationship between disease status measures for AS and the EQ-5D generic utility and (2) which set of variables best explain EQ-5D while ensuring model parsimony.
Methods: Data from a sample of 66 Dutch patients with AS that are under control of rheumatologists and not treated with TNF inhibitors were used. These patients were followed every 2 months for up for two years, resulting in 264 records of age, gender, symptom duration, disease duration, BASDAI, BASFI, BASMI and EQ-5D utility. EQ-5D utility was calculated using the UK tariff. Full multiple linear regression model (MLM) and proportional odds model (POM) were first fitted to data. Stepwise selection of the explanatory variables was performed based on Akaike's Information Criterion (AIC). The selected models after stepwise procedures were used in Monte Carlo simulation to regenerate EQ-5D utility. Models were compared by means of range, quantile, histogram, mean absolute error (MAE) and root mean squared error (RMSE).
Results: Although the MAEs and RMSEs resulted from the MLM and POM were comparable, the range, quantile and histogram of the MLM-simulated values are far more deviated from the observed values in comparison with those of the POM-simulated values. Variables with high predictive power included BASDAI, BASFI, BASMI, age and gender.
Conclusions: POM appears to be more relevant than MLM in prediction of EQ-5D utility. Demographics as well as different disease status as explanatory variables should be taken into account.



P 11

CAN PATIENTS WITH ANKYLOSING SPONDYLITIS (AS) DISTINGUISH BETWEEN HEALTH, WELL BEING AND QUALITY OF LIFE (QOL): A MIXED QUANTITATIVE AND QUALITATIVE STUDY

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Background: In the assessment of the global impact of disease on patients, a distinction is made between global health, well-being and quality of life (QoL). Commonly numeric rating scales (NRS;0-10) are used. Although these concepts are different from theoretical point of view, there is doubt whether patients can distinguish them.
Objective: To know whether patients with ankylosing spondylitis (AS) score their global health, well-being and QoL different and to understand whether patients attach different attributes to these concepts.
Methods: Patients with AS (OASIS) completed during the 12th year of the cohort's evaluation an additional questionnaire on global impact of disease. Patients were asked first to score on a NRS (0-10) global impact on health, well being ($BASG_1$) and QoL during the last week. On the next page, they were asked to write down for each of the questions what they are taking into account when completing the score. Finally, the global questions were repeated, to know whether score would be different when having considered to content of the concepts.
Results: 60 patients completed the questionnaire. The Table presents the results of the globals before and after considering the attributes:

	Health	Well-being	QoL
Before	3.8 (2.5)	3.8 (3.7)	3.5 (2.6)
After	3.8 (2.4)	3.9 (2.4)	3.6 (2.4)

Interquartile range of the difference between health and well-being was [0-0], between well-being and QoL [-1to1] and between health and QoL [1-to1].
Notwithstanding, 1/3rd of patients stated there were differences between the three concepts. While pain, function and fatigue were considered attributes of each concept, psychological factors were more frequently mentioned to be related to well-being and social factors to QoL.
Conclusion: Although 1/3rd of AS patients state that global health, well-being and QoL are different concepts, they score these globals exactly the same. Asking patients first to think about these concepts does not change the result. It is possible that for patients with a chronic disease, health is the major contributor to well-being and QoL. To be able to understand results better, comparable questionnaire was sent to health controls, matched for gender and age.

P 12

TUBERCULIN SKIN TEST AND BOOSTER PHENOMENON PREVALENCE AMONG PATIENTS WITH RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS IN USE OF TNF BLOCKERS AGENTS

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Introduction/ Objectives: There are many difficulties to diagnosis latent tuberculosis infection (LTbI), particularly in countries with high incidence of tuberculosis as Brazil. In order to identify patients with LTbI, the Brazilian Society of Rheumatology recommends that epidemiological aspects, tuberculin skin test (TST) and lung X-ray must be performed in all patients with chronic inflammatory joints diseases (CIJD) and selected to receive anti-TNFα therapy. Our aim was evaluate the prevalence of the booster phenomenon among patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and to receive TNF-α blockers.
Patients and Methods: A total of 202 patients (109 with RA, ACR criteria 1987; 93 with AS, New York criteria, 1984), with moderate or severe activity and indication for anti-TNFα therapy, were recruited and prospectively followed for 12 months. Healthy controls were 215 individuals. Clinical data, including details about the disease and epidemiological aspects, were recorded, as well as thorax X-ray and TST (PPD) were performed in all patients. A second TST was performed among patients that had TST lower than 5 mm. Boosting was defined as an induration higher than 10 mm in the second test, with an increase of at least 6 mm over the first TST. During 12 months, all of them were followed in order to identify clinical features of tuberculosis infection. The association of boosting with independent variables was evaluated using multivariate analysis.
Results: At baseline, the prevalence of the first TST was 12.8% and 37.6% in RA and AS patients, respectively. The positivity of TST in control group was 10,1%. Twenty-four RA patients and 14 AS patients performed the second TST. The positivity for this was 8.3% and 28.6%, respectively. Boosting phenomenon did not associate with gender, age, race, BMI, time of disease, DAS28, BASDAI, HAQ, concomitant diseases or other treatments, epidemiological items, BCG history or X-ray changes. All the patients with positivity for second TST received isoniazide (INH) for 6 months.
After 12 months follow-up, none of them had any symptom or clinical feature of micobateria infection, as well as event adverse related to INH.
Conclusion: The positivity to the first or second TST was significantly more frequent in AS patients than RA patients (3:1). Boosting had relevant clinical meaning because can avoid false-negative first TST and identify more patients with probable LTb, especially in countries with high prevalence of tuberculosis. Besides, it increased the rate of prophylaxis with INH. However, more studies are necessary in order to demonstrate if this therapeutic strategy is reasonable and cost-effectiveness.

P 13

ENTEROPATHIC SPONDYLOARTHRITIS CHARACTERISTICS COMPARED WITH THOSE OF ANKYLOSING SPONDYLITIS

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Objectives: Aiming to assess differences between enteropathic Spondyloarthritis (entSpA) (SpA related to Crohn's disease and Ulcerative colitis) and Ankylosing spondylitis (AS) we analysed data from a multicultural cohort comprising of 40 [(M:F=9: 31; 22.5%: 77.5%) age (mean+sd) (49.6±14.1)] patients with enteropathic SpA and 84 [(M: F=41: 43; 48.8%: 51.2%) age (43.4±12.8)] patients with AS.
Methods: Patients were asked age at diagnosis, (ad) disease duration, (dd) delay in diagnosis, (de.d) enthesitis pain, night pain (np), BASDAI, BASFI. Well being over past week (wbw) well being over past 6 months (wb6m) treatment effectiveness (txe). Disease activity was assessed by ESR and CRP.
Regression analysis was used to identify correlations between the disease characteristics in each group and t-test was used to assess statistical significant differences between the 2 groups.
Results: Patients race distribution in the AS and entSpA group were in %: Caucasians (C), Asians (As), Africans (Af) 45.9: 41.2: 12.9 vs 43.9: 39: 14.6 respectively. Ad was for AS 37.8±14 vs 45±13.7 for entSpA; dd was 11.5 (±9.7) vs 9.3 (±12.7). enthesitis pain reported by 32.5% of AS patients and 40% of entSpA. Np, BASDAI and BASFI was 6.1 (±2.8) vs 5.7 (±3.2); 6.2 (±1.7) vs 5.7 (±1.9) and 4.8 (±2.7) vs 4.7 (±2.9) respectively. Wbw was 5.6 (±2.6) vs 5.6 (±2.7) wb6m was 6.3 (±2.4) vs 6.2 (±2.7) txe was 3.8(±2.8) vs 3.5 (±2.8), while ESR and CRP were: 16.2 (±17) vs 21.5 (±18) and 7.4 (±7.9) vs 10.8 (±14.5) respectively.
Statistical analysis revealed that the 2 groups have similar disease with the only exceptions the delay in diagnosis being longer for the AS group (p=0.01) and the enthesitis being more frequently reported by entSpA (p=0.002) than AS patients. No differences between races are seen. Within the 2 groups night pain found associated with age (0.002)and age at diagnosis (0.01) in the entSpA and age at diagnosis (0.001) in the AS group. CRP in entSpA is associated with BASDAI score [(0.05) and (BASDAI 5; morning stiffness (0.009)], while no such association is seen in AS. BASFI score is associated with disease duration in AS (p=0.006) but not in EntSpA.

P 14

HOW THE DISEASE PRESENTS IN ENTEROPATHIC SPONDYLOARTHRITIS COMPARED WITH ANKYLOSING SPONDYLITIS

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Objectives: Aiming to assess how musculoskeletal (msk) symptoms present at disease onset in patients with Crohn's disease and ulcerative colitis (UC) collectively called enteropathic SpAs (entSpA), we analysed the frequency of symptoms at presentation from patients with entSpA and we compared them with those msk symptoms at presentation reported by patients with AS (AS being considered prototype disease of the SpAs).
Methods: From a list of 7 msk symptoms that can be present at disease onset (back pain, neck pain, shoulder pain, hip pain, knee pain, buttock pain, foot pain) patients with AS and entSpA were asked to respond as to which ones were present when the disease from the msk system had started. More than 1 symptom could be reported by each patient. Statistical analysis performed using non parametric tests (t-test and Wilcoxon rank sum test).
Results: A total of 124 patients were questioned. They were 84 with AS and 40 with entSpA (AS: entSpA 2.1:1) The entSpA group had 12 patients with Crohn's disease and 28 with Ulcerative colitis. The mean age for AS was 49.6 (sd 14.1) and for entSpA (43.4+12). The mean age at diagnosis was 37.8 (±14) for AS and 45 (±13.7) for entSpA. The BASDAI and BASFI scores were 6.2 (±1.7) for AS and 57 (±1.9) for ent SpA and 4.8 (±2.7) for AS and 4.7 (±2.9) for entSpA respectively. Patients from both groups reported back pain as most frequent symptom at presentation (70% reported by AS and 57% by entSpA (p=NS). Although AS patients reported neck pain as the most frequent symptom (reported by 35.9%) entSpA patients reported knee pain as the 2nd most frequent (51.4%), which in AS is reported only by 22.1% (p=0.004 Wilcoxon) and ranked 5th in frequency in AS. Shoulder pain reported as the 3rd in frequency by both groups 26.6% by AS patients and 48.6% by entSpA (wilcoxon rank sum p=0.01). Neck pain reported 4th in frequency by EntSpA (37.1%) but the difference between the 2 groups was not significant (35.9% reported by AS). Hip pain is reported by 24.7 % of AS patients and 28.6 % entSpA patients (NS). Finally foot pain is reported by significantly more entSpA patients (31.4%) than AS (13%) (p=0.02).
Conclusion: EntSpA have collectively taken more peripheral disease at presentation (knees, feet shoulders) than AS despite the fact that both groups confirm back pain as main symptom at disease onset.

P 15

THE SMALL INTESTINAL INVOLVEMENT IN PATIENTS WITH ANKYLOSING SPONDYLITIS IN ACCORDING WITH THE DATA OF PILL ENDOSCOPY

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Background: The involvement of the small intestine is possible visceral complication in the AS. This pathology may be independent visceral manifestation of chronic rheumatic diseases or symptoms associated with inflammatory bowel disease (such as Crohn's disease). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) can also cause an injury of small bowel's mucosa. There is currently no clear data concerning frequency and risk factors of this pathology, as it not sufficiently studied.
Objectives: To exam frequency analysis of the involvement of the small intestine in patients with AS and to evaluate the clinical factors' influence on the development of this complication.
Methods: 18 patients with AS (fulfilled the modified NY criteria) were involved in study group (females 8, males 10, age 27-61, mean age 42,4±14,1 yrs). HLAB27 – 17, HLAB40 - 2. All of patients were treated with NSAIDs in high anti-inflammatory doses (not less than 1 month). 4 patients had iron - deficiency anemia (Hb less than 100 g/l). However, none of the patients had obvious clinical symptoms of Crohn's disease. Diagnosis of pathology of the small intestine was based on data of pill endoscopy (system GIVEN®).
Results: Erosions (numbers from 3 to >20) and ulcers of the small intestine were detected in 12 patients (66.7%). Three patients had serious damages in the terminal portion of ileum and cecum (multiple ulcers, signs of bleeding), which required a colonoscopy. After colonoscopy in 2 of them were found typical endoscopic signs of Crohn's disease. There was no dependence revealed between presence of injury in the small intestine, age, sex, disease activity, duration of NSAID intake, and type of this drugs (selective and nonselective NSAIDs). However, all the patients with an anemia had serious damages of small intestine.
Conclusion: Capsule endoscopy can detect changes in the small intestine in most of the patients with AS. The exact definition of the nature of these changes requires further investigation. Our study confirms that often there is a combination AS and inflammatory bowel disease. It is important that the active search allows you to identify Crohn's disease in patients with AS who do not have clear symptoms of this disease.

P 16

SUPPRESSION OF HUMAN NATURAL KILLER T CELL FUNCTION BY $CD4^+CD25^+FOXP3^+$ REGULATORY T CELLS

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Invariant natural killer T cells (iNKT) and $CD4^+CD25^+FOXP3^+$ T cells (Tregs) are thymus-derived immunomodulatory cells that are important in the control of pathological autoimmune responses. iNKT cells are well known for their capacity to secrete copious amounts of T helper (Th)1 and Th2 cytokines upon recognition of glycolipids presented by CD1d on APC, thereby influencing various immune responses. Here we evaluated a potential functional interplay between human iNKT cells and Tregs in the context of glycolipid induced Thelper cytokine responses.
Therefore, TCRVα24Jα18+TCRVβ11+ (iNKT) and CD4+CD25highCD127low (Treg) cells were isolated from the peripheral blood of healthy individuals by means of FACS-sorting and CFSE labeled iNKT cells were cocultured with increasing numbers of Tregs. iNKT cell proliferation and cytokine production was measured in response to different modes of iNKT activation using the prototypical iNKT agonist α-galactosyl ceramide (α-GalCer), novel Th cytokine polarizing α-GalCer structural analogues or anti-CD3 antibodies. Tregs were able to suppress iNKT cell proliferation and cytokine production in a dose and cell contact dependent manner. The potency of the Treg suppression was related to the strength of the glycolipid iNKT cell agonist, IL-2 levels and iNKT cell activation status. In addition, iNKT cell induced IL-4 secretion was more prone to Treg mediated inhibition as compared to IFN-γ production.
In conclusion, there seems to be a profound suppression of iNKT glycolipid responses by Tregs dependent on the mode of iNKT cell activation. Interactions between these subtypes of regulatory T cells could play a highly important role in immune surveillance and tolerance.

P 17

ULTRASOUND (US) ENTHESEAL INVOLVEMENT IN ASYMPTOMATIC INFLAMMATORY BOWEL DISEASE (IBD) AND ITS CORRELATION WITH IBD CLINICAL FEATURES

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Background: In IBD, enthesopathy -a major feature of spondyloarthropathies (SpA)- is frequently under-diagnosed.
Objective: To investigate US lower limb entheseal abnormalities in patients with IBD without signs and symptoms of SpA and their correlation with IBD clinical variables, familiarity and HLA.
Methods: 81 patients (55 Crohn-CD- and 26 Ulcerative rettocolitis -RCU-, 43 female and 38 male, 41,3±12,4 years old, BMI 24±2) with low active (12) and inactive (67) disease were consecutively studied with US (LOGIC5 General Electric 10 MHz linear array transducer) and compared with 40 healthy controls matched for sex, age and BMI (22 female and 18 male, 49,6±11,1 years old, BMI 24±2). Achilles, quadriceps, patellar entheses and plantar aponeurosis were scored according to the 0-36 GUESS score (1) and total Power Doppler (tPD), calculated by summing semiquantitive method (0-3) The intra- and interobserver agreements were estimated in IBD and controls. Correlation between GUESS, single components of GUESS (thickness, enthesophytes, bursitis and erosions) and tPD, with IBD clinical variables (CDAI and Truelove score, durations of symptoms, difference between CD and RCU, between patients treated with surgery and not), familiarity (for psoriasis, IBD, celiac syndrome, spondyloarthropathies), and HLA aplotypes A,B,C,D were investigated.
Results: 92,6% (71/81) of patients presented almost one tendons alteration with mean GUESS 5,1±3,5/36: 81,5% thickness, 67,9% enthesophytes, bursitis (27,1%), erosions (16,1%). tPD was positive in 13/81 (16%; mean 2,38±2,1) patients. Thickness of tendons in IBD patients was higher than in controls (p<0,05). Intra and interobserver agreement was high (ICC 0,98). GUESS and tPD did not correlate with IBD clinical variables and familiarity. HLADRB1-11 (34%) and the other aplotypes were not different between positive and negative patients. All patients were HLA B27 negative.
Conclusions: US is sensitive tool that may help in IBD to identify patients at risk by evolution to SpA and is not correlated to clinical features of disease.

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P 18

UP-REGULATION OF AUTOPHAGY IN SMALL INTESTINE PANETH CELLS OF PATIENTS WITH ANKYLOSING SPONDYLITIS AND SUBCLINICAL INTESTINAL INFLAMMATION

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Background: Intestinal inflammation occurring in Ankylosing spondylitis (AS) patients has been proposed as a model of early immune alteration related to Crohn's disease (CD). We have recently demonstrated that Paneth cells (PC), play a major role in the control of gut immune homeostasis in AS and CD patients (1). Autophagy, a lysosomal mechanism of degradation of cell self-constituents, is selectively required for maintaining the integrity of the PC granule exocytosis, bacterial handling and generation of major histocompatibility complex (MHC) class II antigen specific CD4(+) T cell responses (2). Furthermore ATG16L1 was identified as a CD susceptibility gene.
Objectives: Aim of this study was i) to evaluate expression of autophagy-related genes ATG16L1, IRGM and MAP1LC3A and ii) to identify cells with active autophagosome formation in ileal biopsies of AS patients.
Methods: Multiple biopsies from terminal ileum were obtained from 25 patients with AS, 30 CD and 15 healthy controls (HC). Expression of human ATG16L1, IRGM and MAP1LC3A molecules was assessed by quantitative Taqman rt-PCR on mucosal samples. Immunohistochemistry with rabbit-anti-human LC3II (a marker of autophagosome formation) and mouse anti-human CD15 (a marker of PC) antibodies was performed on snap frozen ileal biopsies of patients and controls. Genotyping of the ATG16L1 T300A variant (rs2241880) was also performed.
Results: In both AS and CD patients, strongly increased transcript levels of ATG16L1 (20 fold and 10 fold increase, respectively), IRGM (10 fold and 8 fold increase, respectively) and MAP1LC3 (4 fold and 3 fold increase, respectively) were observed compared to normal controls. No influence of the ATG16L1 T300A variant was observed on autophagy genes transcripts levels. The up-regulation of the autophagy pathway was confirmed by immunohistochemical analysis of LC3 protein. The intensity of LC3 immunoreactivity was significantly higher in AS and CD patients, with its prevalent expression in cells located at the bottom of the small intestinal crypt. These cells were further identified as Paneth cells by their pyramidal shape and immunoreactivity for CD15 receptors.
Conclusion: In this study we provide evidence that process of autophagy is enhanced within the intestinal epithelium of AS patients. We also demonstrate that active formation of autophagosomes selectively occurs in Paneth cells of AS and CD patients, highlighting the role of PC in the control of intestinal immune homeostasis.

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P 19

IL-32: A NOVEL PROINFLAMMATORY CYTOKINE OVER-EXPRESSED IN THE INFLAMED GUT OF ANKYLOSING SPONDYLITIS PATIENTS

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Subclinical gut inflammation observed in Ankylosing Spondylitis (AS) patients is immunologically characterized by activation of innate immune system (1, 2). Interleukin (IL)-32 is a recently described pro-inflammatory cytokine that has been reported to be induced by bacterial and viral infection, acting as an important player in innate immune response. IL-32 also exerts an essential pathogenetic role in promoting autoimmunity and chronic inflammation in several models of autoimmune diseases, such as rheumatoid arthritis (3) and Crohn's disease (CD) (4). In this study we aimed to investigate the m-RNA expression and protein tissue distribution of IL-32 in ileal biopsy specimens from patients with AS.
Patients and Methods: Quantitative gene expression analysis, by rt-PCR, of IL-32 was performed on ileal biopsies of 15 AS and 15 CD patients, and 15 healthy subjects (HS). IL-32 tissue distribution and identification of IL-32–producing cells were evaluated by immunohistochemistry and flow-cytometry.
Results: We demonstrated a strong and significant up-regulation of IL-32 transcripts in chronic inflamed AS and CD compared to non-inflamed AS and HS ileal specimens. Epithelial cells and lamina propria T lymphocytes and CD68+ macrophages displayed intense IL-32 positivity in both chronic inflamed AS and CD patients. Finally, abundant IL-32+ intra-epithelial cells were found in the inflamed ileal specimens of both AS and CD and flow cytometric analysis demonstrated these cells to be mainly lymphocytes expressing the gamma delta T-cell receptor.
Conclusions: This is the first study to assess the expression of IL-32 in the subclinical gut inflammation of AS patients. Our findings implicate IL-32 as an important pro-inflammatory cytokine that seems to participate in intestinal innate immune responses. Targeting of IL-32 may provide a novel therapy to treat chronic inflammatory disorders.

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P 20

EFFECT OF HLA-B27 EXPRESSION ON RANKL AND TNF-ALPHA INDUCED OSTEOCLAST DEVELOPMENT IN TRANSGENIC RATS

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The role of HLA-B27 in spondyloarthritis pathogenesis remains undefined. Pathogenesis of these diseases involves inflammation mediated in part by TNF-α, and dysregulated bone formation. The discovery that HLA-B27 misfolding can generate ER stress and activate the unfolded protein response (UPR), suggests that it may have biological effects in cells that are not principally involved in antigen presentation. Therefore, we examined whether HLA-B27 expression influences RANKL and TNF-α induced osteoclast differentiation in a rat model of spondyloarthritis.
Bone marrow (BM) derived CD11b$^+$ cells from 6-week old wild type (WT) and HLA-B27 transgenic (B27-Tg) rats prior to the onset of inflammatory disease, were treated with M-CSF (20 ng/ml) and either RANKL (10-100 ng/ml) or TNF-α (7.5-30 ng/ml) for 5 days and osteoclast formation was quantified by counting TRAP positive multi-nucleated (>3 nuclei) cells. HLA-B27 and BiP expression were visualized by immunoblotting and unfolded heavy chains were analyzed after immunoprecipitation.
TNF-α induced osteoclast formation was increased 2-3 fold in BM cells derived from B27-Tg rats (p<0.05). RANKL had no differential effect on osteoclast numbers however, osteoclasts derived from HLA-B27 expressing preosteoclasts were larger than wild type osteoclasts (>10 nuclei in 50% of B27 Tg cells vs. 10% of WT; p<0.05). HLA-B27 (2 fold) and BiP expression (1.5 fold) were upregulated with TNF-α, and misfolded forms accumulated, suggesting that the UPR was activated in HLA-B27 expressing cells. In contrast, RANKL had no effect on HLA-B27 expression or misfolding, or on BiP expression.
Our results indicate that HLA-B27 expression accelerates the formation of osteoclasts in response to TNF-α, and results in larger osteoclasts under the influence of RANKL. This demonstrates that HLA-B27 expression may have important biological effects in cells that are involved in bone homeostasis. The mechanisms underlying these effects, and the consequences for the regulation of bone formation are currently being investigated.

P 21

CROSS TALK OF ER STRESS AND TOLL-LIKE RECEPTOR SIGNALLING PATHWAYS: MECHANISM OF IL-23 REGULATION

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We have previously shown that ER stress and TLR signalling synergistically enhance IL-23 p19 expression in myeloid cells. Furthermore these combined stimuli substantially enhance the secretion of IL-23 but not IL-12 by dendritic cells. The aim of this study is to investigate the mechanism of this synergy.
We examined the human *IL-23* promoter for potential binding sites for ER stress induced transcription factors and identified a putative site for CHOP10. Chromatin Immunoprecipitation assays confirmed that CHOP10 bound the IL-23 promoter following stimulation of dendritic cells with both ER stress and LPS stimulation. Knock down of CHOP10 mRNA expression in THP-1 cells significantly reduced the induction of IL-23p19 mRNA following stimulation with LPS and ER stress stimuli. CHOP10 knockdown had no significant effect on the induction of a panel of other LPS responsive genes including IL-1β, IL-8, CCL3 and SOD2.
To identify whether ER stress induction of IL-23 mediated by CHOP10 expression plays a role in a more physiological setting, we examined the role of CHOP10 in the induction of IL-23p19 gene expression following intracellular infection with *Chlamydia trachomatis* (CT). Infecting U937 cells with live, but not γ-irradiated, CT induced the expression of ER stress genes including CHOP10.
Furthermore, CHOP10 knockdown significantly reduced the expression of IL-23 in response to infection, confirming the importance of this transcription factor in the induction of IL-23 by infection.
Conclusion: We have shown that ER stress signals make a significant contribution to the control of IL-23 expression, and favour IL-23 over IL-12. Here we show that the ER stress induced transcription factor, CHOP10, is a critical factor that regulates IL-23p19 gene expression. These data suggest that the initiation of ER stress by infection or other physiological processes would contribute significantly to diseases in which IL-23 plays an important role in pathogenesis, including spondyloarthritis.

P 22

SUBJECTS WITH A HISTORY OF YERSINIA-TRIGGERED REACTIVE ARTHRITIS (ReA) SHOW NORMAL INFLAMMASOME ACTIVATION

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Background: The pathogenesis of ReA, sterile joint inflammation preceded by infection in body compartments other than joint cavity (1), is not known but it may involve an aberrant inflammatory responsiveness. Because aberrant inflammasome activation plays a central role in the pathogenesis of hereditary auto-inflammatory syndromes (2), such as cryopyrin-associated periodic syndromes (CAPS) with mutations in the CIAS1/NLRP3 gene and Crohn's disease (CD) with 1007fs mutation of CARD15/NOD2 gene, we studied inflammasome activation in patients with history of ReA.
Subjects and Methods: The study comprises 10 HLA-B27-positive patients, who had had ReA triggered by *Yersinia enterocolitica* O:3 enteritis 29-38 years ago and 20 healthy reference subjects, 10 positive and another 10 negative for HLA-B27, and 2 patients with CAPS, one (with familial cold auto-inflammatory syndrome) heterozygous for A493V and the other (with Muckle-Wells syndrome) heterozygous for T348M mutation, and 2 CD patients homozygous for 1007fs mutation. Circulating mononuclear cells and monocyte-derived macrophages were stimulated with *Yersinia,* LPS (lipopolysaccharide) and MDP (muramyl dipeptide), and with LPS in combination with MDP, for 18 h. Mononuclear cells were also stimulated with LPS in combination with MSU (monosodium urate).
Culture supernatant IL-1β levels were quantified with ELISA.
Results: *Yersinia* and combinations of LPS and MDP or MSU all triggered a robust secretion of IL-1β. IL-1β levels in ReA group and two reference groups were comparable. On contrast, stimulated secretion of IL-1β was reduced in CD cells and induced in CAPS cells, as compared to reference cells.
Conclusions: The methods used seem to distinguish reasonably well aberrant inflammasome activation in clinical settings. Subjects with history of *Yersinia*-triggered ReA show normal inflammasome activation.

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P 23

RATES OF SERIOUS INFECTIONS, OPPORTUNISTIC INFECTIONS, INFLAMMATORY BOWEL DISEASE, AND CANCERS IN SUBJECTS RECEIVING ETANERCEPT VERSUS CONTROLS FROM CLINICAL TRIALS IN ANKYLOSING SPONDYLITIS

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Objective: Assess incidence of serious infections, opportunistic infections, IBD, and cancers in RCTs of etanercept (ETN) versus placebo (PBO) or sulfasalazine (SSZ) and follow-up OLE in AS subjects.
Methods: A combined retrospective analysis was performed using 5 RCTs (4 PBO-controlled and 1 ETNvsSSZ) and 4 OLE (all ETN) studies in AS subjects. Rates of the adverse events (AEs) in control and ETN groups were analyzed using Fischer's exact binomial test.
Results: Baseline demographics and disease characteristics were generally similar between the pooled ETN and control groups. Events and exposure-adjusted rates for key outcomes are presented below.

		Treatment	Total Events	Exposure Pt Yr	Rate/100 Pt Yr	Rate Ratio (95% CI)
Serious Infections	RCT	Pbo/SSZ	1	137.32	0.73	2.19
		ETN	4	250.95	1.59	(0.22, 107.79)
	RCT+OLE	ETN	21	1131.28	1.86	
Opportunistic Infections	RCT	Pbo/SSZ	0	137.32	0	
		ETN	0	250.95	0	
	RCT+OLE	ETN	0	1131.28	0	
IBD*	RCT	Pbo/SSZ	1	137.27	0.73	1.09
		ETN	2	250.90	0.80	(0.06, 64.56)
	RCT+OLE	ETN	20	1131.56	1.77	

			Total Events	Expected Events†	Exposure Pt Yr	SIR (95% CI)
Malignancy SEER	RCT	Pbo/SSZ	0		137.32	
		ETN	0		250.95	
	RCT+OLE	ETN	6	4.07	1131.28	1.47 (0.54, 3.21)
Nonmelanoma Skin Cancer AZ-BCC	RCT	Pbo/SSZ	0		137.32	
	RCT+OLE	ETN	1	8.59	1131.28	0.12 (0.00, 0.65)
AZ-SCC	RCT+OLE	ETN	1	1.79	1131.28	0.56 (0.01, 3.11)
MN-SCC	RCT+OLE	ETN	1	0.73	1131.28	1.37 (0.03, 7.65)

Databases: AZ-BCC: Arizona-basal cell carcinoma; AZ-SCC: Arizona-squamous cell carcinoma; MN-SCC: Minnesota-squamous cell carcinoma; SEER: Surveillance, epidemiology and end results; SIR. standardized incidence ratio.
*new/flare events; †calculated from SEER database for malignancies; from AZ-BCC, AZ-SCC, and MN-SCC databases for skin cancers.

Conclusions: These data suggest that etanercept is associated with a favorable safety profile in AS as reflected by the low rates of these AEs in controlled and long-term OLE trials. Pharmacovigilence continues for these AEs.

P 24

EVALUATION OF THE NEW ASAS INSTRUMENT TO ASSESS DISEASE ACTIVITY, THE ASDAS, IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH TNF BLOCKERS OVER 8 YEARS

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Background: Clinical parameters for disease activity (BASDAI) or response to therapy (ASAS-criteria) in AS mainly rely on patient's opinion. The recently developed ASDAS includes clinical measures and CRP.
Objective: To compare the performance of established tools with the ASDAS in patients with active AS (n=33) treated with infliximab over 3, 5 and 8 years.
Methods: The outcome of the long-term infliximab therapy was calculated according to the ASDAS definitions and compared to established outcomes (BASDAI, ASAS response).
Results: The mean BASDAI decreased from 6.4±1.9 at baseline to 2.3±2.0 at 3y (64% decrease), to 2.4±2.0 at 5y (63% decrease), and to 2.6±1.9 (59% decrease) at 8y (all $p<0.05$). In comparison, the ASDAS decreased from 4.3±0.8 at BL to 1.5±1.0 (65% improved) at 3y, to 1.6±1.0 at 5y and to 1.6±0.9 at 8y (63% decrease). Overall, a BASDAI<3 was achieved by 66.7% patients at 3y and by 63.6% patients at 5y and 8y years. In comparison, at 3y, 5y and 8y, an ASDAS<1.3 ('inactive) was found in 46%, 39% and 52% patients, respectively. Response rates were also similar, with 93.9% and 84.8% patients achieving ASAS 20 ad 97.7% and 93.9% patients achieving ASDAS improvement >1.1 units ('minimally-important change') at 3-months and 8-years, respectively.
Similarly, BASDAI-50% response was seen in 66.7% and 63.6% patients, compared to 72.7% and 69.7% patients achieving ASDAS improvement >2.0 units ('major improvement') after 3 months and 8 years, respectively.
Conclusions: The ASDAS, a new composite disease activity score for AS proposed by the ASAS, was more sensitive than the conventional scores for disease activity and change, confirming recent data on short-term outcomes. More studies are needed to establish the ASDAS as a standard tool for assessment of disease activity in patients with AS in clinical practice.

P 25

SHORT-TERM RESPONSE PREDICTS LONG-TERM OUTCOME AND DISCONTINUATION IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH TNF BLOCKERS

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Background: Anti-TNF therapy was shown to be efficacious in patients with ankylosing spondylitis (AS) over 8 years. There is limited knowledge about predictors of long-term response and maintenance of treatment.
Methods: In a multicenter RCT, patients with active AS (BASDAI>4) were treated with infliximab (5mg/kg i.v./6w) vs. placebo over 3 months (FU1) and continued with open-label infiliximab for up to 8 years (FU2). Differences in the clinical response at FU1 in the group of completers were compared to patients who had dropped out of the study for any reason. As proposed recently, high and low disease activity were defined as BASDAI>4 and BASDAI<3, respectively, while clinically important difference (CID) in BASDAI and BASFI was defined as improvement of at least one score unit. Multivariate transition models were applied to investigate the predictive value of early response patterns to the outcome after 8 years.
Results: Out of 69 patients at BL, 33 patients (48%) completed FU2. Response to treatment at FU1 was predictive for status at FU2: in the multivariate transition model, patients under infliximab treatment who improved in BASDAI and in BASFI from >4 units at BL to <3 units at FU1, had a likelihood of 22% for partial remission at FU1 and a high probability (>75%) to remain on medication, as compared to patients not achieving this disease state. Similarly, patients with improvement less than the CID in BASDAI and BASFI had a likelihood of drop out of 71% during the study, as compared to 24% for patients achieving CID.
Conclusions: Low BASDAI and BASFI levels and partial clinical remission after 3 months of anti-TNF treatment predicted the probability of response and the likelihood for treatment discontinuation over 8 years of treatment. These data argue for an evaluation of the treatment effect of TNF blockers after 3 months as recently recommended by ASAS.

P 26

DISEASE MODIFYING EFFECT OF ETANERCEPT VERSUS SULPHASALAZINE ON SPINAL MOBILITY FOR SUBJECTS WITH ANKYLOSING SPONDYLITIS

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Purpose of Analysis: In the recently completed ASCEND study conducted by Wyeth Pharmaceuticals (now Pfizer Inc.), the etanercept group showed significantly better improvement in BASMI over the sulfasalazine group in subjects with ankylosing spondylitis. In this post hoc analysis, we estimated the disease modifying effect of etanercept over sulfasalazine.
Method: A treatment effect could be from symptomatic (short-term) or disease modifying effects (long-term), or both. The Natural History Staggered Start (NHSS) estimates the disease modifying effects of a treatment based on a single phase controlled trial. The approach uses the relationship between the baseline scores and the short-term treatment effect to estimate changes in symptomatic effects over time. All other changes over time are assumed to be disease modifying.
A mixed model with a quadratic effect over time was fit to the data. Resampling was performed to generate confidence intervals for the disease modifying effect of etanercept over sulfasalazine.
Summary of Results: At week 12, the total improvement of the etanercept group over the sulfasalazine group in BASMI is 0.57, based on the model, of which, 0.21 (36.9%) is estimated to be from disease modifying effects. At week 16, the total improvement is 0.62 based on the model, of which, 0.32 (51.8%) is estimated to be due to disease modification, with a 90% confidence interval of (0.02, 0.61). As the confidence interval does not include 0, the disease modifying effect of etanercept versus sulfasalazine is significant at 90% significance level, though not at 95% level.
Conclusions: In this analysis of the ASCEND data, approximately half (51.8%) of BASMI improvement of etanercept over suphasalazine is estimated to be due to disease modification at week 16 in subjects with ankylosing spondylitis.

P 27

THE INFLIXIMAB EFFICACY AND TOLERABILITY ANALYSIS AFTER THE FORCED THERAPY INTERRUPTION IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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It is known, that the infliximab therapy in patients with ankylosing spondylitis should be carried out on a regular basis spaced no more than 8 weeks apart. However, in a real clinical practice often arise some treatment interruptions for a number of reasons.
The **Objective** of our long-term follow-up was to update the infliximab efficacy and tolerability in AS patients, who had treatment interruptions of 16 weeks and more.
Methods: 17 patients with documented AS, chronically (not less than one year) treated with infliximab at the SRI anticytocine therapy office of Russian Academy of Medical Science were included into the study. All patients had forced increased interruptions of infliximab infusions from 16 weeks to 3 years. Following parameters were measured in all patients at screening and before each infliximab infusion: BASDAI index and BASFI index, global assessment of AS activity, number of the inflamed joints, blood-sedimentation test. ASAS criteria were provided for the improvement assessment. Infusions tolerability was carefully estimated.
Results: Average patients age was 31.8 (20-53), average AS duration was 11.6 (4-20) years, average treatment duration was 1.9 (1-5) years. The reasons of infliximab treatment interruptions were the following: drug absence (n=11), PPD-test alteration (n=2), pregnancy (n=2), the adverse events (n=2). Mean therapy interval was 20.7 (16-144) weeks. After the therapy reinstitution all patients demonstrated the stable infliximab efficacy. At the therapy reinstitution all patients had received premedication with H1-histamine antagonist – cetirizine 10 mg/day within 2 days prior to infusion and 3 days after the infusion. 10 patients received premedication with 50 mg prednisolone or 4-12 mg dexametasone during the first infusion, 7 patients were retreated without premedication with glucocorticoids (GC). Infusion reactions were observed in 4 (18 %) subjects during 2-nd (after the interruption) infusion without GC-premedication (GC premedication was only during first infusion). Two subjects (12%) were withdrawn from the infliximab therapy because of recurrent infusion reactions after 5-th and 10-th infusions. Infusion reaction occurance in patients, experienced infliximab therapy interruption with duration more than 16 weeks was documented higher, than in patients with continuous therapy – (24 % and 5 %, respectively (p=0,04, two-sided Fischer's test).
Conclusions: In the case of forced treatment interruption infliximab efficacy did not decrease after treatment reinstitution. Infliximab tolerability went down a little, infusion reactions were observed in 24 % of patients, the infliximab withdrawn because of infusion reactions were required in 12 % of patients.

P 28

SEQUENTIAL BASFI MEASUREMENT IN ANKYLOSING SPONDYLITIS PATIENTS TREATED WITH TNF BLOCKERS

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Purpose: To explore the variation in sequential score of the BASFI measurement in Ankylosing Spondylitis (AS) patients treated with anti-TNF agents and to see whether the expected functional improvement was sustained over a 24 month period.
Method: Patients with AS on anti-TNF treatment are followed up in a specialist clinic with their clinical markers measured at each visit. This retrospective study looked at the BASFI measurements on patients completing 24 months of treatment. Patients who started treatment but failed by NICE guidelines and those who had not reached the 24 month threshold were excluded. Their sex, age, anti-TNF agent and sequential BASFI scores were recorded.
Results: Of 72 patients attending the clinic 30 were eligible for inclusion. There were 25 males, 5 females with an average age of 49.9 years. The spread of anti-TNF agents used was 10 Infliximab (INF), 8 Etanercept (ETN) and 12 Adalinumab (ADL). There was a marked improvement in score at month 3 (mean 2.78) which was sustained to month 12 but there was a trend to worsening of score at month 24. Patients treated with INF and ADL improved quicker than those on ETN. The scores for those treated with INF were more volatile.
Conclusion: TNF blockade induces a marked early response in the BASFI score though the rate of improvement seems to differ with agent used. The volatility in scores in INF patients may be related to the timing of the assessment viz their infusion. The trend that the BASFI deteriorated by month 24 might fit with the view that TNF blockade is not affecting long term structural change.

P 29

GOLIMUMAB, A NEW, HUMAN, TNF-ALPHA ANTIBODY ADMINISTERED SUBCUTANEOUSLY EVERY 4 WEEKS, IN ANKYLOSING SPONDYLITIS: 104-WEEK EFFICACY AND SAFETY RESULTS OF THE RANDOMIZED, PLACEBO-CONTROLLED GO-RAISE STUDY

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Purpose: To assess golimumab (GLM) efficacy/safety in active AS.
Methods: 356pts were randomized (1.8:1.8:1 ratio) to GLM50 or 100mg or PBO q4wks. Eligible pts had definite AS, BASDAI≥4 and back pain score≥4. At wk16, PBO or GLM50mg pts with <20% improvement in total back pain and morning stiffness entered early escape (EE) to GLM50 and 100mg q4wks, respectively (double-blind). At wk24, pts still receiving PBO crossed over to blinded GLM50mg q4wks; others continued regimen through wk100, with evaluation 4wks later. Key data summaries are based on randomized treatment groups with no statistical comparisons; other summaries show observed data by regimen followed.
Results: The primary endpoint (proportion of pts with ASAS20 at wk14), was achieved. Benefit seen at wks14&24 was maintained through wk104 (Table). BASMI linear scores improved from baseline to wk52; improvements were maintained through wk104, as were improvements in SF-36 MCS&PCS. Pts not responsive to GLM50mg who increased to 100mg had lower rates of ASAS response and less improvement in other parameters vs other GLM-treated pts (Table). AEs through wk104 were reported for 94% of GLM pts (little variation across doses). Through wk104, 11% GLM pts had a serious AE; rate of GLM injection-site reactions was 1.4% (106/7705 injections) through wk104. No deaths were reported.
Conclusion: Clinical improvements in AS pts previously seen at wk24 were maintained through wk104, with no major differences in efficacy/safety between GLM doses. GLM was generally well tolerated through 2yrs of this 5yr study.

Table:

	Placebo	GLM50mg	GLM100mg
Pts randomized	78*	138**	140
ASAS20[+]	30 (38.5%)	83 (60.1%)	100 (75.6%)
ASAS40[+]	30 (38.5%)	77 (55.8%)	76 (54.3%)
ASAS partial remission[+]	17 (21.8%)	44 (31.9%)	43 (30.7%)
BASDAI[++]	6.02 (1.36,7.79)	2.65 (0.84,6.08)	2.73 (1.08,5.34)
BASFI[++]	4.93 (0.98,7.07)	2.22 (0.52,5.80)	1.77 (0.49,4.79)

Note: Intent-to-treat analysis
+n in response(%)
++median(interquartile range)
*Includes 35pts who did not meet EE criteria at wk16 and 41pts who did.
** Includes 25pts who entered EE from 50 to 100mg.

P 30

GOLIMUMAB, A NEW, HUMAN, TNF ALPHA ANTIBODY, ADMINISTERED SUBCUTANEOUSLY EVERY 4 WEEKS IN PSORIATIC ARTHRITIS PATIENTS: 104-WEEK EFFICACY AND SAFETY RESULTS OF THE RANDOMIZED, PLACEBO-CONTROLLED GO-REVEAL STUDY

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Purpose: To assess long-term efficacy & safety of golimumab (GLM) in PsA.
Methods: PsA pts with ≥3swollen and ≥3tender joints and psoriasis were randomized to PBO or GLM50 or 100mg q4wks. At wk16, pts with <10% improvement in swollen& tender joints entered early escape (EE). All pts received GLM from wk24-104. Investigators could dose-escalate pts receiving GLM 50mg to 100mg based on clinical judgement after all pts reached wk52. Results are through wk104. Analyses were based on pts with data. No wk104 statistical comparisons were made.
Results: 405 active PsA pts were randomized (PBO, n=113; GLM50mg, n=146; GLM100mg, n=146). GLM was significantly better than PBO in improving signs & symptoms of PsA at wk24; efficacy was maintained through wk52. At wk104, respective responses for GLM50 and 100mg grps were 91.4% (64/70) and 73.1% (95/130) for ACR20; 65.7% (46/70) and 53.8% (70/130) for ACR50; and 44.3% (31/70) and 36.9% (48/130) for ACR70. For pts with ≥3% BSA in GLM50 and 100mg grps, 68.8% (33/48) and 76.0% (73/96) achieved PASI75; mean improvement in HAQ scores were 0.54 (69pts) and 0.46 (127pts). At wk104, GLM50mg pts who switched to 100mg achieved clinically meaningful ACR20,50,&70 responses (56.6%, 35.5%,&22.4%, respectively), although lower than in GLM50 or 100mg grps. PASI75 response for pts switching from GLM50mg to 100mg was 62.5%; mean HAQ score improvement was 0.36. Overall, 8.6% (34/394) GLM-treated pts experienced SAEs and 5.8% (23/394) d/c treatment due to AE through wk104. Injection site reactions occurred in 8.9%(35/394pts). One histoplasmosis case was reported (GLM100mg) & successfully treated.
Malignancies reported with GLM50mg included basal cell skin (1pt), colon (1pt), and small cell lung (1pt) cancers; and with GLM100mg, basal cell skin (3pts), prostate (1pt), and small cell lung (1pt) cancers. Two deaths occurred (GLM50mg pts): 1 from small cell lung cancer, 1 from climbing accident.
Conclusion: GLM50 and 100mg q4wks maintained high levels of improvement through wk104. GLM was generally well-tolerated, with a safety profile similar to that of other anti-TNFs.

P 31

GOLIMUMAB INHIBITS PROGRESSION OF RADIOGRAPHIC DAMAGE IN PATIENTS WITH PSORIATIC ARTHRITIS: 52 WEEK RESULTS FROM THE GO-REVEAL STUDY

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Objective: To evaluate golimumab (GLM) on the progression of structural damage in psoriatic arthritis (PsA) pts.
Methods: Adult PsA pts with ≥3 swollen and ≥3 tender joints were randomized to placebo (PBO) or GLM 50 or 100mg q4wks. At wk16, pts with<10% improvement in swollen and tender joint counts entered early escape in a double-blinded manner to GLM50mg (PBO pts) or GLM100mg (GLM50mg pts). All pts randomized to PBO received GLM50mg from wk24-52. Hand&foot radiographs were obtained at wks0,24&52. Erosions (ERO) and joint space narrowing (JSN) were evaluated by independent readers unaware of treatment and image time sequence using the van der Heijde-Sharp(vdH-S) method modified for PsA. Changes from baseline in vdH-S scores were compared at wk24 using ANOVA with pts' baseline MTX usage as a factor in the model based on the van der Waerden normal score (primary endpoint). Wk24 comparisons were between GLM and PBO grps, based on the original randomized grp. No statistical comparisons were performed at Wk52.
Results: 405pts (mean age:46-48yrs, median swollen/tender joint counts:12-14/22-24, HAQ:1.0-1.1, CRP:0.6 mg/dL, total vdH-S scores:9.00-10.50) were enrolled. At wk24, GLM50mg pts had less radiographic damage than PBO, as measured by meanΔ from baseline in total vdH-S score (-0.16±1.31 versus 0.27±1.26, p=0.011; -0.02±1.32 for GLM100mg, p=0.086 versus PBO).
Significantly more GLM-treated pts had no progression as defined by meanΔ in total vdH-S score (78.8% for GLM50mg, p=0.007; 76.6% for GLM100mg, p=0.020) compared with PBO-treated pts (62.7%). In pts without baseline ERO or JSN, 87.1%, 89.1%, and 71.6% of GLM50mg, GLM100mg, and PBO pts, respectively, maintained erosion-free status; in these respective grps, 97.0% (p=0.008), 96.4% (p=0.013), and 88.2% maintained JSN-free status. GLM-randomized pts had less progression at wk52 (-0.22±1.64 for GLM50mg and -0.14±1.53 for GLM100mg) versus PBO-randomized (0.22±1.38) who began GLM at wk16/24.
Conclusion: GLM demonstrated inhibition of structural damage through wk24 with maintenance of this benefit through wk52.

P 32

TUMOR NECROSIS FACTOR-ALPHA BLOCKING THERAPY IMPROVES QUALITY OF LIFE IN PATIENTS WITH ANKYLOSING SPONDYLITIS IN DAILY CLINICAL PRACTICE

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Introduction: The availability of tumor necrosis factor-alpha (TNF-α) blocking therapy has significantly improved clinical outcome in Ankylosing Spondylitis (AS). The aim of the present study was to investigate the effect of TNF-α blocking therapy on quality of life in AS patients in daily clinical practice.
Methods: Two-hundred and twenty-nine consecutive AS patients from the MCL and UMCG were included in this observational study. All patients fulfilled the modified New York criteria for AS. One-hundred and eighty-nine patients started TNF-α blocking therapy because of active disease according to the ASAS consensus statement. Infliximab (5mg/kg) was administered intravenously at 0, 2, and 6 weeks and then every 8 weeks; etanercept (50mg once a week or 25mg twice a week) and adalimumab (40mg on alternate weeks) were given subcutaneously. Quality of life was assessed using ASQoL at baseline and after 3 and 6 months of TNF-α blocking therapy. Forty patients were not treated with TNF-α blocking therapy because of lack of indication for TNF-α blocking therapy (n=37), medical reasons (n=2), or own choice (n=1). ASQoL was assessed once in these patients.
Results: Mean age of the 229 AS patients was 42.2 years (SD±11.6), median disease duration was 15 years (range 1-59), and 69% were male. At baseline, 189 patients who planned to start TNF-α blocking therapy had significantly higher ASQoL compared to 40 patients who were not treated with TNF-α blocking therapy. After 3 and 6 months, TNF-α blocking therapy resulted in a significant decrease in ASQoL. Moreover, no significant difference was found between ASQoL of patients without TNF-α blocking therapy and ASQoL of patients after 3 and 6 months of TNF-α blocking therapy (p=0.988 and p=0.662, respectively) (Table I).
Conclusion: This study indicates that TNF-α blocking therapy significantly improves quality of life in AS patients in daily clinical practice.

Table I. Ankylosing Spondylitis Quality of Life (ASQoL) at baseline and after 3 and 6 months of etanercept (n=119), infliximab (n=28), or adalimumab (n=42) treatment.

	ASQoL baseline	ASQoL 3 months	ASQoL 6 months
AS patients treated with TNF-α blocking therapy (n=189)	10 (0-18)†	5 (0-18)*	5 (0-17)*
AS patients without TNF-α blocking therapy (n=40)	5 (0-14)		

Values are median (range).
† Statistically significant difference (p<0.001) compared to values of AS patients without TNF-α blocking therapy.
* Statistically significant difference (p<0.001) compared to values recorded at baseline.

P 33

CHANGES IN BONE TURNOVER MARKERS IN PATIENTS WITH ANKYLOSING SPONDYLITIS DURING THE FIRST 6 MONTHS OF TNF-ALPHA BLOCKING THERAPY

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Introduction: Ankylosing spondylitis (AS) is characterized by both bone formation and bone loss in the spine. The aim of the present study was to investigate the effect of tumor necrosis factor-alpha (TNF-α) blocking therapy on bone turnover markers (BTM) in AS patients with active disease.
Methods: One-hundred and twelve consecutive AS outpatients, fulfilling the modified New York criteria, and treated with TNF-α blocking therapy because of active disease were included.
Excluded were patients with recent fractures or drug intake affecting bone metabolism (bisphosphonates or corticosteroids). Infliximab (5mg/kg) was administered intravenously at 0, 2, and 6 weeks and then every 8 weeks; etanercept (50mg once a week or 25mg twice a week) and adalimumab (40mg on alternate weeks) were given subcutaneously. Bath AS Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ASAS-endorsed disease activity score (ASDAS), bone formation markers bone-specific alkaline phosphatase (BALP) and procollagen type 1 N-terminal peptide (PINP), and bone resorption marker serum C-telopeptides (sCTX) were assessed at baseline and after 6 months of TNF-α blocking therapy. Z-scores of BTM were calculated using matched 10-year-cohorts of a Dutch reference group (150 men or 350 women) to correct for the normal influence that age and gender have on bone turnover.
Results: Mean age of the 112 patients was 41.8 years (SD ± 11.0), median disease duration was 15 years (range 1-47), and 69% were male. TNF-α blocking therapy resulted in a significant improvement in BASDAI, ESR, CRP, and ASDAS scores. Furthermore, there was a significant increase in BALP and PINP Z-scores and a significant decrease in sCTX Z-score after 6 months of therapy (Table I).
Conclusion: This study indicates that the bone turnover balance favors bone formation in AS patients during the first 6 months of TNF-α blocking therapy.

Table I. Clinical and laboratory measures at baseline and after 6 months of etanercept (n=76), infliximab (n=14), or adalimumab (n=22) treatment.

	Baseline	6 months	P-value
BASDAI	6.1 ± 1.7	3.0 ± 2.1	0.000
ESR	22 (2-90)	6 (2-71)	0.000
CRP	15 (2-99)	3 (1-196)	0.000
ASDAS	3.7 (1.7-5.9)	1.9 (0.6-5.1)	0.000
BALP Z-score	0.27 (-2.64-4.80)	0.57 (-1.26-5.65)	0.000
PINP Z-score	0.26 (-1.75-8.86)	0.50 (-1.47-5.33)	0.015
sCTX Z-score	-0.35 (-2.28-5.38)	-0.58 (-2.34-3.99)	0.013

Values are mean ± SD or median (range).

P 34

ANTI-TNF AGENTS IN FAMILIAL MEDITERRANEAN FEVER RELATED SPONDYLITIS

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Objective: Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent fever, peritonitis/pleuritis or arthritis attacks. One of the well characterized types of involvement is spondyloarthritis with typical sacroiliitis and spondylitis resembling ankylosing spondylitis. Spondylodisciitis and typical structural damages could seldom occur in FMF however the association with HLA B27 is not well documented. We herein present three patients (all HLA B27+) with typical spondylitis associated with FMF who were successfully managed with anti-TNF agents.
Case 1: Thirty-seven years old male patient who was diagnosed with FMF at age 4, developed spondylitis with bilateral hip (hip replacements at age 24 and 26) and peripheral joint involvement after age 16. He was also diagnosed with Crohn's disease and amyloidosis at age 30. Patient responded infliximab (5 mg/kg continued for 3 years) and proteinuria and hypoalbuminemia due to amyloidosis were well managed with sustained improvement in BASDAI scores. The patient was switched to adalimumab (ADA) because of raised acute phase responses at the end of third year and favorable response is still maintained with ADA.
Case 2: Twenty-four years old female patient had FMF diagnosis since age 7. At 21 she developed sacroiliitis and spondylitis. She had severe and frequent abdominal attacks which required opioid use during attacks. She was started etanercept and continued for 4 months and switched to infliximab (5mg/kg) (loss of efficacy of ETN) and continued for 1 year. IFN lost its efficacy after 6 months and patient switched to ADA with favorable outcome throughout 6-months of follow up.
Case 3: Thirty-one years old female patient had FMF diagnosis since age 18. She had developed spondylitis with bilateral knee and ankle involvement at age 30. She did not respond conventional treatments with DMARDs and colchicine. Adalimumab was started. She had favorable response to ADA throughout 4-months of follow up.
Conclusion: Anti-TNF treatment can be a good choice for the management of patients with FMF who are not responding to colchicine and conventional treatments. Biologics could modify FMF attacks even in colchicine resistant patients.

P 35

BASELINE AND DISEASE-RELATED CHARACTERISTICS THAT MAY PREDICT TREATMENT RESPONSE TO ETANERCEPT IN PATIENTS WITH ANKYLOSING SPONDYLITIS: ASCEND

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Objective: Our objective was to determine baseline characteristics that were predictive of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) response in subjects with ankylosing spondylitis (AS) in the ASCEND trial.
Methods: Subjects were randomized to ETN 50 mg once weekly (n=379) or SSZ up to 3 g daily (n=187) for 16 weeks. Stepwise regression models were performed on baseline characteristics to determine which parameter(s) best predicted week 16 continuous BASDAI response, for all subjects and for each treatment group.
Results: In subjects overall, ETN treatment, younger age, lower baseline BASDAI and BASMI, and positive HLA-B27 were significantly predictive of better Week 16 BASDAI score. In the ETN group, younger age, lower baseline BASDAI and BASMI, and positive HLA-B27 were also predictive of better response. In the SSZ group, lower baseline BASDAI, BASMI, and swollen joint count were predictive of better response.

Baseline Predictors of BASDAI Response at Week 16

	Parameter Estimate (SE) for Stepwise Regression Models					
	Overall	*P*	ETN	*P*	SSZ	*P*
Treatment (ETN vs. SSZ)	–12.24 (1.99)	<0.0001				
BASDAI	0.52 (0.06)	<0.0001	0.46 (0.07)	<0.0001	0.64 (0.11)	<0.0001
Age	0.32 (0.08)	0.0001	0.38 (0.10)	0.0001		
BASMI	1.64 (0.44)	0.0002	1.52 (0.51)	0.0032	2.39 (0.81)	0.0039
HLA-B27 (positive vs. negative)	–7.06 (2.78)	0.0113	–7.75 (3.35)	0.0215		
Swollen joint count					1.92 (0.76)	0.0123

For continuous parameters, the magnitude of the estimate is the slope steepness; the steeper the positive slope, the larger the week 16 BASDAI. For dichotomous variables, the estimate is the difference in mean BASDAI score between the two comparators.

Conclusion: In ASCEND, etanercept had a better treatment response than sulfasalazine in subjects with AS. Similar significant baseline predictors of response were identified overall and for subjects treated with etanercept; sulfasalazine predictors were somewhat different. These data may facilitate clinical decision making in the treatment of ankylosing spondylitis patients.

P 36

FEW CLINICAL PARAMETERS MARK OUT ANTI-TNF USE AMONG PATIENTS WITH ANKYLOSING SPONDYLITIS – DATA FROM THE SCOTLAND AND IRELAND REGISTRY FOR ANKYLOSING SPONDYLITIS (SIRAS)

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Aims: (1) To determine the proportion of ankylosing spondylitis (AS) patients on anti-TNF therapy; and (2) To characterise these patients with respect to routine clinical markers and disease severity.
Methods: The Scotland and Ireland Registry of Ankylosing Spondylitis (SIRAS) is a research database of patients with AS in Scotland and Northern Ireland. Data collection is ongoing and includes AS history; co-morbidities; blood laboratory results; and Bath Indices. The relationship between clinical parameters and anti-TNF use is expressed using risk ratios (RR) with 95% confidence intervals (95%CI).
Results: Data is currently available from 493 patients from six hospitals across Scotland, of whom 95 (19%) had ever been prescribed anti-TNF therapy. Age was an important determinant of anti-TNF use: patients >60yrs were one-third as likely to be prescribed anti-TNFs compared to those <30yrs (RR: 0.3; 95%CI: 0.1-0.7). Patients with peripheral joint involvement were 70% more likely to have received anti-TNFs (1.7;1.1-2.6). However, there was no significant increase in anti-TNF use among patients with a history of uveitis (1.3;0.9-1.9); psoriasis (1.3;0.7-2.1); bowel disease (1.2;0.7-2.0); nor with $ESR_{>15mm}$ (0.8;0.5-1.2), $CRP_{>10mg/L}$ (1.0;0.6-1.6) nor HLA-B27+ (1.1;0.4-2.8). Patients with a BASDAI >4 were no more likely to have received anti-TNFs than other patients (0.8;0.5-1.2).
Conclusions: Approximately one-fifth of AS patients in Scotland have received anti-TNF therapy.
Although younger patients are more likely to receive these drugs, few clinical parameters characterise this patient sub-group. A limitation of this data is its cross-sectional nature. In the UK, BASDAI >4 is a prerequisite for starting anti-TNF therapy and, thus, it is possible that the lack of association is due to subsequent improvements in disease activity after starting treatment. Future research should collect prospective data on patients beginning anti-TNF therapy and should determine the effect of the disease (and treatment) on non-clinical aspects – such as quality of life and work productivity.

P 37

IDENTIFICATION OF ANTI-TNF CANDIDATES BASED ON PREDICTED RESPONSE AND REMISSION IN ANKYLOSING SPONDYLITIS

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Purpose: To identify AS patients who are candidates for anti-tumor necrosis factor (anti-TNF) therapy.
Methods: ASSERT and GO-RAISE data were analyzed. Matrix models were developed to predict probability for achieving response or remission from AS after initiating anti-TNF therapy or continuing conventional therapy. In the separate and combined datasets, univariate analyses identified possible baseline predictors for BASDAI50 at wk12 and ASAS partial remission at wk24.
Individual variables were explored using Spearman correlation analysis. Multivariate regression, ROC analysis, and Spearman correlation were used to select predictors for the final model. Logistic regression was used to calculate probable BASDAI50 response and ASAS partial remission state respective to combined predictors at baseline.
Results: 479 patients treated with anti-TNFs and 156 patients treated with placebo+conventional therapy (NSAIDs/DMARDs/corticosteroids) for AS were included. Predictors included: age, BASFI, enthesitis score, therapy (anti-TNF/conventional), CRP, and HLA-B27 genotype (±). Area under the ROC curve was 82%, 75%, &77% for BASDI50 at week 12 and 80%, 77%, & 78% for ASAS partial remission at wk24 for ASSERT, GO-RAISE, &combined data, respectively. After categorization of age (≤40 vs>40yrs), enthesitis score (0 vs>0), CRP (≤0.6, >0.6 ≤2.0, >2.0mg/dL) and BASFI (≤4.5, >4.5 ≤ 6.5, >6.5cm), AUC of combined dataset prediction model was 80% for BASDAI50 and 77% for ASAS partial remission, suggesting a good prediction model. A matrix model was developed to represent increasing proportion of BASDAI50 response (range:1%-80%) and ASAS partial remission (range: 0%-54%) respective to the characteristic at baseline. Only 2% of patients without BASDAI50 at week12 had ASAS partial remission at week24.
Conclusions: Most AS patients with elevated disease activity and back pain respond to anti-TNFs while few respond to continued conventional therapy. Younger patients and patients without peripheral enthesitis receiving anti-TNFs demonstrate an improved response. CRP, functionality, and HLA-B27 measurements can help in assessing which patients will respond and subsequently achieve an improved disease state and who, therefore, might be better candidates for anti-TNFs.

P 38

FEAR OF MOVEMENT AND (RE)INJURY AS AN INDEPENDENT CONTRIBUTOR TO SELF-REPORTED ACTIVITY LIMITATION BUT NOT SPINAL MOBILITY IN PATIENTS WITH SPONDYLARTHROPATHY: AN APPLICATION OF THE ICF-MODEL

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Background: The International Classification of Functioning, Disability and Health (ICF)-model postulates a role for personal factors in explaining human functioning and disability. Preliminary data point to the possible relevance of fear of movement and (re)injury and the resulting avoidance behavior in the explanation of disability in patients with Spondylarthropathy (SpA) and merit further investigation.
Objectives: To establish the independent contribution of the personal factor fear of movement and (re)injury to self-reported activity limitations and spinal mobility impairment.
Methods: We subjected 95 patients with axial SpA to measures of anthropometrics (BMI), medication (BIOLogics, NSAIDS), self-reported activity limitation (BASFI), self-reported stiffness (BASDAIstiff: averaged items 5 and 6), momentary pain (NRS), spinal mobility (BASMI) and fear of movement and (re)injury (TSK11[1]). We used a stepwise multiple linear regression modeling approach with BASFI and BASMI as dependent variables. Gender and BASFI were not a priori entered into the BASFI and BASMI model respectively.
Results: BASMI (mean=3,4 (1,8); stβ=, 410; *p*=,000), BASDAIstiff (mean=4,2 (2,8); stβ=,307; *p*=,000), NRS (mean=3,8 (2,7); stβ=, 293; *p*=,000), BIOL (no/yes: 47/48; stβ=,134; *p*=,022) and TSK11 (mean=25,6 (6,7); stβ=,194; *p*=0,002) significantly contributed to the BASFI (mean=4,0 (2,5) model, which explained 73% of the variance (adjusted R^2). Disease duration (13,7 (10,2); stβ=,091; *p*=,126) and BMI (26,2 (4,6); stβ=,010; *p*=,866), NSAIDS (no/yes: 36/59; stβ=,011; *p*=,848) were not entered during analysis. Disease duration (stβ=,344; *p*=,000), BMI (stβ=,223; *p*=,013), Gender (stβ=-,244; *p*=,005), NRS (stβ=,235; *p*=,008) and BIOL (stβ=,291; *p*=,001) significantly contributed to the BASMI model, which explained 37% of the variance (adjusted R^2). TSK11 (stβ=,088; *p*=,350), NSAIDS (stβ=,075; *p*=,403) and BASDAIstiff (stβ=-,056; *p*=,600) were not entered during analysis.
Conclusion: Fear of movement and (re)injury significantly contributes to self-reported activity limitation. Repeated exposure to spinal mobility measures in clinical practice might explain the lack of significant association between TSK11 and BASMI. Further exploration in this area is both justified and needed.

Reference:
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P 39

INSTRUCTIONS GIVEN TO PATIENTS WITH ANKYLOSING SPONDYLITIS BY THEIR DIAGNOSING DOCTORS

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Background: After the diagnosis of ankylosing spondylitis (AS), patients need extended instructions what is to be regarded with this disease. We investigated to which extent patients have really been instructed in connection with their diagnosis.
Methods: A cross-sectional survey was performed with a questionnaire consisting of 82 questions regarding demographics, diagnosis, smoking, disease activity, function, quality of life, treatment, disability to work, educational level, and also instruction received from their diagnosing doctor. The questionnaire was distributed to AS patients by rheumatologists and was also sent to 3400 randomly selected members of the German AS patient organisation. Data collection and analysis was done anonymously.
Results: 1273 AS patients responded. Almost all of them indicated to have received with the diagnosis at least one hint what to regard after having the disease. 63% of them received more than 2 such hints and only 27% more than four. Most instructions received concerned physiotherapy and rehabilitation courses. 36% were urged to keep a straight posture, and only less than 30% about suited sports, suited working places, suited furniture or about joining a disease-specific patient organisation. On the question, what the patients especially regarded since their diagnosis, 55% indicated sufficient movement at work and leisure, 53% a plain firm mattress, 50% daily exercises, 42% a not too large pillow for sleeping, 38% an upright position at work, 36% suited sports, and 34% a straight position at leisure. Apparently some (but by far not all) patients received the necessary information later elsewhere.
Conclusion: Most patients have with their diagnosis only been informed about possible therapies and not about how they themselves may contribute to a favourable disease outcome. Doctors making a diagnosis of AS, should not forget to inform their patients also about the patient's own possibilities to contribute to the course of their disease.

P 40

A MULTI-CENTER SURVEY OF STATUS OF DRUG THERAPY WITH ANKYLOSING SPONDYLITIS IN CHINA

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Objective: To investigate the drug use in patients with ankylosing spondylitis and to analyze drug use in different types of patients with ankylosing spondylitis and its effects.
Methods: 1702 patients with ankylosing spondylitis were surveyed face to face by doctors in 10 big hospitals from the whole country. SPSS13.0 software were used to analyse the relationship between drug use and clinical features.
Results: (1)Among 1702 patients, 430 cases (25.26%) used non-steroidal antiinflammatory drugs (NSAIDs) intermittently; 714 cases (41.95%) used NSAIDs continued; a total of 1144 cases (67.22%) patients used NSAIDs; 670 cases (39.37%) used sulfasalazine (SASP); 282 cases (16.57%) used oral hormones; 84 cases (4.94%)used local corticosteroids; 376 cases (22.09%) used methotrexate (MTX); 188 cases (11.05%) have used hydroxychloroquine (HCQ); 768 cases (45.12%) used traditional Chinese medicine; 213 cases (12.51%) used biological agents; 292 cases (17.16%) received physiotherapy. (2) The patients were divided into two groups according to clinical manifestations. There were 636 patients without peripheral manifestations,1066 cases with peripheral performance (including peripheral arthritis, hip joint involvement, dactylitis-uveitis).There is no difference of medication rate of NSAIDs, MTX, HCQ, SASP and biological agents between the two groups ($p > 0.05$), but hormone usage was higher in patients with peripheral manifestations than patients without peripheral manifestations (29.23%, 17.54%), the difference was statistically significant ($p<0.001$). (3) Patients without peripheral manifestations had good response to continued NSAIDs or biological agents, the efficacy was statistically significant, p values were $p<0.001$, $p= 0.009$. The efficacy of Intermittent use of NSAIDs or the use of MTX, SASP, HCQ, hormones, Chinese medicine and physiotherapy for patients without peripheral manifestations is not obvious, the efficacy was not statistically significantly, $p> 0.05$. (4) Patients with peripheral manifestations of had good response to NSAIDs, MTX, SASP, and oral hormones, p values were<0001, 0.002, <0.001, 0.009, respectively. The efficacy of HCQ, biological agents, local hormones, traditional Chinese medicine, physical therapy is not obvious, p-values were 0.129, 0.715, 0.412, 0.193, >0.05, respectively.
Conclusions: At present, the status of clinic drug therapy for AS patients with or without peripheral manifestations is basically the same. Recommended NSAIDs or biological agent should be used continual but not interruption on the axial AS patients which have a more reliable clinical efficacy.
The response of NSAID, hormones, MTX and SASP are effective for the patients with peripheral manifestations. Although traditional Chinese medicine and physical therapy are widely used in clinic in AS patients, but their efficacy is imprecise and suggest to do the further study.

P 41

BASELINE DISEASE PARAMETERS PREDICTIVE OF CLINICAL EFFICACY WITH INFLIXIMAB TREATMENT OF EARLY ANKYLOSING SPONDYLITIS

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Objectives: Assess: 1) ability of baseline parameters to predict infliximab clinical efficacy in early ankylosing spondylitis (AS) and 2) infliximab clinical efficacy in early AS patients.
Methods: Patients had early AS (disease duration ≥0.5-≤2 years and MRI sacroiliitis score ≥4) received infliximab 5 mg/kg intravenous infusion at weeks 0, 2, 6, 12, 18 and 24. The abilities of baseline parameters to predict ASAS20 response at week 12 (receiver operator characteristic [ROC] curve) and week-2 disease severity/clinical response to predict clinical response at week 12 (logistic regression) were assessed. ASDAS socre and ASAS20 responses were evaluated in early AS patients.
Results: 70 early AS were enrolled. All enrolled patients completed the week-12 visit, and 61 patients completed the week-24 visit. Nine cases were withdrew infliximab treatment at week 12. Three of them were ascribed to adverse events (2 allergy and 1 tuberculosis) and 5 cases were unsatisfied response. For early AS patients, baseline sacroiliac joint magnetic resonance imaging (MRI) scores were significant predictors of ASAS20 response at weeks 12 (area under the ROC curve=0.791; p=0.005);C-reactive protein (CRP) and ASDAS were significant predictors of ASAS20 response at week 12. Logistic regression analysis indicated that the clinical response after just one infliximab infusion, i.e., at week 2, was a valuable predictor of subsequent clinical responses at week 12.
ASAS20, ASDAS score, BASDAI score, BASFI score, CRP, ESR and MRI score got a significant improvement after six infliximab therapy.
Conclusions: ASDAS score and inflammation detected by baseline MRI and CRP may predict subsequent clinical efficacy of infliximab in early AS patients. it is a beneficial in early AS patients with infliximab therapy. the clinical response after just one infliximab infusion, i.e., at week 2, was a valuable predictor of subsequent clinical responses at week 12.

P 42

DOES THE ADDITION OF A QUANTIFERON® TEST REDUCE THE USE OF CHEMOPROPHYLAXIS IN RHEUMATOLOGY PATIENTS COMMENCING ANTI-TUMOUR NECROSIS FACTOR AGENTS?

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Background: Reactivation of latent tuberculosis (TB) is a known risk of anti-TNF therapy. Routine screening commonly includes tuberculin skin tests (TST) such as the Mantoux (€1.20). These guidelines were developed prior to the availability of Interferon gamma release assays (IGRA) such as the QuantiFERON® test (€40 per test). In the UK, teenagers routinely receive the BCG vaccine, resulting in a high background positivity of TSTs.
Methods: A retrospective review was conducted of all patients who had a QuantiFERON®-TB Gold In Tube (QFT-IT) test over a 20 month period from 2007 to 2008 at a large teaching hospital rheumatology centre prior to starting TNF-α blocking therapy. Routine assessment includes a detailed history for risk of TB, chest x-ray and TST. QFT-IT test is performed in the event of a positive TST or in the presence of any TB risk factors.

Results: A total of 412 patients were screened for TB prior to commencing their first TNF-α blocker.
Nine were excluded as the notes were unavailable. TST only was performed on 333 patients, 8 patients had a QFT-IT test only and 62 patients had both. Clinical notes for 70 patients who underwent a QFT-IT were reviewed. Diagnoses included RA (49%), AS (19%), undifferentiated IA (13%) and PsA (13%). 23 patients (33%) were on either a DMARD or prednisolone.

	Mantoux not done	Mantoux 0-9mm	Mantoux ≥10mm
QFT-IT positive	2	2	8
QFT-IT indeterminate	0	1	3
QFT-IT negative	6	5	43

Overall, 54 patients had a positive TST and went on to have a QFT-IT test which was negative in 43 (80%). One patient received isoniazid prophylaxis as there was a history of TB exposure and an abnormal chest x-ray. Of the remaining 42 patients, 37 (88%) proceeded on to TNF-α blocking therapy. No cases of TB reactivation were seen. Five patients with a negative QFT-IT test had a baseline chest x-ray suggestive of previous TB exposure. Four of the five had risk factors for TB.
Conclusions: The QFT-IT test identified that most of the TST positive results were highly likely to be "false positives", due to previous BCG vaccination or non tuberculous mycobacterial exposure.
These data suggest use of the QFT-IT test avoids unnecessary chemoprophylaxis, minimising potential drug toxicity.

P 43

EFFICACY AND SAFETY OF INFLIXIMAB IN PATIENTS WITH ACTIVE SPONDYLOARTHRITIS: RESULTS OF A LONG-TERM FOLLOW-UP STUDY

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Objective: To evaluate long-term efficacy and safety of infliximab in patients with spondyloarthritis (SpA).
Methods: Between 1999 and 2002, SpA patients, with active axial and/or peripheral disease, were treated with infliximab (ankylosing spondylitis (AS) n=63, psoriatic arthritis n=36, undifferentiated SpA n=10). All patients received an induction regimen of infliximab (5 mg/kg at weeks 0, 2 and 6) and were continuously retreated. Initially different retreatment dosages and intervals were used, but for the last 8 years all patients were retreated with 5 mg/kg every 8 weeks. At all visits, patient assessment of disease activity (visual analogue scale (VAS)), patient assessment of pain (VAS), Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) were collected. Swollen Joint Count (SJC) was performed in patients who had peripheral arthritis at baseline. BASDAI and BASFI were evaluated in patients with AS. Data have been collected meticulously until May 2006. From that timepoint, patients were evaluated at yearly intervals. All patients have reached the year 7 evaluation.
Results: In April 2010 a total follow-up of 688 patient years was reached. In only 4 patients the retreatment interval had to be decreased to 6 weeks. Efficacy results are provided in the table. Forty-seven patients had peripheral arthritis at baseline, of which 25 had oligoarticular (< 5 swollen joints) and 22 polyarticular disease (≥ 5 swollen joints), mostly seen in patients with psoriatic arthritis or inflammatory bowel disease related SpA. In the oligoarticular group the median SJC decreased from 3 to 0 at year 1 and remained 0 during follow-up; in the polyarticular group a median SJC of 10 dropped to 0 at year 1 to remain 0 during follow-up.

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Global Assessments										
Nr. Of pts	107	101	90	90	77	61	49	42	37	25
Pt Global	66 (11-100)	20 (0-98)	17 (0-95)	12 (0-82)	20 (0-80)	20 (0-80)	20 (0-100)	30 (0-90)	10 (10-90)	20 (0-80)
Pt Pain	61 (3-100)	22 (0-100)	16 (0-100)	11 (0-100)	20 (0-100)	20 (0-100)	20 (0-100)	25 (0-70)	10 (0-90)	20 (0-80)
ESR	20 (1-101)	10 (1-90)	10 (1-90)	8 (1-74)	9 (1-59)	7 (1-68)	7 (1-62)	7 (2-76)	7 (2-84)	11 (2-65)
CRP	2 (0-29)	0.6 (0-13.4)	0.4 (0-9.3)	0.3 (0-12)	0.25 (0-8.5)	0.2 (0-9)	0.3 (0-6)	0.2 (0.1-4.6)	0.2 (0.1-9.2)	0.2 (0.1-7.2)
AS Assessments										
Nr.of pts	63	59	53	49	41	30	23	22	21	10
BASDAI	51 (13-95)	21 (0-88)	16 (0-71)	9 (0-76)	10 (0-79)	13 (0-100)	12 (0-68)	14 (0-63)	9 (0-84)	10 (0-67)
BASFI	58 (10-98)	39 (0-95)	27 (0-92)	27 (0-86)	23 (0-85)	27 (0-100)	21 (0-86)	25 (0-83)	19 (0-78)	19 (0-82)

From 2004 onwards, TNF-blocking agents became commercially available and reimbursed in Belgium. As a consequence, patients returned for follow-up and further treatment to their referring rheumatologist (n=12) or were electively switched to another TNF-blocker (n=21): in all these patients low disease activity was observed at the time of their last evaluation (median patient global assessment 20). Until May 2006, a total of 33 serious adverse events were observed, including 12 serious infections requiring hospitalisation, 3 malignancies (1 transitional cell carcinoma of the bladder, 1 spinocellular skin carcinoma, 1 basocellular skin carcinoma) and 1 death (respiratory insufficiency related to a neurological degenerative disease). Five patients stopped treatment with infliximab for medical reasons (1 patient with CLL, 1 patient with proven skin lupus and a previous epithelioma of the vocal cord, 1 patient with recurrent diverticulitis, 2 psoriatic arthritis patients with secondary loss of response).
Conclusion: In this cohort of patients, a highly significant improvement in all disease manifestations was maintained over a follow-up period of nearly 10 years. No new safety signals were observed.

P 44

RELATIONSHIPS BETWEEN PERFORMANCE-BASED MEASURES OF PHYSICAL FUCNTION AND THE BASFI-QUESTIONNAIRE IN ANKYLOSING SPONDYLITIS PATIENTS

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Background: Physical function is one of the most important outcome parameters in Ankylosing Spondylitis (AS) for evaluating the disease course and the effectiveness of interventions. Currently, physical function is measured with a questionnaire, the Bath Ankylosing Spondylitis Functional Index (BASFI). However, the assessment of the actual level of physical function of AS patients could be hampered using only a questionnaire.
Objective: The aim was to investigate the association between performance-based measures of physical function and the BASFI questionnaire and assess the contribution of exertion and pain on this relationship.
Methods: 112 patients with AS completed 8 performance tests and a BASFI questionnaire. The performance tests were bases on items of the BASFI. For tests 1-6 and 8 the time to actually perform the test was measured. For test 7 the ability to look over one shoulder was measured by the range of vision while looking over the shoulder. Exertion and pain associated with the test were assessed directly following each test (using the modified Borg score en 100 mm. VAS). Associations between performance-based measures of physical function (taking into account time, exertion and pain) and BASFI-questionnaire were assed using univariable and multivariable linear regression analyses.
Results: Univariable relationships between all performance-based components of physical function (time exertion and pain) and the BASFI questionnaire in AS patients are moderate (R^2 varying between 6-38%). Multivariable relations between performance-based measures (time and taking into account associated exertion and pain) and the BASFI questionnaire are also moderate (R^2 varying between 28-50%) and influenced by associated exertion and pain.
Conclusion: This study clearly demonstrates that time-based performance tests and self-reported questionnaires of physical functioning measure different components of the domain physical function and give relevant additional information on in the ability to perform daily activities. For future assessment of physical function both performance tests and BASFI-questionnaire are recommended.

P 45

PREVALENCE AND ANTIMICROBIAL SUSCEPTIBILITY OF OPPORTUNISTIC MICROORGANISMS ORAL ISOLATES FROM PATIENTS WITH ANKYLOSING SPONDYLITIS USING TNF BLOCKERS

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Conventional therapy for ankylosing spondylitis (AS) includes non-steroidal anti-inflammatory drugs (NSAIDs). Nowadays, the use of immunobiological agents, such as antagonists TNF, has been considered an excellent therapeutic option. Nevertheless, previous studies reported the rate of infections increases after using it.

Oral reservoirs of opportunist microorganisms may increase the risk to systemic infections. The aim of the present study was to evaluate the prevalence and antimicrobial susceptibility of *Candida* spp., staphylococci, Enterobacteriaceae and *Pseudomonas* spp. from the oral cavity of patients with AS under conventional therapy and anti-TNF in comparison to healthy individuals. The study included: biological group (BioG) (n=35, 17-63 years) – patients under anti-TNF therapy for at least 60 days; conventional group (ConvG) (n=35, 21-74 years) – patients under conventional treatment; and respective control groups (n=70) – healthy individuals paired to the test groups regarding age, gender and oral conditions. After clinical examination, oral rinses samples were collected and plated in specific culture media. The number of colony-forming units per milliter (cfu/ml) was obtained. Isolates were identified by API system and antimicrobial susceptibility tests were performed. Staphylococci counts for BioG and ConvG were statistically higher than the control group ($p<0.0001$). *C. albicans* and *S. epidermidis* were the most frequently identified species in all the groups. *Serratia marcescens* was the most prevalent species in BioG and *Klebisiella oxytoca* in the ConvG. Two *Candida* isolates from BioG (2.8%) and five (10.8%) from the ConvG were classified as resistant to amphotericin B and 5-fluorocytosine, respectively.
High percentage of Enterobacteriaceae/Pseudomonadaceae isolates was resistant to the tested antibiotics. However, most of the isolates were susceptible to ciprofloxacin and norfloxacin. Low percentage of staphylococci isolates was resistant to amoxicillin, ciprofloxacin, doxycycline and tetracycline. Higher counts of staphylococci in BioG and ConvG might suggest increased risk of opportunistic infections among these patients.

P 46

ACCESS TO ANTI-TNF DRUGS FOR ANKYLOSING SPONDYLITIS IN THE UK - A SURVEY OF RHEUMATOLOGY DEPARTMENTS

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Introduction: In May 2008 etanercept and adalimumab were approved by NICE for treating patients with severe ankylosing spondylitis (AS). As part of a project to determine what services are available for AS patients in secondary care in the UK, we asked consultant rheumatologists about access to anti-TNF drugs. This forms part of the 'Looking Ahead – Best practice for the care of people with ankylosing spondylitis (AS)' project, led by the National Ankylosing Spondylitis Society (NASS).
Materials and Methods: A web-based survey with 41 questions examining the service provision for patients with AS was emailed as a link to consultant rheumatologists at all 171 acute trusts in England, Scotland, Wales and Northern Ireland. Patients were considered to have AS if they met the modified New York criteria.
Results: A total of 117 responses (68%) were received. Eighty percent of units were District General Hospitals, 18% tertiary referral centres and 2% polyclinics. Fifty-five percent of respondents reported a clinician with a special interest in AS within the department, though 64% of departments had a multidisciplinary team with responsibility for AS. Forty-two percent of departments ran dedicated AS clinics. Twenty-three units (21%) reported a restriction in access to anti-TNF therapy, due to Primary Care Trusts restricting numbers in terms of funding allocation (77%) or hospitals having insufficient staff to deliver the service (31%).
Conclusions: Despite NICE approval over 2 years ago for the use of anti-TNF drugs in severe AS, access is still being restricted, and patients are being denied optimal treatment.
Acknowledgements: This work has been made possible by an educational grant from MSD by way of a secondment of A K Gilbert, independent researcher and employee of MSD.

P 47

ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE (ASDAS): DEFINING CUT-OFF VALUES FOR DISEASE ACTIVITY STATES AND IMPROVEMENT SCORES

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Background: ASDAS is a new composite index to assess disease activity in ankylosing spondylitis (AS). Criteria for disease activity states and improvement scores are important for trials and clinical practice and have not been developed so far.
Objectives: To determine clinically relevant cut-off values for disease activity states and improvement scores using the ASDAS.
Methods: The ASDAS is calculated using BASDAI questions 2, 3 and 6, patient global assessment (all 0-10cm VAS) and CRP (mg/L). We performed receiver operating characteristic (ROC)-curve analysis against several external criteria (ExCr) and used several approaches to determine the optimal cut-off. The final choice was made on clinical and statistical grounds, after debate and voting by ASAS members. For the identification of proposed cut-offs we used baseline (BL) and 3-month (M) data of NOR-DMARD (N=295-477), a registry that includes AS patients starting a conventional DMARD or a TNF-blocker. Cross-validation was performed in ASSERT, a database of AS patients participating in a randomized placebo-controlled trial with infliximab.
Results: Four disease activity states were chosen by consensus: inactive disease, moderate-, high- and very high disease activity. The 3 cut-offs for separating them were: 1.3 (ExCr: ASAS partial remission, patient and physician global <10), 2.1 (ExCr: patient and physician global <30) and 3.5 (ExCr: patient and physician global >60). Selected cut-offs for improvement scores were: change ≥1.1 for clinically important improvement (ExCr: patient reporting as being "better" or "much better" since start of treatment) and change ≥2.0 for major improvement (ExCr: patient reporting as being "much better" since start of treatment). Results of the cross-validation strongly supported the cut-offs (tables 1 and 2).
Conclusions: Cut-off values for disease activity states and improvement scores using the ASDAS have been developed. They proved to have external validity and a very good performance compared to existing criteria.

Table I. Disease activity states (%) in ASSERT: Infliximab *vs* Placebo (Chi^2, p-value)

Time-point	n	ASAS Partial Remission	ASDAS <1.3	ASDAS 1.3-2.1	ASDAS 2.1-3.5	ASDAS >3.5
BL	166 vs 57	0 *vs* 0 (NA)	0 *vs* 0 (NA)	1.2 *vs* 1.8 (0.1, 0.756)	30.1 *vs* 26.3 (0.3, 0.586)	68.7 *vs* 71.9 (0.2, 0.645)
3M	163 vs 56	21.5 *vs* 1.8 (11.8, 0.001)	25.8 *vs* 1.8 (15.2,<0.001)	26.4 *vs* 3.6 (13.3, <0.001)	38.7 *vs* 39.3 (0.01, 0.933)	9.2 *vs* 55.4 (53.5, <0.001)
6M	163 vs 56	23.3 *vs* 1.8 (13.2, <0.001)	31.9 *vs* 0 (23.4, <0.001)	23.3 *vs* 12.5 (3.0, 0.084)	32.5 *vs* 33.9 (0.04, 0.846)	12.3 *vs* 53.6 (40.6, <0.001)

Table 2: Improvement criteria (%) in ASSERT: Infliximab *vs* Placebo

Improvement criteria	3 months (n=164 vs 56)	Chi^2 (p-value)	6 months (n=163 vs 56)	Chi^2 (p-value)
Δ ASDAS≥1.1	71.3 *vs* 19.6	45.9 (<0.001)	69.3 *vs* 23.2	36.3 (<0.001)
Δ ASDAS≥2.0	43.9 *vs* 3.6	30.4 (<0.001)	50.9 *vs* 5.4	36.3 (<0.001)
Δ BASDAI≥2	60.4 *vs* 23.2	23.1 (<0.001)	62.6 *vs* 19.6	30.8 (<0.001)
BASDAI50	50.6 *vs* 10.7	27.6 (<0.001)	51.5 *vs* 12.5	26.1 (<0.001)
ASAS20	64.0 *vs* 25.0	25.6 (<0.001)	63.2 *vs* 21.4	29.2 (<0.001)
ASAS40	50.6 *vs* 16.1	20.5 (<0.001)	47.2 *vs* 14.3	19.1 (<0.001)

P 48

LONG-CHAIN POLYUNSATURATED FATTY ACID COMPOSITION IN PLASMA, ADIPOSE TISSUE AND DIET AMONG PATIENTS WITH ANKYLOSING SPONDYLITIS

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Objectives: In a cross-sectional design, dietary intake of long-chained polyunsaturated fatty acids (LCPUFAs), composition in plasma phospholipids and adipose tissues and disease activity were assessed among patients with AS who were not on treatment with biologics.
Methods: Blood samples and gluteal fat biopsy were drawn from sixty-six patients (51 male, 15 female, mean age 48 years). Dietary intake of LCPUFAs was calculated on the basis of a semi-quantitative food frequency questionnaire. Plasma phospholipid and adipose tissue content were assessed using gas chromatography. Disease activity was measured with erythrocyte sedimentation rate (ESR, Westergren), high sensitive C-reactive protein (hiCRP) and BASDAI.
Results: The phospholipid plasma level of AA correlated significantly with disease activity according to both the total BASDAI score, and five of its six sub-scores (Table 1). Contents of LCPUFAs in gluteal adipose tissue and dietary intake did not correlate with BASDAI. Patients with higher ratings on BASDAI had higher hiCRP and ESR, although the difference did not reach statistically significant level.
Conclusion: The plasma phospholipid content of AA correlated with BASDAI, and may be regarded as a biomarker for disease activity. The lack of correlation between BASDAI and LCPUFAs in diet and adipose tissue, suggests that the endogenous production and incorporation of AA in phospholipids may be involved in the pathogenesis of AS.

Table I. Correlation (R_s) between plasma content of arachidonic acid (AA), dihomo gammalinolenic acid (DGLA), eicosapentaenoic acid (EPA) and disease activity according to BASDAI and its six questions (BASDAI 1-6).

	BASDAI	Fatigue	Back pain	Pain/swelling peripheral joints	Enthesitis	Severity morning stiffness	Duration morning Stiffness
AA	0.39**	0.26*	0.40**	0.13	0.29*	0.41**	0.30*
DGLA	-0.13	0.02	-0.12	-0.09	-0.16	-0.18	-0.13
EPA	0.07	0.09	0.05	0.02	0.14	0.08	0.01

**p<0.01, *p<0.05.

P 49

THE RELATIONSHIP OF BIOMARKERS AND RADIOGRAPHIC PROGRESSION IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH TNF-BLOCKERS

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Background: Structural damage in patients with ankylosing spondylitis (AS) is characterized by new syndesmophytes. The role of biomarkers in this scenario is still unclear.
Objective: To examine different biomarkers in prediction of radiographic progression in AS patients under anti-TNF treatment.
Methods: Complete data from radiographs and the following biomarkers from ASSERT were available at baseline and after 2 years: IL-6, VEGF, TGFβ for inflammation and BAP, OC, CTX, NTX, OPG and COMP for bone turnover. Clinical parameters (BASDAI, BASFI, BASMI, CRP, ESR), radiographs and MRIs were also available. Analyses were performed based on 'severe radiographic progression' (SRP, increase of ≥3 mSASSS units/year) and/or the development of new syndesmophytes.
Summary statistics were used for baseline data, and linear and logistic regression to test for association of biomarkers, clinical indices and radiographic progression. ROC analysis was used for cut-point determination.
Results: Data of 148 patients could be analyzed, 15% showed SRP and 19% syndesmophyte formation. Baseline characteristics and mean serum levels of biomarkers were not significantly different in patients with and without syndesmophytes/radiographic baseline damage. Only OPG serum levels correlated significantly with SRP. The best cut-off for OPG in discriminating between patients with and without SRP was 3.1 units (OR (95%CI):8.0 (2.6-24),p<0.001), sensitivity 67%, specificity 71% (AUC 0.66, LR+:1.7, LR-:0.54). Baseline radiographic damage (OR (95%CI):31 (3.2-298),p=0.003) was also predictive of SRP. HLA-B27 could not be investigated due to low prevalence of HLA-B27 negativity. Among markers for inflammation, only IL-6 showed a trend towards higher levels for patients with vs. without SRP.
Conclusion: Increased levels of OPG, an osteoclastogenesis inhibitory factor, were predictive of SRP over 2 years on the group level in anti-TNF-treated AS patients. In contrast to previous studies with AS patients under anti-TNF treatment and to patients with active RA or OA, none of the biomarkers indicative of bone degradation or hyperproliferation were predictive of radiographic progression in this study.

P 50

MEFV (MEDITERRANEAN FEVER) GENE MUTATIONS IN ANKYLOSING SPONDYLITIS: IMPACT ON RADIOGRAPHIC SEVERITY

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Objectives: To evaluate the MEFV gene mutation frequency and their effect on radiographic severity in Anklosing Spondilitis (AS).
Methods: Ninety-seven AS patients (Male/Female=49/48) diagnosed according to modified New York criteria were screened for FMF related symptoms using the revised Tel Hashomer criteria. Disease activity was assessed by the Bath Ankylosing Spondylitis Activity index (BASDAI) and assessment of functional loss and radiographic damage by the Bath Ankylosing Spondylitis Funtional Index (BASFI), Bath Ankylosing Spondylitis Radiology Index (BASRI) and the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), respectively. DNA samples were obtained from peripheral blood.MEFV mutations of Exon 10 (M694V, M680I and V726A) were identified by the Amplification Refractory Mutation System (ARMS) method and the E148Q mutation in Exon 2 was detected by the Restriction Fragment Length Polymorphism (PCR-RFLP) method. Results from the study patients were compared to a control group of 186 patients with non-inflammatory diseases.
Results: Mean disease duration of study patients were found to be 40.5±(11,5) years. Sixty-four percent were HLA-B27 positive and 32% of the AS patients had a history of uveitis. Carrier frequency for the studied MEFV mutations was not different than the control group. MEFV mutation carriers were all heterozygouts in the AS group. There was only one single compound heterozygout patient in the AS group carrying the E148Q/M680I mutation. Disease activity and functional status, HLA-B27 status and the prevalence of uveitis did not differ between non-carriers and MEFV mutation carriers. The presence of MEFV mutations (18.6%) did not affect radiographic severity assessed by mSASSS and BASRI (Carriers vs. non-carriers; mSASSS 12.2±20.4 vs. 10.7±17.4, p=0.97; BASRI 6±3.8 vs. 5.8±3.1, p=0.92).
Conclusion: Our results suggest that the carrier rate for the common four MEFV mutations is not increased in Ankylosing spondylitis and disease severity is not affected by their presence.

P 51

DISCONNECT BETWEEN DISEASE ACTIVITY AND JOINT SPACE NARROWING FOR PATIENTS WITH PSORIATIC ARTHRITIS TREATED WITH ADALIMUMAB PLUS METHOTREXATE BUT NOT FOR PATIENTS TREATED WITH METHOTREXATE ALONE

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Background: Joint space narrowing (JSN) is a critical outcome in rheumatoid arthritis (RA) because it is more strongly associated with disability than bone erosions. The relationships between disease activity, treatment, and JSN have not been fully explored in psoriatic arthritis (PsA).
Objectives: This post hoc analysis explored whether treatment with adalimumab (ADA)±methotrexate (MTX) resulted in greater inhibition of JSN than placebo±MTX for PsA patients in the ADEPT study.[1]

Methods: ADEPT was a 24-week, randomized, placebo-controlled trial of ADA for the treatment of active PsA. Treatment groups were randomized following stratification of subjects with methotrexate usage (≥3 months duration, 50.5% of patients). Time-averaged 28-joint Disease Activity Scores (TA-DAS28) were calculated at 12 and 24 weeks. JSN was assessed at week 24. Post hoc analyses evaluated the relationship between TA-DAS28 categories and JSN change (ΔJSN) from baseline to week 24 in the intention-to-treat population.
Results: Mean overall ΔJSN at week 24 was –0.2 for the ADA±MTX group and 0.4 for the placebo±MTX group (p<0.001). Mean ΔJSN appeared to increase with TA–DAS28 in the placebo group but not the ADA group (table).

ΔJSN ± SD (n)	TA-DAS28 Category			
Week 12	≤2.6	>2.6-3.2	>3.2-5.1	>5.1
Placebo±MTX[a]	–0.5 ± 1.0 (6)	0.0 ± 0.0 (8)	0.1 ± 0.6 (76)	0.7 ± 1.8 (48)
ADA±MTX[a]	–0.1 ± 0.8 (34)	0.0 ± 0.3 (27)	–0.2 ± 1.3 (55)	0.0 ± 1.2 (15)
P value[b]	0.17	0.98	0.02	0.05
Week 24				
Placebo±MTX[a]	–0.3 ± 0.9 (8)	0.0 ± 0.2 (11)	0.1 ± 0.5 (72)	0.8 ± 1.8 (47)
ADA±MTX[a]	0.0 ± 0.4 (43)	–0.4 ± 1.2 (26)	–0.3 ± 1.3 (49)	0.4 ± 1.1 (13)
P value[b]	0.41	0.62	0.02	0.66

[a] MTX used by subjects with ≥3 months MTX duration before baseline.
[b] *P* value for difference between treatment groups.

Conclusion: JSN was associated with TA-DAS28 in the placebo±MTX group, but not the ADA±MTX group. These data suggest that ADA may inhibit JSN independent of inflammation, potentially through inhibition of chondrocytic release of matrix-degrading substances.

Reference:
1. MEASE PJ *et al*.: *Ann Rheum Dis* 2009; 68: 702-9.

P 52

HOW EARLY CAN WE PREDICT REMISSION AT 24 WEEKS IN PATIENTS WITH PSORIATIC ARTHRITIS?

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Background: It is unclear whether remission should be a treatment goal in psoriatic arthritis (PsA). In patients with persistent, active PsA, therapy adjustment is recommended at least every 6 months. While the DAS28 was validated for rheumatoid arthritis, DAS28<2.6 is sometimes a proxy measure for remission in PsA.
Objectives: To assess the time for evaluating effectiveness and the need to change therapy for active PsA; to explore whether this timing is affected by treatment type.
Methods: ADEPT was a 24-week, randomized, placebo-controlled trial of adalimumab for treatment of active PsA.[1] Treatment groups were randomized following stratification of subjects with methotrexate usage (≥3 months duration). Data from the intention-to-treat population were analyzed post hoc.
Predicted probability of remission, defined as DAS28<2.6 at week 24, was evaluated for 4 DAS28 categories (<2.6, 2.6–≤3.2, >3.2–≤5.1, and >5.1) and 2 categories of change from baseline DAS28 (ΔDAS28, improvement >0.6 or ≤0.6) at weeks 4, 8, 12, and 16 in each treatment group.
Results: Probability of remission at week 24 was greater for patients treated with adalimumab±methotrexate than placebo±methotrexate for each level of DAS28 or ΔDAS28 at all time points. Patients with greater ΔDAS28 were more likely to be in remission at week 24. Of patients treated with placebo±methotrexate with little improvement at week 16, few were predicted to reach remission at week 24 (placebo, 4%; placebo+methotrexate, 5%). In contrast, approximately 16% of adalimumab-treated patients with little improvement at week 16 were predicted to reach remission at week 24 (adalimumab, 17%; adalimumab+methotrexate, 15%).
Conclusion: These data suggest that timing of treatment modification for active PsA varies by treatment type and response. Patients treated with methotrexate demonstrating little improvement could be candidates for early treatment adjustment, while clinicians should consider waiting ≥16 weeks before adjusting therapy in patients treated with adalimumab±methotrexate.

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P 53

MODIFICATION OF MINIMAL DISEASE ACTIVITY (MDA) SCORE BY REPLACEMENT OF PASI WITH PGA FOR PATIENTS WITH PSORIATIC ARTHRITIS TREATED WITH ADALIMUMAB

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Background: We compared a new method for measuring minimal disease activity (MDA) in psoriatic arthritis[1] (PsA) using the Psoriasis Activity and Severity Index (PASI) and the Physician's Global Assessment of psoriasis (PGA), which was reported to be a more appropriate measure[2], using data from a randomized, placebo-controlled trial of adalimumab[3].
Methods: MDA is defined by 5 of these 7 criteria: TJC (0–78) ≤1, SJC (0–76) ≤1, PASI ≤1 or BSA ≤3%, patient pain on a 0–100-mm visual analog scale (VAS) ≤15, Patient's Global Assessment of disease activity (0–100-mm VAS) ≤20, HAQ score ≤0.5, and tender entheseal points ≤1[1]. Only patients with active Ps (≥3% affected BSA) were included in this posthoc analysis. A heel-limited enthesitis score (0–4) and PASI≤1 were used to calculate MDA. We replaced PASI with PGA "Clear" (MDA_mod1) and PGA "Clear" or "Almost Clear" (MDA_mod2). The kappa coefficient compared performance of PASI and PGA using data from combined treatment groups.
Results: Baseline MDA characteristics were similar between groups. At week 24, MDA/MDA_mod1/MDA_mod2 was achieved by 40%/38%/40% of 60 adalimumab-treated patients and 7%/5%/8% of 60 placebo-treated patients (p<0.001, all treatment comparisons). Using PASI yielded results similar to using either PGA criteria. PGA "Clear" or "Almost Clear" agreed slightly better with PASI≤1 than PGA "Clear" (table).

PASI≤1	PGA "Clear"		Observed agreement, %	Kappa	PGA "Clear" or "Almost Clear"		Observed agreement, %	Kappa
	Yes	No			Yes	No		
Yes	20	15	87	0.65	34	1	86	0.69
No	0	83			16	67		

Conclusion: A new method to assess MDA in PsA demonstrated that significantly more adalimumab- treated patients achieved MDA by week 24. More than one-third of patients with active arthritis and active Ps achieved MDA after 24 weeks of adalimumab treatment. The new MDA was not altered when PASI was replaced with PGA criteria.

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P 54

REDUCED LEVELS OF THE TGFB FAMILY MEMBER GDF15 IN SPONDYLOARTHRITIS VERSUS OTHER RHEUMATIC DISEASES

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Introduction: The transforming growth factor-β (TGF-β) superfamily consists of a number of molecules that regulate a variety of cellular processes such as growth, differentiation and oncogenesis. Growth differentiation factor 15 is a distant member of this TGF-β family. GDF15 was previously shown to be elevated in serum of RA-patients compared to healthy controls. This study aims to compare GDF15 serum and synovial fluid levels in several inflammatory rheumatic diseases.
Methods: GDF15 levels were determined by ELISA in two different cohorts. A first group included serum samples from patients with an indication for an arthroscopic procedure for diagnostic purposes. A total of 37 RA patients, 63 SpA patients and 17 OA patients was analyzed. Synovial fluid levels in RA and SpA patients from this cohort were determined as well. A second confirmatory cohort constituted of a consecutive cohort of 555 patients visiting the outpatient clinic of the department of Rheumatology at Ghent University Hospital.
Results: SpA samples show a significant lower serum concentration of GDF15 compared to RA patients. When SpA patients were stratified according to the subdiagnosis (USpA, AS or PsA) no statistically significant differences could be ob-

served between the groups. Interestingly, SpA patients, but not RA-patients, show a significant higher concentration of GDF15 in the synovial fluid compared to serum (serum=516,38 pg/ml ± 71,09 vs syn fluid 803,2167 pg/ml ± 99,14; paired sample t-test, $p<0,001$), pointing to a local production of GDF15 in the synovial joint. No significant correlations were observed between GDF15 concentration and routine biochemical (CRP, ESR) or clinical markers (number of swollen joints, DAS28), indicating that GDF15 serum levels might be indicative for a distinct underlying disease process. Analysis the second group consisting of a consecutive cohort of 555 patients confirmed the lower concentration of GDF15 in serum samples of SpA patients compared to RA patients. To estimate the diagnostic potential to discriminate SpA from RA patients, a ROC curve analysis was performed, characterized by a AUC of 0,76. In addition, it was demonstrated that GDF15 levels might have an added value to anti-CCP and Rheumatoid Factor to discriminate RA and SpA patients.
Conclusion: GDF15 serum concentrations are significantly lower in SpA patients compared to other inflammatory joint diseases. The serum levels are not directly correlated to inflammatory or known diagnostic parameters and thus may serve as an additional marker for diagnostic purposes in inflammatory joint diseases.

P 55

HIGH SENSITIVE CRP INCREASES SENSITIVITY AND RESPONSIVENESS OF ASDAS

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Background: ASDAS, a new measure of disease activity for patients with axial spondyloarthritis (SpA) (1), comprises BASDAI questions 2, 3 and 6, patient global assessment (all 0-10 cm VAS) and serum C-reactive protein (CRP). CRP is not routinely measured by high sensitive (hs) methods in daily clinical practice in patients with SpA, and this may affect scores.
Objectives: To investigate the performance of ASDAS including hsCRP and "normal routine" CRP.
Methods: ASDAS was calculated at baseline and week 22 in 56 patients with axial SpA initiating anti-TNF therapy. Patients were classified according to disease activity and improvement in ASDAS (2).
Serum CRP was measured by the hsCRP method. Values <8 mg/l were afterwards transformed to 8 mg/l.
Results: ASDAS(CRP) was higher than ASDAS(hsCRP) at baseline (median 4.04 (IQR: 2.26-4.55) vs. 3.86 (2.99-4.56), $p=0.001$) and at week 22 (2.22 (1.69-2.91) vs. 1.63 (1.02-2.45), $p<0.0001$). The reduction in ASDAS(CRP) from baseline to week 22 was lower as compared to ASDAS(hsCRP) (1.41 (0.69-2.43) vs. 1.94 (0.97-2.90), $p<0.0001$). When using ASDAS(hsCRP) as the reference, 15 (27%), 12 (21%) and 1 (2%) patients were classified by ASDAS(CRP) into a higher category of disease activity at week 22 (i.e. from inactive to moderate, moderate to high and from high to very high, respectively).
Furthermore, 6 (13%) and 8 (17%) patients were classified into a lower ASDAS response category (i.e. from minimal important to no improvement, and from major to minimal important improvement). Moreover, ASDAS(hsCRP) had higher standardized response mean (2.04 vs 1.79) than ASDAS(CRP).
Conclusion: ASDAS-based assessment of disease activity and treatment response is dependent on the methodology of CRP-measurements (hsCRP versus conventional CRP). This potential advantage of using hsCRP needs further investigation.

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P 56

DISEASE ACTIVITY ASSESSMENT BY ASDAS DOESN'T PREDICT SACROILIAC INFLAMMATION WITH MRI IN AXIAL SPA

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Objective: The ASDAS (Ankylosing spondylitis disease activity score) is a newly developed composite index to measure disease activity in AS. It incorporates items of back pain, morning stiffness, patient global assessment of disease activity, pain/swelling of the peripheral joints and the CRP using a weighted formula. In the present study we aimed to test the construct validity of ASDAS comparing it with active inflammation of the sacroiliac joints (SIJs) as shown by MRI.
Methods: Twenty-three patients (n=23) with axial SpA according to the ASAS criteria were included. All patients were questioned for the parameters included in ASDAS and had an MRI scan of the SIJs. ASDAS values were categorized according to the different cut-off levels recently presented at OMERACT 10 and compared to the MRI findings according to the guidance of ASAS proposals. Further scoring to identify patients with severe MRI sacroiliitis (grade 3 according to the Leeds MRI SIJ Scoring System) and total MRI scores (sum of scores at all quadrants with a maximum score of 24) were also available.
Results: All patients had active disease according to ASDAS (scores >1.3) (table I). Moderate disease was found in 13%, 39 % had active and 48 % had very active disease. No relationship was found between the different states of disease activity according to ASDAS and MRI findings, including severity of the MRI. Similarly, ASDAS levels were found comparable in groups with/without sacroiliitis by MRI (3.5 ±1.1 vs 3.1±0.9, $p=0.5$, respectively) and severe sacroiliitis by MRI (3.5 ±1.8 vs 3.4±0.9, $p=0.8$, respectively). MRI scores were also independent from ASDAS categories.
Conclusion: Besides the clinical benefits of ASDAS, there does not appear to be a relationship between ASDAS and the presence of bone marrow oedema on MRI at the SIJ of axial SpA patients.

Table I: Distribution of ASDAS according MRI findings:

Disease activity according to ASDAS	ASDAS cut off levels	Positive MRI (n)		Severe sacroiliitis by MRI (n)		MRI scores median (range)
		+ n = 18	- n = 5	+ n = 4	- n = 19	
inactive disease	<1.3	0	0	0	0	NA
moderate activity	1.3-2.1	2	1	1	2	5 (0-16)
high activity	2.1-3.5	7	2	1	8	1 (0-18)
very high activity	>3.5	9	2	2	9	2 (0-12)
		p = NS			p = NS	p = NS

P 57

CORONARY FLOW RESERVE AND ADMA LEVELS: NEW PARAMETERS TO IDENTIFY THE SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH PSORIATIC ARTHRITIS

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Objective: To identify the presence of subclinical atherosclerosis in psoriatic arthritis (PsA) patients compared to a control group using intima-media thickness (IMT), coronary flow reserve (CFR), and plasma concentration of asymmetric dimethylarginine (ADMA) and to evaluate the correlation between ADMA and IMT and CFR.
Methods: A total of 22 patients with PsA who fulfilled the CASPAR criteria and a cohort of 35 healthy controls with no history or current signs of cardiovascular disease (CAD) were recruited. Common carotid IMT was measured in both right and left carotid artery by using high resolution B-mode ultrasound.
Dipyridamole trans-thoracic stress echocardiography was performed to evaluate CFR. Blood samples were obtained in order to assess ADMA levels. The related clinical manifestations were recorded. All the patients were treated with DMARDs, but no patients had received any biological or steroid therapy.
Results: CFR was significantly reduced in the PsA patients group compared to controls (2.86±0.70 *vs* 3.3±0.43; $p<0.01$). Common carotid IMT was greater in the PsA patients, although the difference wasn't significant (0.64± 0.26 vs 0.62±0.5 mm). A significant correlation between CFR and plasma ADMA levels in the PsA patients group (R= 0.28; $p<0.01$) was dected, but no correlation was found between plasma ADMA levels and IMT (R=0.02; P= 0.32), DAS28 ($p=0.52$) and PASI ($p=0.98$).
Conclusion: PsA patients exhibited a worse profile of subclinical atherosclerosis (CFR and ADMA). ADMA might be an important effect modifier of the relation between PsA and CFR outcome.

P 58

MULTIPLEX ASSAY OF A PANEL OF 58 BIOMARKERS IN ANKYLOSING SPONDYLITIS: IDENTIFICATION OF HIGH PRIORITY CANDIDATES FOR PREDICTION OF STRUCTURAL DAMAGE

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Background: Radiographic progression in ankylosing spondylitis (AS) requires 2 years before it can be reliably detected and prospective studies have consistently identified only baseline radiographic damage as an independent predictor. Prior reports suggest that biomarkers reflecting joint inflammation and bone turnover may be useful predictors.
Objective: To simultaneously analyze a large panel of serologic biomarkers reflecting pathophysiological processes in AS as predictors of radiographic progression.
Method: We used multiplexed sandwich immunoassays to simultaneously quantify a panel of 58 biomarkers. Serum was obtained at a single time point from 60 patients with AS and 60 age- and sex-matched controls. For subgroup analysis we defined rapid progressors (baseline mSASSS at least 10 units, progression over 2 years at least 5 units, at least one new syndesmophyte) and non-progressors (disease duration at baseline of at least 10 years, baseline mSASSS of less than 5 units, and no change in mSASSS over 2 years).
Results: A total of 23 biomarkers demonstrated significant differences between AS patients and controls, especially osteocalcin and Rantes (both $p<0.0001$). Ten biomarkers demonstrated significant differences from controls when analysis was stratified according to progressor phenotype: in the rapid progressor subgroup MMP-9, transforming growth factor alpha, and tumor necrosis factor alpha were significantly elevated compared to controls (all $p<0.0001$). Eotaxin, interferon alpha-2, and monocyte chemotactic protein-3 were significantly increased in the non-progressor subgroup. Three biomarkers, interleukin-17, interferon-gamma, and macrophage inhibitory protein-beta, demonstrated significantly increased levels in AS patients that were further increased in the rapid progressor subgroup. Six biomarkers were significantly increased only in male patients and particularly the rapid progressor subgroup, especially macrophage derived chemokine and CD40 ligand (both $p<0.0001$).
Conclusion: Multiplexed assay of an extensive panel of biomarkers reflecting pathophysiological processes implicated in AS has identified several biomarkers as high priority candidates for predictors of structural damage in AS.

P 59

SCREENING FOR AXIAL SPONDYLOARTHRITIS IN A PRIMARY CARE: COMPARISON OF TWO STRATEGIES IN A MULTICENTER PROSPECTIVE STUDY

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Objective: To evaluate two referral strategies for axial spondyloarthritis (SpA) in patients with chronic low back pain on a primary care level.
Methods: Primary care physicians (orthopedists, n = 259) were randomly assigned either to the strategy 1 or strategy 2 in order to refer patients with chronic back pain (duration of more than 3 months), age of back pain onset <45 years to a cooperating rheumatologist (n = 54) for a further diagnostic workup. According to strategy 1 patients were referred if at least one of the following 3 screening parameters was present: HLA-B27, inflammatory back pain or sacroiliitis detected by imaging. According to strategy 2 patients were referred if 2 out of 5 parameters were positive: the same 3 parameters from strategy 1 and additionally a positive family history for SpA, and a good treatment response to non-steroidal anti-inflammatory drugs. The final decision on a diagnosis was made by the rheumatologist.
Results: 560 consecutively referred patients were included in the analysis. Among 318 patients referred via the 1st strategy 133 patients (41.8%) were diagnosed with axial SpA: ankylosing spondylitis in 82 (25.8%), non-radiographic axial SpA in 51 (16.0%), while in 142 patients (44.7%) axial SpA was definitively excluded. Similarly, among 242 patients referred via the 2nd strategy, 89 patients (36.8%) were diagnosed with axial SpA: ankylosing spondylitis in 55 (22.7%), non-radiographic axial SpA in 34 (14.1%), while in 115 patients (47.5%) axial SpA was definitively excluded.
Conclusion: Both referral strategies performed well as screening methods for patients with a high probability of axial SpA among large population of individuals with chronic back pain the primary care level. Referral strategy 1 can be recommended as an easy and reliable screening method of axial SpA on the primary care level.

P 60

VARIATION DURING DIFFERENT DECADES OF DIAGNOSTIC AND THERAPEUTIC DELAY IN PATIENTS OF ANKYLOSING SPONDYLITIS (AS)

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Background: Ankylosing Spondylitis (AS) is a chronic, progressive, and disabling disease, but the diagnosis is often missed and markedly delayed (1). The early diagnosis is important to establish a treatment to reduce disability and modify the natural course of disease (2).
Objective: To investigate the diagnostic (DD) and therapeutic (TD) delay according to the decade of diagnosis and the correlation between DL and radiological severity score. The influence of different imaging techniques on TD has been also investigated.
Methods: 125 AS patients (45 female and 90 male, 36,5±10,2 years old at diagnosis) with disease onset between 1950 and 2008, were investigated: the time between onset and first rheumatologic visit, diagnosis (DD) and treatment (TD); the New York and ASAS criteria (3), the New York sacroiliac radiological score, the bamboo spine presence at first visit; the new imaging technique employed (magnetic resonance -MRI-, computerized tomography -CT- and scintigraphy for sacroiliac and ultrasonography -US- for periperipheral joints) at diagnosis. The difference of DD, TD and imaging technique between different onset decades ('50, '60, '70, '80, '90, '00), the correlation between DD and radiological severity, between TD and new imaging were analyzed.
Results: At first visit, 87% and 96% patients respectively met New York and mASAS criteria, with onset of symptoms 8,1±8,2 years before (28,3±10,2 years old). The delay since onset of symptoms to diagnosis and treatment was 9±8 and 12±11 years, respectively, but decreased significantly between different decades ($p<0,001$, Kruskal Wallis). The severity of sacroileitis (mean 2±1, 13% IV grade at diagnosis) and bamboo spine (7,4% at diagnosis) correlated with DD ($p<0,001$, Pearson correlation) and decreased during decades ($p<0,001$, Kruskal Wallis). The employment of new imaging technique increased significantly during decades ($p<0,001$) but only sacroiliac MRI significantly decreased TD ($p<0,05$, Mann Whitney test).
Conclusions: DD, TD, radiological severity significantly and progressively decreased during decades. In particular, the employment of sacroiliac MRI decreased time to first treatment.

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P 61

CHARACTERISTICS OF PERIPHERAL SPONDYLOARTHRITIS IN KOREAN PATIENTS

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Objectives: Our previous study has reported that peripheral arthritis is more frequent in Korean SpA patients compared to western patients. We investigated the clinical application of the new criteria developed by ASAS and characteristics of pSpA in Korean patients. We were also interested to see whether aSpA with peripheral arthritis truly differs from pSpA with inflammatory back pain (IBP).
Methods: We studied 221 consecutive patients with SpA who visited the rheumatology clinic of Gil Hospital from 1 November 2009 to 31 April 2010. All patients met the criteria of axial or peripheral SpA developed by ASAS.
Results: Of the 221 patients, 17% (38) had peripheral SpA. Mean age of disease onset did not differ between pSpA and aSpA. Male to female ratio was lower in pSpA than in aSpA (1.2 vs. 4.2; $p=0.002$).
Peripheral arthritis and enthesitis was presenting predominant symptom, on the first visit, in 84% and 18% of pSpA patients, respectively. Sixty-one percent (23) patients experienced IBP. Extra-articular features, including uveitis, inflammatory bowel disease and psoriasis, were observed in 21% of pSpA patients. The most of pSpA patients were undifferentiated form (92%). HLA-B27 was detected in 74% of the patients. In pSpA patients with history of IBP, moderate to severe radiographic

sacroiliitis (grade 3/4) was found in 9%, compared to 43% in aSpA patients with peripheral arthritis (p=0.04). Modified Stokes Ankylosing Spondylitis Spine Score of lumbar spine was significantly lower in pSpA patients with IBP than in aSpA ones with peripheral arthritis (1.0 vs. 4.6; *p*=0.002).
Conclusion: Peripheral SpA occupied 17% of SpA frequencies in Korean patients. Most of pSpA patients were undifferentiated form. It occurred in women as common as in men. Patients with pSpA, even though they had IBP episodes, showed more favorable spine disease in terms of radiographic change, compared to those with aSpA.

P 62

THE NEW ASAS CRITERIA FOR AXIAL SPA DOES NOT PREDICT THE DEVELOPMENT OF MNYC AS AT 8 YEARS IN A COHORT OF VERY EARLY IBP PATIENTS

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Objective: Axial SpA can be identified by using the new ASAS criteria. We aimed to test the predictive value of the imaging (MRI) and HLA-B27 arms of these criteria for the future development of Ankylosing Spondylitis (AS).
Method: An inception cohort of 33 patients with early inflammatory back pain (IBP) (median symptom duration 24 weeks) were retrospectively evaluated against both arms (imaging and HLA-B27) of the criteria. Plain radiographs and MRIs of the SIJs at baseline and radiographs after a mean duration of 8-years were assessed. MRIs were scored according to the ASAS definition of a "positive MRI" and the predictive value of both arms was compared. Further scoring to identify patients with severe MRI sacroiliitis (grade 3 according to the Leeds MRI SIJ Scoring System) was also available.
Results: All patients could be classified as axial SpA with more patients fulfilling the imaging (85%, n=28/33) than the clinical arm (58%, n=19/33) of the criteria. Eight patients with baseline evidence of radiographic sacroiliitis fulfilling the mNYC were excluded from the predictive analysis. Of the rest (25/33), n=4 patients developed AS at follow-up (all had a positive baseline MRI and 2 were HLA-B27+ve) and 11/33 had an increase in the radiographic sacroiliitis scores at 8 years. For prediction of new AS the MRI arm showed 100% sensitivity and 19% specificity whereas the HLA-B27 arm had 50% sensitivity and 43% specificity. No differences were seen between both arms for developing new AS or for progression of sacroiliitis when applying the ASAS definition of a positive MRI (Table I). However an association was seen between development of AS (PPV 67%, NPV 91%, LR: 10) and progression of sacroiliitis (PPV 71%, NPV 76%, LR: 4.8) when using the Leeds definition of severe MRI sacroiliitis.
Conclusion: Neither arm of the new ASAS classification criteria predicted the progression of radiographic sacroiliitis (including the development of mNYC AS) over an 8 year period in this cohort of very early IBP.
This may be due to the inclusion of "mild" MRI sacroilitis in the ASAS definition of a "positive MRI" since severe MRI sacroiliitis was a better predictor.

Table I: New AS or worsening of sacroiliitis by X-rays according to the MRI findings and HLA-B27 positivity

		Positive MRI (ASAS definition)			Severe MRI (Leeds Scoring System)			HLA-B27		
		+	-	p	+	-	p	+	-	p
New AS (mNYC) n=25	+	4	0	1	2	2	0.057	2	2	1
	-	17	4		1	20		12	9	
Progression of sacroiliitis n=33	+	10	1	0.6	5	6	0.03	7	4	0.7
	-	17	4		2	19		11	10	

P 63

ESTIMATING THE RISK OF VALVULAR AND NONVALVULAR CARDIOVASCULAR DISEASE IN INDIVIDUALS WITH ANKYLOSING SPONDYLITIS: A POPULATION-BASED STUDY

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Objective: To estimate the population-based incidence, and increased risk, of cardiovascular and cerebrovascular disease (CVD) in AS, compared to the general population, in the Canadian province of Québec.
Methods: A retrospective cohort study was conducted using the Québec administrative physician-billing databases. The cohort included individuals with at least one ICD-9 billing code for AS between 1998 and 2006, with no such diagnosis in the preceding two years. A comparison cohort was generated using a 1% random sample of individuals without AS. CVD was classified into 7 categories: valvular, aortic, ischemic or other CVD; heart failure; hypertensive, and cerebrovascular CVD. Incidence rates per person-year, and crude and age- and sex-standardized incidence rate ratios (IRRs) with 95% confidence intervals (CIs) of CVD compared with the general population were calculated.
Results: 7,663 individuals with AS were identified between 1998 and 2006; 55% were male and the median age at diagnosis was 42.5 years. The age-specific incidence of CVD increased from 30.9 to 90.7 events per 1,000 person-years among patients with AS aged 20–39 and >60 years, respectively. The IRR for CVD was highest among younger patients with AS; decreasing from 1.5 (1.4–1.5) to 1.1 (1.1–1.1) for those aged 20–39, to >60 years, respectively. After adjusting for age and sex, the IRRs (95% CI) were: any CVD 1.2 (1.1–1.3); valvular disease: 1.6 (1.4–1.7); aortic disease: 1.5 (1.3–1.9); hypertensive CVD: 1.2 (1.1–1.3); ischemic disease: 1.3 (1.2–1.4); heart failure: 1.3 (1.3–1.4); and other CVD: 1.4 (1.3–1.4).
Conclusion: Patients with AS are at increased risk for many types of CVD, with excess risk being greatest for young patients with AS. These data support consideration of cardiovascular risk assessment in the clinical evaluation of patients with AS.

P 64

HIGH FREQUENCY OF VERTEBRAL FRACTURES IN EARLY SPONDYLARTHROPATHIES

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Introduction: Vertebral compression fractures due to osteoporosis are a well known complication of longstanding Ankylosing Spondylitis (AS), but data in early Spondylarthropathies (SpA) are scarce.
Objectives: To examine the prevalence of vertebral fractures in early SpA patients and the association between vertebral fractures and disease-related variables.
Methods: Early Spondylarthropathy patients were included consecutively and radiographs of the spine, and bone mineral density (BMD) measurements of the lumbar spine and hips were made. Vertebral fractures were defined as a reduction of ≥20% of the vertebral body height (Genant et al) and radiographic damage was assessed (mSASSscore). Descriptive statistics, t-tests, and logistic regression analyses were used to study the relationship between vertebral fractures and disease related variables (diagnosis, disease duration, ESR, BASDAI, etc), radiographic damage and the BMD.
Results: 113 early SpA patients were included with a median disease duration of seven months (IQR=2.1-14.4), mean age of 37 years, 66% males and a low mean MsASSscore of 2.0 (range 1.0-4.7).
Seventeen patients (15%) showed fractures, mainly of the thoracic spine:14 had one fracture, 3 patients had two fractures. In patients with fractures, the BMD of the lumbar spine was lower compared to those without fractures (t-test: *p*=0.043), but the majority did not fulfil the criteria for osteoporosis (T-score <-2,5). Axial Psoriatic Arthritis (PsA) was significantly associated with a higher risk for vertebral fractures (OR: 4.62, 95% CI 1.15-18.58, *p*=0.031). No significant associations were found with disease activity variables or radiographic severity.
Conclusion: In 113 early, young SpA patients, with a median disease duration of 7 months, 15% already had at least one vertebral fracture. Most vertebral fractures were undetected by routine clinical diagnostic procedures and located at the mid-thoracic spine. The vertebral fractures were associated with a low BMD of the lumbar spine and with the diagnosis axial PsA.

P 65

DECREASED RECURRENCE RATE OF ANTERIOR UVEITIS IN ANKYLOSING SPONDYLITIS TREATED WITH ADALIMUMAB – AN INTERIM ANALYSIS

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Introduction: Many (30-40%) patients with Ankylosing Spondylitis (AS) suffer from acute anterior uveitis (AAU). Local treatment of AAU with corticosteroids is beneficial but TNF blocking agents also appear to be effective. However, prospective studies investigating AAU in AS during anti-TNF treatment are lacking.
Objective: To examine the frequency of attacks of AAU in patients with AS, who receive adalimumab because of their spinal disease activity.
Methods: Consecutive AS patients, treated with 40 mg of adalimumab every other week according to the international ASAS consensus statement, were included. The number of attacks of AAU before and after treatment was assessed by patient history and ophthalmological controls at baseline and yearly thereafter.
Results: A total of 60 patients were enrolled. This interim analysis includes 29 patients who completed the first year follow up and 6 patients after 2 years. Fourteen out of these 29 (48 %) patients did not have any attacks of uveitis before and after treatment with adalimumab. Fifteen patients (52 %) suffered from a mean number of attacks of 3.8/year (range 1-12) with a recurrence rate of one in 11 cases (73%), reduction of 5 attacks to one in 2 cases (13%) and remained equal in 2 patients (13%, one attack) during one year of adalimumab treatment. Interestingly, even the patient with a very high number of attacks of AAU (12 per year) was completely free of attacks after the start of adalimumab, after 2 years of follow up.
The recurrence rate decreased significantly (p=0.001) from 15/29 (52%) to 4/29(14%), with a 73% reduction in the recurrence of uveitis.
Conclusions: Our interim analysis revealed a significant reduction of recurrence rate of attacks of acute anterior uveitis during adalimumab treatment, even in patients with a high recurrence rate of the attacks.

P 66

INTERPLAY OF PEPTIDE BINDING, MOLECULAR STABILITY AND OTHER BIOLOGICAL FEATURES OF HLA-B27

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Natural subtypes and site-directed mutants were used to analyze the effect of altering the peptide-binding site of this molecule on its stability, interaction with tapasin, folding and export. The disease-associated subtypes B*2705, B*2702 and B*2704 showed higher thermostability than all other subtypes and mutants, except some mimicking B*2702 polymorphism. The lowest values were found among pocket B mutants, most of which interacted strongly with tapasin, but otherwise there was no correlation between thermostability and tapasin interaction. Mutants resulting in increased hydrophobicity frequently acquired their maximal thermostability faster than those with increased polarity, suggesting that this process is largely driven by the thermodynamics of peptide binding. Folding, export and tendency to misfold were influenced by polymorphism all along the peptide-binding site and were not specifically dependent on any particular region or structural feature. Frequent uncoupling of thermostability, folding/misfolding and export can be explained by distinct effect of mutations on the acquisition of a folded conformation, the optimization rate of B27/peptide complexes, and their quality control in the endoplasmic reticulum, all of which largely depend on the ways in which mutations alter peptide binding, without excluding additional effects on interactions with tapasin or other proteins involved in folding and export. The similarity of the disease-associated B*2707 to non-disease-associated subtypes in all the features analyzed suggests that molecular properties other than antigen presentation may not explain the relationship between HLA-B27 polymorphism and ankylosing spondylitis.

P 67

ERAP1 Q730E VARIANTS AFFECT THE MHC-I FREE CHAIN EXPRESSION ON MONOCYTES OF PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: The Endoplasmic Reticulum Aminopeptidase 1 (ERAP1) gene associated with ankylosing spondylitis (AS) is involved in antigen presentation. We studied the surface expression of HLA B27 and free heavy chains (FHC) on PBMC of patients with AS in the context of their ERAP1 genotype.
Methods: Caucasian HLAB27 positive AS patients, not on any biologic treatment, were enrolled. The BASDAI, BASFI, BASMI, ESR and CRP were noted. Genotyping for the *rs30187* and *rs27044* SNPs of the ERAP1 gene were performed. PBMC were acquired in a FACSCalibur after staining with ME1 (intact HLA B27), HC10 (FHC), APC tagged anti-CD14 (monocytes) and PE tagged anti-C19 (B cells) antibodies for their respective surface molecules. The mean fluorescence intensities (MFI) of ME1 and HC10 on whole PBMC, monocytes and B cells were analyzed using FlowJo. The MFI were compared between the genotypic groups.
Results: Twenty nine patients (5 females) with a median (interquartile range –IQR) age of 37 (24, 47) years and median (IQR) disease duration of 15.3 (9.5, 24) years, were included in the study. The frequency of patients with the different genotypes of *rs30187* was 3, 13, 13 (TT, CT, CC) and for *rs27044* was 4, 13, 12 (CC, CG, GG). There was no significant difference in the demographic or clinical variables between the genotypic groups. The MFI for HC10 staining but not ME1 was significantly different across the genotypic groups by Kruskal-Wallis test (H=6.28, df=2; p=0.04). In the dominant model, there was significantly higher FHC (Z=-2.4, p=0.01) on the monocytes of patients who had the *rs27044* minor allele G compared to those with only the major allele C. There were no significant differences between the *rs30187* groups.
Conclusions: This novel finding indicates a functional relevance of ERAP1 association with AS. The patients with the Q730 variant (*rs27044 [C]*) had significantly more FHC on monocytes.

P 68

ANKYLOSING SPONDYLITIS PATIENTS WITH THE ERAP1 K528 VARIANT HAVE SIGNIFICANTLY FASTER RADIOLOGICAL PROGRESSION

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Background: Endoplasmic reticulum aminopeptidase 1 (ERAP1) and ERAP2 genes are associated with AS. We studied the effect of the ERAP1 and ERAP2 polymorphisms on radiological progression in AS.
Methods: Caucasian AS patients (modified New York criteria) were followed prospectively with clinical evaluation (including BASDAI, BASFI and BASMI) annually and radiographs biennially. DNA was isolated from peripheral blood and genotyped for the rs30187, rs27044 and rs10050860 SNP of ERAP1 and rs2549782 of ERAP2. Independently, two blinded readers calculated the mSASSS scores. The rate of change in mSASSS scores were noted by dividing the change in mSASSS (ΔmSASSS) by the intervening duration. The ΔmSASSS rates were compared between the genotypic groups using the Kruskal-Wallis test.
Results: Seventy patients (10 females) had at least 2 x-rays at a mean ±SD gap of 2.7±0.9 years. The mean age and disease duration were 37.2±13 years and 15.1±10 years respectively. Forty-six patients were on anti-TNF medications for a mean duration of 15.7±2.2 months. The mean baseline and follow up mSASSS scores were 17.2±22.8 and 18.9 ± 23.2 respectively with a ΔmSASSS of 1.7±2.6 and ΔmSASSS rate of 0.8±1.5 units/year. The age, disease duration, BASDAI, BASFI, BASMI, baseline mSASSS scores and the mean duration of anti-TNF intake were comparable between the genotypic groups of ERAP1 and ERAP2. There was significant difference in the ΔmSASSS rate between the genotypic groups of only the rs30187 SNP of ERAP1 ((H=5.9, df=2; p=0.05). Patients with K528 variant of ERAP1 (C allele of rs30187) progressed faster than patients with only the 528R variant with an OR of 9.3 (CI: 1.9-44.2; p<0.01).
Conclusion: This novel finding suggests that ERAP1 polymorphisms can affect radiological severity in AS. Patients with the ERAP1 K528 variant have significantly faster radiological progression.

P 69

IMPACT OF ANKLOSING SPONDYLITIS-ASSOCIATED ERAP1 VARIANTS ON ITS AMINOPEPTIDASE ACTIVITY

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Introduction: The genetic association between *ERAP1* and ankylosing spondylitis (AS) was first reported in 2007 by the WTCCC. We have subsequently identified all AS-associated non-synonymous single nucleotide polymorphisms (nsSNPs). In the endoplasmic reticulum ERAP1 trims antigenic peptides 10-16 residues in length to 8-9 residues, the optimal length for binding MHC class I molecules. The aim of this study was to investigate the impact of AS-associated ERAP1 nsSNPs on its aminopeptidase activity.
Methods: Wild-type (WT) ERAP1 and ERAP1 containing individual AS-associated amino acid substitutions were expressed in insect cells using the baculovirus expression system. ERAP1 activity was studied using two different substrates. Initially we measured the fluorescent signal produced upon digestion of the substrate Leu-AMC. Subsequently we measured the rate at which ERAP1 cleaved the N-terminal tryptophan residue from three peptide substrates, also measured by a fluorescence method (Evnouchidou *et al* 2008).
Results: The activity of the ERAP1 variant with the Lys528Arg substitution was ~3 fold lower than WT ERAP1 towards Leu-AMC (p=0.00014). Similarly the Arg725Gln substitution resulted in a ~35% reduction in activity (p=0.0076). In contrast, the Gln730Glu substitution increased ERAP1 activity towards Leu-AMC (~69%) compared to WT (p=0.0061). The ERAP1 substitutions Lys528Arg, Arg725Gln and Gln730Glu all had reduced activity towards the three peptides studied (p<0.01). The Lys528Arg substitution resulted in the largest decrease in activity (~40%) towards WRVYEKC^{DNP}ALK, the peptide trimmed at the greatest rate by WT ERAP1 (p=0.0094).
Conclusions: Specific ERAP1 variants appear to alter its activity towards a range of substrates. Further *in vitro* and *in vivo* studies are required to investigate the activity of these ERAP1 variants.

P 70

INVESTIGATING THE ROLE OF ENDOPLASMIC RETICULUM AMINOPEPTIDASE-1 (ERAP1) IN ANKYLOSING SPONDYLITIS

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Background: Recent studies have shown that genetic variation within *ERAP1*, encoding endoplasmic reticulum aminopeptidase 1, is strongly associated with ankylosing spondylitis (AS). Within the endoplasmic reticulum, ERAP1 is involved in the trimming of peptides to the optimal length for their presentation by major histocompatibility complex (MHC) class 1 proteins, such as HLA-B27 that is also associated with AS. Here, we investigate the differential activity of WT-ERAP1 and the ERAP1 mutant (Lys528Arg) that is strongly associated with AS.
Methods: The N-terminal-extended HLA-B27 Chlamydia peptide epitope (13-mer, QITANRELIQQEL) was incubated with WT-ERAP1 and with the K528R mutant in time course experiments at 37°C (Up to 6h). The reaction was stopped by the addition of 0.6% trifluoroacetic acid. After 15 min on ice, the precipitated protein was moved by centrifugation. Then the supernatants were analyzed on a Chipcube-coupled Agilent 6520 Q-TOF mass analyzer. For each time point, extracted ion chromatograms of the trimming intermediates were generated and integrated.
Results: The K528R mutant was able to degrade the 13-mer at a comparable rate to WT-ERAP1, but trimmed the 12-mer (ITANRELIQQEL) with reduced efficiency compared to the WT-ERAP1. The difference between WT-ERAP1 and the K528R mutant became more significant when it came to the11-mer (TANRELIQQEL): the K528R mutant seemed unable to further process the 11-mer while the WT-ERAP1 continued to cleave off N-terminal amino acids until it generated 8/9 mers.
Conclusions: WT-ERAP1 is able to trim the N-terminal extended HLA-B27 Chlamydia peptide more efficiently than the K528R ERAP1. The differences in activity between the K528R mutant ERAP1 and WT-ERAP1 may alter the array of B27-peptide complexes at the cell surface in vivo, which may be involved in the pathogenesis of AS.

P 71

USE OF MRI FOR EARLY DIAGNOSIS OF AXIAL SPONDYLOARTHROPATHY: COMPARISON TO "THE BERLIN ALGORITHM"

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Background: MRI of sacroiliac joints is increasingly used for the early diagnosis of axial spondyloarthropathy, but is expensive and may place a burden on radiology services. An algorithm for the early diagnosis of spondyloarthropathy, including the use of MRI, was published in 2004[1].
Aim: To compare our department's requesting of sacroiliac joint MRI for early diagnosis of axial spondyloarthropathy to the Berlin algorithm.
Methods: We conducted a retrospective review of MRI requests over 5 months, including all patients who had MRI sacroiliac joints for suspected new diagnosis of axial spondyloarthropathy. Data were collected regarding whether the patients had: pain for ≥3 months, inflammatory back pain (IBP), normal radiographs, other features of SpA, HLA-B27 requested, MRI findings.
Results: 43 MRIs were requested. 38 patients (88%) had back pain for ≥3 months. 20 (47%) had IBP. 38 (88%) had normal radiographs. HLA-B27 was requested on 9/17 (53%) of the recommended occasions.
15 patients (35%) had sacroiliitis on MRI. Nature of pain was not documented in 11 patients (25%).
Only 1 patient met the criteria for MRI according to the Berlin algorithm (positive MRI).
21 MRI requests were inappropriate according to the algorithm. 3 patients, who would have had SpA excluded without MRI, had sacroiliitis on MRI. 4 patients with negative MRIs would have been diagnosed with SpA without MRI. One of these was discharged after normal MRI. One was followed up with ongoing suspicion of SpA.
Conclusions: If the pathway for MRI had been followed, 18 normal MRIs would have been avoided and 3 patients would have had MRI sacroiliitis missed. However, normal MRI may facilitate early discharge.
We note that MRI whole spine may be more sensitive at detecting early inflammatory lesions[2]. Before re-audit, we propose a checklist for MRI requests, to improve documentation of IBP and radiographic findings.

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P 72

HIGH RESOLUTION MAGNETIC RESONANCE IMAGING TO EXPLORE NAIL CHANGES AND ENTHESITIS IN PATIENTS WITH PSORIASIS

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Introduction: The pathogenesis of nail disease in psoriasis and psoriatic arthritis (PsA) is poorly understood. We have previously used high resolution MRI and micro-anatomical studies to show that the distal interphalangeal joint (DIP) in PsA is intimately associated with enthesitis, or inflammation at tendon and ligament attachment sites in the small joints. The purpose of the present work is to report on the first use of high resolution MRI for the assessment of nail disease in cases of psoriasis without PsA.
Methods: Patients with active, moderate to severe psoriasis (PASI >10) are being recruited from the dermatology clinic. Patients receiving biologic therapies are excluded. High resolution MRI is performed using a 3T magnet, with contrast. Two adjacent fingers are scanned, using a dedicated finger coil to image the nail, nailbed structures and DIP joint, with Vaseline applied to the nail to delineate the outer surface contours. Patients also undergo a clinical examination, an assessment of nail pain and tenderness and an ultrasound of asymptomatic entheses and the nails. A group of controls and a group of patients with psoriatic arthritis are also being recruited for comparison.
Results: Thus far, nine normal joints and nine patients with psoriatic arthritis have been scanned. The high resolution MRI is able to give good resolution for study of the nail, the nailbed, entheses and the DIP joint. Vaseline allows measurement of the thickness and any irregularities of the nail. We will present a series of MRI and ultrasound images of normal controls, patients with psoriasis with nail disease but no arthritis, and patients with psoriatic arthritis for comparison.

Conclusion: High resolution MRI is able to delineate the nail and associated structures well, and further imaging will expand our understanding of this disease, as well as helping us understand the differential response to different treatments.

P 73

ACTIVE INFLAMMATORY LESIONS IN THE HIP DETECTED BY MAGNETIC RESONANCE IMAGING IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Hip involvement (HI) in patients with ankylosing spondylitis (AS) is a common and disabling problem. But some pts have HI in the early stage and sometimes in debut of AS. The early HI is an unfavorable prognostic factor in AS.
Objective: This cross-sectional study was undertaken to evaluate MRI possibilities to detect hip arthritis in pts with AS before X-ray changes.
Methods: MRI (1,5 Tesla, T1, T2-FS, 4mm) of the hip was conducted in 37 pts with HI involvement (32 pts were fulfilled the modified NY criteria AS, 5 pts - criteria ASAS for axial SpA), 12 AS pts without HI on the record and 10 healthy persons. All pts had clinical evaluation, pelvis X-ray and ultrasonography (US) of hips simultaneously. X-ray stage hip arthritis was defined by BASRI (hip). Only effusion in hip > 7mm was defined by US. Active HI by MRI was accepted as bone marrow edema (BME) of the head or the acetabulum, effusion in the hip's cavity, cysts of the head or the acetabulum and capsulitis. The examination was performed by a rheumatologist and a radiologist independently with following mutual consent.
Results: Age median (Me) of the AS pts with HI was 25 [20-30], AS pts without HI - 27 [19-29], healthy control - 23 [21-25]. Duration AS with HI (Me) – 6 [3-9] years, without HI – 6 [4-9] years. Duration of the HI (Me) – 12 [6-36] months. HLA B27 (+) AS pts – 87%. The characteristics of the rate and the type of MRI's in AS pts with HI subject to BASRI are showed in the table.

	Hip involvement BASRI (hip) - 0 (n=20)	Hip involvement BASRI (hip) – 1-3 (n=54)	AS without hip involvement (n=24)	Healthy group (n=20)
BME in head of hip, n (%)	1 (5)	6 (11)	0	0
BME in acetabulum, n (%)	3 (15)	24 (44)	0	0
Cysts in head, n (%)	4 (20)	4 (7.4)	0	0
Cysts in acetabulum, n (%)	0	17 (31.4)	0	0
Effusion in cavity of hip, n	11 (55)	32 (59.2)	4 (16.6)	5 (25)
Thickening of capsule, n, (%)	1 (5)	16 (29.6)	0	0
Total number of hips with MRI's changes n (%)	11 (55)	32 (59.2)	4 (16.6)	5 (25)
Effusion by ultrasonography ≥ 7mm n, (%)	11 (55)	10 (18.5)	7 (29.1)	1 (5)

n – number of hips

Conclusion: Active inflammatory lesions by MRI were detected in 55% pts without X-ray changes in the hip. The more reliable inflammatory changes in the hip were bone marrow edema of the head or acetabulum, cysts of the head or acetabulum, thickening of the capsule. Effusion into the hip also was observed in 25% healthy persons and 17% AS pts without hip involvement so it is necessary to accurate its value.

P 74

ULTRASOUND EXAMINATION OF KNEE JOINT: A COMPARISON BETWEEN PSORIATIC ARTHRITIS AND RHEUMATOID ARTHRITIS

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Introduction: The knee joint is frequently involved in psoriatic arthritis (PsA) and in rheumatoid arthritis (RA). Very little is known about the possible differences of such involvement in these arthritides.
Aim of the Study: To investigate the features of knee involvement in PsA and RA by ultrasound examination (US).
Methods: Bilateral US examination of the knee was performed by the same rheumatologist, experienced in US, in 30 PsA patients (F:M=15:15; disease duration: 78.41±79.45 months) and in 30 RA patients (F:M=23:7; disease duration: 123.12±79.56 months) using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with a linear probe operating at 10MHz for the evaluation of joints and 14MHz for the assessment of tendons.
Results: Joint effusion with synovial proliferation was observed in 31 out of 60 (51%) knees of PsA patients and in 41 out of 60 (68%) knees of RA patients. In 7 PsA and in 4 RA patients also a positive PD signal was visualized. Baker's cyst was detected in 24 knees in the RA group and in 11 knees in the PsA.
No bone erosions were imaged in any of the PsA patients while 2 out of the 30 (6.7%) RA subjects showed erosions. Quadricipital tendon enthesopathy was present in 20 PsA (66%) and 5 RA (16%), while patellar tendon enthesopathy was visualized in 3 RA (10%) and 11 PsA patients (36%).
Conclusion: We observed a more frequent prevalence of enthesopathy in the PsA than in the RA group.
No significant difference in the occurrence of joint effusion and synovitis was detected. Further investigations on knee involvement, by US technique, in a larger number of PsA and RA patients would be useful to establish the prevalence and the features of articular and periarticular involvement.

P 75

ULTRASOUND (US) AND X RAYS (XR) ENTHESEAL, SYNOVIAL AND SACROILIAC MODIFICATIONS IN EARLY PSORIATIC ARTHRITIS (EPSA)

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Objective: To identify in ePsA the ultrasound (US) and traditional X rays (XR) entheseal/synovial and sacroiliac respectively and to investigate correlation with PsA characteristics (familiarity, psoriasis, inflammatory markers, HLA) useful for diagnosis.
Methods: 92 ePsA patients (51±15 years old, 51 female and 41 male,), with duration of symptoms <1 year, diagnosed according to CASPAR criteria (1) were consecutively studied with US (My Lab 70 XVG US Esaote 7-18 MHz linear array transducer) of entheses (Achilles, quadriceps, patellar and plantar fascia) and joints (radiocarpal, intercarpal, hands MCP, IFP and IFD, tibio-tarsal, feet MTP and IP) joints and with radiography (XR) of sacroiliac joints. Patients were scored respectively for entheses with Glasgow Ultrasound Enthesitis Scoring System (GUESS) (2) and Power Doppler signal (PD) (semiquantitative system, score 0-3), for peripheral joints with presence/absence of PD active synovitis, for sacroiliac joints with New York score (NYS) (3). We studied the correlation between GUESS and PD of entheses, active synovitis, NYS of sacroiliac joints with familiarity (for psoriasis and spondiloarthropathies), psoriasis area and severity Index (PASI), distribution -hand, feet, lower limbs- and characteristics -vulgaris, eritrodermic, pustulosus, guttata-, nail involvement, ESR, CRP, HLA aplotypes (B27, B35, B38, B39, CW6, CW7, DR4) were investigated.
Results: Abnormalities are present in high percentage: in entheses (GUESS 100%, PD 40,2%), in peripheral joints (40,2%), in sacroiliac joints (25%). GUESS and PD of entheses correlated with the presence of lower limb psoriasis (respectively p<0,02, p<0,05, Mann Whitney test) but not with PASI and entheses PD with ESR (p<0,005) (linear correlation Pearson). GUESS was higher (p<0,05 Mann Whitney test) in CW6 positive patients (29,6%) but not other significant difference were found in other aplotypes.
Synovitis and sacroileitis did not correlate with familiarity, psoriasis, ESR/CRP, HLA.
Conclusions: In ePsA patients, entheseal and synovial US and sacroiliac XR modifications are present in high percentage. Our data clearly indicate that a thorough US and XR investigations must be always perform in early phase.

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P 76

ENTHESIS ULTRASOUND VALIDITY IN EARLY SPONDYLOARTHRITIS CLASSIFICATION DIAGNOSIS

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Background: The established classification criteria for spondylarthritis (SpA) rely on the combination of clinical symptoms plus unequivocal sacroiliitis image. But, entheses affectation, a characteristic feature of SpA, is undervalued in these classification criteria. In this sense, ultrasound has a high sensitivity in the examination of enthesis and offer a challenge in this field.
Objective: The aim of this study is to explore the validity of enthesis ultrasound in the early SpA patients.
Material and Methods: Blind and standardized ultrasound was performed, in 113 early SpA patients and 57 controls, using a General Electric ultrasound Logiq 9, with a 9-14 MHz linear probe. The MASEI ultrasound score evaluates the enthesis thickness, structure, calcifications, erosions, bursae and power-Doppler signal of 6 bilateral enthesis. The validity was analyzed by ROC curves, accepted diagnostic classification criteria were used as the gold standard. Values of $p<0.05$ were considered to be significant.
Results: The evolution time of SpA symptoms was 10.9±7.1 months. In the table on can appreciate the different sensitivity, specificity and likelihood ratio of the different cut-off point of the MASEI ultrasound score in early SpA. The ROC area under the curve was 0.82 (95%; CI 0.75 to 0.89).

Cut-off point	Sensitivity	Specificity	Correctly classified	LR+	LR-
≥ 16	76.99%	68.42%	74.12%	2.44	0.34
≥ 18	67.26%	84.21%	72.94%	4.26	0.39
≥ 20	55.75%	89.47%	67.06%	5.30	0.49
≥ 22	49.56%	92.98%	64.12%	7.06	0.54
≥ 24	41.59%	94.74%	59.41%	7.90	0.62
≥ 26	33.63%	94.74%	54.12%	6.39	0.70
≥ 28	28.32%	98.25%	51.76%	16.14	0.73

LR= likelihood ratio.

Conclusion: Entheses are affected early in SpA. The entheses ultrasound score seems to have diagnostic accuracy and could be useful to improve the diagnosis of early SpA.
Acknowledgement:
This study was supported by an unrestricted grant from the ESPERANZA program of the Spanish Rheumatology Foundation and Pfizer.

P 77

RADIOGRAPHIC FINDINGS AFTER 5 YEARS OF INFLIXIMAB TREATMENT IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: Anti-TNF therapy with infliximab significantly reduces inflammatory activity (clinical assessments, MRI) in patients with active ankylosing spondylitis (AS) but does not seem to have a major impact on radiographic progression over 2 years. The European Infliximab AS cohort (EASIC) was started after ASSERT and patients were treated with infliximab in a real-life setting for 5 years.
Objectives: To study the long-term effect of anti-TNF treatment with infliximab on the chronic AS related radiographic changes over 5 years.
Methods: Complete sets of radiographs of the cervical (CS) and the lumbar (LS) spine at baseline (BL) and after 2 (FU1) and 5 years (FU2) were available from 53 patients from EASIC. Images were scored blinded for time order and treatment by an experienced reader using the mSASSS.
Results: At baseline, the mean age was 42.4±7.9, 85% patients were HLA-B27 positive and 86.8% were male. The mean BASDAI was 6.3±1.3, the mean BASFI 4.0±1.7 and the mean BASMI 5.9±1.6. The mean mSASSS at BL was 20.5±19.9 units and the number of patients with syndesmophytes was 31/53 (59%). Radiographic progression was observed in almost all patients, with a mean mSASSS change of 1.0±2.0 and 2.1±2.7 at FU1 and FU2, respectively (both $p<0.05$ as compared to BL). There were no differences between the CS and the LS. Overall, there was a trend for higher radiographic progression for the group with syndesmophytes at BL, as compared to the group without. New syndesmophytes were found in 45.2% patients when BL syndesmophytes were present vs. 9/22 40.1% patients without. Similarly, the overall mSASSS progression at FU2 differed between patients with (2.4±2.7) and without (1.6±2.8) syndesmophytes at BL.
Conclusion: In contrast to RA, patients with AS show ongoing radiographic progression under anti-TNF treatment. Future studies with comparisons to historical cohorts may indicate whether the velocity of new bone formation is changed by this medication.

P 78

NO PROGRESSION OF CHRONIC SACROILIAC CHANGES IN PATIENTS WITH ACTIVE, NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS TREATED WITH ADALIMUMAB OVER 52 WEEKS

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Purpose: To evaluate the progression of chronic changes, as observed in T1 sequences on MRI, over 52 weeks in a 12-week, placebo-controlled study of adalimumab with a 40-week, open-label extension in the treatment of patients with active axial spondyloarthritis (SpA) not yet fulfilling the modified New York Criteria who had previously demonstrated good clinical response.[1]
Methods: T1 sequences of MRIs of the sacroiliac joints (SIJ) were obtained at baseline, at Week 12 (placebo phase), and at Week 52 (40 weeks of open-label extension) in patients treated with adalimumab. MRIs were read in 1 batch blinded for both sequence and therapy regimen by 2 assessors employing a recently developed score for chronic changes. Fatty lesions were scored (0–8), sclerosis was read for each joint (0–2), and erosions were counted for each joint (0–24).
Results: Nine pairs each of MRIs for both the placebo and adalimumab groups were available at baseline and Week 12. In addition, 12 pairs of MRIs for the former placebo group and 14 pairs for the adalimumab group were available at baseline and Week 52. No changes were observed after 40 weeks (former placebo group) or 52 weeks of adalimumab treatment regarding fatty lesions, sclerosis, or erosions in the SI joints. Through analysis of the 12-week placebo-controlled data, significant reductions of fatty lesions were found in the adalimumab-treated patients vs. the placebo-treated patients ($p=0.042$).
No significant changes and no differences between the two groups were found for erosions and sclerosis.
Conclusions: This was the first study analysing chronic SI-joint changes by MRI in patients treated with a TNF antagonist. These data indicate that fatty degeneration and erosions might be stopped. These findings need to be confirmed by longer observation periods. Furthermore, it has yet to be determined how and whether this affects also new bone formation.

Mean Scores for Chronic Changes in T1 sequences by MRIs of Sacroiliac Joints.

	Baseline to Week 12 Placebo Group N=9		Baseline to Week 12 Adalimumab Group n=9		Baseline to Week 52 All Patients n=26	
	BL	Wk 12	BL	Wk 12	BL	Wk 52
Fatty Lesions	5.9	6.0	3.9	1.9[a]	4.9	4.8
Sclerosis	1.9	1.8	1.4	1.6	1.5	1.5
Erosions	2.9	2.2	1.0	0.6	1.6	1.7

[a]$p<0.05$.

Reference:
1. HAIBEL H et al.: *Arthritis Rheum*. 2008; 58: 1981-91.

P 79

RADIOGRAPHIC PROGRESSION OF SPINAL DAMAGE OVER TWO YEARS IN EARLY ANKYLOSING SPONDYLITIS

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Background: Data on radiographic progression in the spine have been reported from patients with longstanding ankylosing spondylitis (AS), but not yet from a cohort of patients with early AS.
Objective: To assess radiographic progression in the spine in a cohort of patients with early AS over a period of two years.
Methods: Patients with definite AS (N=122) according to the modified New York criteria (60% male, mean age 36.2±10.7 years, 80% HLA-B27 positive) with a symptom duration of less than 10 years (< 5 years: n=65; 5-10 years: n=57) who participate in the German Spondyloarthritis Inception Cohort (GESPIC) have been selected for this analysis based on availability of radiographs at baseline (BL) and after 2 years of follow-up. Radiographs of the cervical and lumbar spine at baseline and after 2 years were centrally digitized and images scored independently by 2 trained readers according to the mSASSS. The readers scored both timepoints simultaneously but were blinded for the timepoint and for all clinical data.
Results: The mSASSS at baseline was 5.8±9.8 (<5 y: 5.6; 5-10y: 6.1) and after 2 years 6.8±11.3 (<5y: 6.3, 5-10y:7.4). Thus, there was a progression of 1.03 points for the whole group (<5y: 0.75; 5-10y: 1.35; difference non-significant p=0.7). There was a good intra-classcorrelation with 0.952 [95%CI: 0.92-0.97] between the readers. Subsequently, we analysed those patients in whom both readers agreed that patients either had syndesmophytes or did not have syndesmophytes. From 59 patients without syndesmophytes at baseline only 3% [1% - 11%] had new syndesmophytes after 2 years, while out of 37 patients with baseline syndesmophytes new syndesmophytes were found after 2 years in 49% [32% - 66%] (p<0.0001 for the difference between the 2 groups).
Conclusion: In this cohort of patients with early AS we could confirm previous data from longstanding AS that an mSASSS progression of about 1 point can be expected over 2 years and that patients with baseline syndesmophytes have a greater risk for the development of new syndesmophytes, which was very high in our study. These data indicate, that there seems to be a constant radiographic progression over time and that it might be relevant and possible to identify rapid progressors already early in the course of the disease.

P 80

A POSITIVE BASELINE MRI OF THE SACROILIAC JOINTS IN PATIENTS WITH EARLY INFLAMMATORY BACK PAIN PREDICTS PERSISTENCE OF MRI ACTIVITY IN HLA-B27 POSITIVE INDIVIDUALS

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Background: A diagnosis of axial spondyloarthritis (SpA) currently relies to a great extent on a positive MRI of the SI-joints. Objective of this study was to investigate how active MRI lesions in the SI joints of patients with recent onset inflammatory back pain (IBP) evolve over time, and to study determinants of SI-joint MRI activity.
Methods: A 2 year follow-up study was conducted in patients (38% male) with IBP of less than 2 years duration (Early Spondyloarthritis Cohort (ESpAC)). MRI of the SI joints was obtained at baseline, 1 and 2 years follow-up. The images were scored for bone marrow edema and Gd-enhancement. A MRI was considered positive when at least one lesion was present on 2 successive slices or in case of > 1 lesion in 1 slice (ASAS/OMERACT consensus). The likelihood of finding a positive MRI was modelled with generalized estimating equation analysis.
Results: Of the 68 patients enrolled at baseline, 6 patients did not have a follow-up MRI, 18 had one and 44 patients had 2 follow-up MRIs with one-year intervals. Twenty-four patients (35%) had a positive MRI at baseline (66% HLA-B27 positive). Forty-four patients (65%) had a negative MRI at baseline (34% HLA-B27 positive). Both HLA-B27 status (OR (95%CI): 8.1 (2.3 – 28.3); p<0.001) and MRI status at baseline (22.0 (6.1 – 79.6); p<0.001) were strong and independent factors in determining the likelihood of finding a positive MRI (Figure 1). The likelihood of a positive MRI during follow-up is 88% in case of a HLA-B27 positive patient with a positive MRI at baseline and <5% in case of a HLA-B27 negative patient with a negative baseline MRI.
Conclusion: In patients with early IBP, one negative MRI suffices to exclude SpA if HLA-B27 is absent. One positive MRI suffices to make a diagnosis of SpA if HLA-B27 is present.

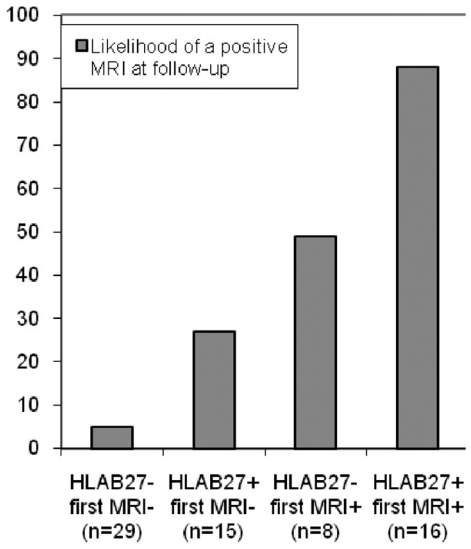

Figure 1: Likelihood of a positive MRI at follow-up in all 68 patients included in ESpAC, in function of the result of the baseline MRI (negative or positive) and HLA-B27 status.

P 81

DEFINING THE SMALLEST DETECTABLE CHANGE FOR THE SPARCC SPINE AND SACROILIAC JOINT MRI INDEX FOR ANKYLOSING SPONDYLITIS

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Background: The Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) index is a scoring method for spinal and sacroiliac joint (SIJ) inflammation in ankylosing spondylitis (AS).
Objectives: To define the cut-off for the smallest detectable change (SDC) on the SIJ and spine SPARCC MRI index.
Methods: Spine and SIJ MRIs were performed at baseline (BL), Week 12, and Week 52 in AS patients randomized to adalimumab 40 mg every other week (eow) or placebo for a 24-week double-blind period, followed by an 80-week open-label period (adalimumab 40 mg eow). Two independent, blinded readers, scored the MRIs using the SPARCC index and a global evaluation of change (much worse, worse, no change, better, or much better) for visit comparisons. Change categories were pooled. Mean change in absolute SPARCC scores and 95% confidence intervals (95%CIs) were determined. Receiver operating characteristic (ROC) curves and Youden indices were generated, and sensitivity and specificity of the category change reported as functions of absolute change in SPARCC score.
Results: A total of 82 patients were enrolled. Reader agreement on the evaluation of change was 77%-83% for the SIJ and 66%-74% for the spine. For the global evaluation category of change and no change, the 95%CIs of absolute change in SPARCC scores showed comparability between treatments and visit comparisons. Therefore, all cases were combined across treatment groups and visit comparisons. The ROC curves demonstrate that absolute change in SPARCC score is significantly associated with global evaluation of change (area under the curves: 0.960, SI joints; 0.839, spine). The Youden index reached maximum, separating change from no change at 2.0 for SI joints and 4.0 for the spine.
Conclusion: We propose that changes of 2.0 and 4.0 for the SIJ and spine, respectively, define the numerical cut-off for SDC on the SPARCC MRI index for AS.

P 82

THE GLASGOW MRI SACROILIITIS SCORE (GMSS) – PART I: THE ASSESSMENT OF A NEW MRI SCORING SYSTEM AS APPLIED TO A COHORT OF ANKYLOSING SPONDYLITIS PATIENTS – A COMPARISON OF A NEW COMPUTED ANALYTICAL APPROACH WITH CONVENTIONAL GRADING SYSTEM

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Background: Magnetic Resonance Imaging (MRI) has been used in several studies to detect sacroiliitis and inflammatory spinal lesions in Ankylosing Spondylitis (AS) before Xray abnormalities are evident.
Several MRI scoring systems have been developed in order to quantify the degree of inflammation in patients with AS. These have been shown to be limited by including only one feature or by an unwieldy and time consuming assessment of structural damage and inflammation in more than one plane.
Method: We have developed the Glasgow MRI Sacroiliitis Score (GMSS) using both a conventional grading assessment of hard copy MRI examinations (Method 1) and also by a computerised semi automated objective analytical approach (Method 2). These two methods will be compared and inter- and intra-observer variability will be assessed using weighted kappa statistics. Oedema was graded as were features reflecting chronicity (erosions, sclerosis, joint width).
Results: The features that were extracted that were likely to represent active inflammatory disease were derived. High grade oedema was documented in 32% joints. Features likely to represent chronicity were graded (erosions present in 63%, sclerosis in 59%, partial fusion in 45% and complete fusion in 17%).
Intraobserver and interobserver variation were calculated for both methods. This demonstrated that the computed analytical method (method 2) had significantly better agreement and reliability than the conventional approach (method I).
Conclusion: The new computed analytical MRI scoring system (GMSS) is simple, robust and reliable.
The next paper in this series will assess its correlation with clinical parameters of AS clinical disease activity.
Disclosure:
Part of this research was funded by Abbott Laboratories Ltd.

P 83

THE GLASGOW MRI SACROILIITIS SCORE (GMSS) – PART II: THE APPLICATION OF A NEW COMPUTED ANALYTICAL APPROACH MRI SCORING SYSTEM TO A COHORT OF ANKYLOSING SPONDYLITIS PATIENTS

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Method: The Glasgow MRI Sacroiliitis Score (GMSS) was developed using both a conventional grading assessment of hard copy MRI images of the sacroiliac joints and also by a computerised semi automated objective analytical approach. These two methods will be compared using features that reflect acuteness (oedema) and those features that reflect chronicity and applied to a total of 146 joints in 73 unselected AS patients attending an AS clinic. The MRI images were anonymised and read in a random order without the knowledge of the clinical details of the patients. The clinical features extracted by examination at the time of the MRI scan by Rheumatology clinical staff and physiotherapist were correlated with the MRI image features.
Results: Initial univariate analysis shows no association between the combined measure of erosion and sclerosis and any rheumatology feature. The acute measure demonstrated some evidence of an association with CRP and BASFAI total score.
Conclusion: The new MRI scoring system has been correlated with clinical data from the cohort of AS patients and found to be simple, robust and reliable. The study sought to compare clinical assessment and patient self assessment with MRI of the sacroiliac joints in a large cohort of patients. The data assesses the validity of the ASAS guidelines and clarifies the complementary roles of clinical assessment, BASDAI and MRI scanning in the diagnosis and monitoring of spondylitis and sacroiliitis in AS. The study determined the frequency and severity of inflammation of the sacroiliac joints as measured in a group of patients with AS and hence it is expected that this would inform the logistical and financial planning for the provision of anti-TNF therapy in AS in the UK.
Disclosure:
Part of this research was funded by Abbott Laboratories Ltd.

P 84

THE PREVALENCE OF ENTHESOPATHY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AND ANKYLOSING SPONDYLITIS BY ULTRASONOGRAPHY

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Background and Objective: Musculoskeletal symptoms are commonly accompanied as extraintestinal manifestations of inflammatory bowel disease (IBD). Enthesopathy is recognized as a pathognomic finding of spondyloarthritides including ankylosing spondylitis (AS). This study aims to compare the prevalence and characteristics of enthesopathy between IBD and AS using musculoskeletal ultrasound.
Methods: 47 patients with IBD (Crohn's disease or ulcerative colitis) and 50 AS patients were examined by bilateral ultrasonography at 5 enthesial sites (patella at insertions of the rectus femoris and patellar tendons, tibial tuberosity at insertions of patellar tendon, calcaneus at insertion of Achilles tendon and plantar aponeurosis). Each tendon thickness, bursitis, bony erosions, enthesophytes, and the increase of vascularization were observed. The patient was diagnosed as having enthesopathy when at least one or more abnormal findings were seen.
Results: 670 enthesial sites in 67 patients were examined. 43 among 47 patients in IBD group and 48 among 50 AS group showed the findings of enthesopathy. There was no significant difference in prevalence between the two groups (IBD 93.6% vs. AS 96%, p=0.627). The mean tendon thickness of the Achilles tendon and plantar aponeurosis was significantly thicker in AS than IBD group (for Achilles tendon: 4.85±1.28 mm vs. 4.47±0.94 mm, p=0.048; for plantar aponeurosis: 3.47±0.63 mm vs. 3.06±0.59 mm, p=0.000). AS group tended to have a thicker rectus tendon than IBD group, but the result was not statistically significant. Other findings did not show any significant difference between the two groups. The most common ultrasonographic finding of enthesopathy was the increased thickness of rectus and patellar tendons at the knee (90.3% in IBD and 84.1% in AS). Enthesophyte was the most common abnormal finding at the foot (47.2% in IBD and 32.8% in AS).
Conclusion: Our study suggests that the prevalence of subclinical enthesopathy in IBD is much higher than expected.

P 85

PREVALENCE OF VERTEBRAL FRACTURES IN ANKYLOSING SPONDYLITIS PATIENTS WITH ACTIVE DISEASE

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Introduction: Early vertebral bone loss in Ankylosing Spondylitis (AS) can be accompanied by severe complications. Previous studies have shown that, in contrast to non-vertebral fractures, the risk of clinical vertebral fractures is increased in AS patients. Our aim was to study the prevalence of vertebral fractures in AS patients with active disease.
Methods: One-hundred and six patients with AS based on the modified New York criteria and active disease defined by Bath AS Disease Activity Index (BASDAI) ≥ 4 (range 0-10) or based on expert opinion were included. Anterior, middle, and posterior heights of vertebrae T4 to L4 were measured on lateral radiographs by two independent observers using a ruler. According to the Genant classification[1], a vertebral fracture was defined based on reduction in anterior, middle, and/or posterior height: grade 1–20-25% reduction, grade 2–25-40% reduction, and grade 3–>40% reduction. In case of discrepancy between the two observers, a third independent observer measured vertebral height in order to confirm the presence or absence of a vertebral fracture.
Results: Mean age of the 106 AS patients was 41.1 years (SD ±11.1), median disease duration was 14 years (range 1-53), and 75% were male. Forty-one patients (39%) had at least 20% reduction in anterior, middle, and/or posterior vertebral height, indicating vertebral fracture. Twenty-seven of these patients had maximal a grade 1 fracture and 14 patients had maximal a grade 2 fracture. No grade 3 fractures were detected. In total, 74 vertebral fractures were detected; 59 wedge fractures, 14 biconcave fractures, and 1 crush fracture.
Conclusion: The high prevalence of vertebral fractures in AS patients with active disease underlines the importance of timely investigation of bone loss in AS.

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P 86

COMPARISON OF ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING FOR THE ASSESSMENT OF CLINICALLY DEFINED KNEE ENTHESITIS IN SPONDYLOARTHRITIS

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Background: Both ultrasonography (US) and magnetic resonance imaging (MRI) are considered to be good imaging methods to visualize enthesis. The aim of this study was to compare the ability of US and MRI to detect subclinical enthesitis in patients with spondyloarthritis (SpA) presenting with knee swelling and making a lesion by lesion comparison.
Methods: Twenty-one SpA patients presenting with knee synovitis were recruited and had clinical assessment for enthesitis at 8 sites in the involved knee joints. The knees were scanned both by US and MRI. The structural changes at the insertions of tendons and ligaments around the knee were scored and a lesion by lesion comparison of two imaging methods with clinical assessment was made.
Results: Clinically, enthesitis was evident in 18 of 21 patients in 61 of 168 evaluated sites. Clinically defined enthesitis was associated with more hypoechogenicity (16 vs 4 %, p=0.007) and thickening (16 vs 6 %, p=0.03) by US compared to non-tender sites. Within the MRI findings only increased signal in the surrounding tissues was higher at tender sites (41 % vs 20 %, p=0.01) and MRI findings inside the insertion points were not related to physical examination. The positive agreements between individual lesions by both methods was very low (10-26%) with low kappa values (0.06-0.18) and no correlations between the MRI and US scores (r^2= 0.059).
Conclusion: Although both MRI and US correlate with clinical findings there is a considerable discrepancy of individual lesions and a lack of correlation by both imaging modalities. This may be explained by the fact that both modalities measure different changes, with US showing changes within enthesis but MRI showing changes in soft tissues adjacent to insertions.

P 87

FAT INFILTRATION IN SPONDYLOARTHRITIS: AN IMAGING BIOMARKER REFLECTING RESOLUTION OF INFLAMMATION

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Background: MRI of the spine in SpA frequently shows focal fat infiltration in the spine on T1W scans, especially at vertebral corners (VC). It is assumed that this fat reflects post-inflammatory change but there have been no prospective studies.
Objective: To test the hypothesis that an active vertebral corner inflammatory lesion (CIL) visible on the MR STIR sequence is more likely to evolve into a *de novo* VC fat lesion on TIW scans than a VC which demonstrates no CIL on baseline MRI.
Method: MRI scans were performed at baseline and 2 years in 61 AS patients of whom 28 received TNF blocking agents in open label follow up of clinical trials while 33 received either TNF blocking agents (n=16) or standard therapy (n=17) in an observational cohort. We recorded VC fat infiltration and CIL at anterior and posterior VC on any central sagittal slice. Fat lesions and CIL on anonymized MRI scans were independently recorded dichotomously (present/absent) from lower C2 to the upper sacrum of the spine by 2 readers who were blinded to treatment and time point. The primary analysis was based on concordant data (fat, CIL).
Results: New VC Fat lesions developed significantly more frequently in those VC with as compared to those without inflammation on MRI at baseline in the anti-TNF (32/83 (38.6%) vs 69/2647 (2.6%), p<0.0001) but not the standard therapy group (1/14 (7.1%) vs 8/1161 (0.7%), p=NS). VC Fat developed significantly more frequently from CIL that resolved (16/77 (20.8%)) compared to VC with persistent (1/20 (5%)) or no CIL (34/2612) (1.3%)) in the anti-TNF therapy group (p<0.0001) but differences were non-significant in the standard therapy group.
Conclusion: VC Fat occurs more frequently at sites of prior inflammation and especially after inflammation has resolved following institution of anti-TNF.

P 88

TNF BLOCKING AGENTS PROMOTE RESOLUTION OF EROSIONS IN PATIENTS WITH SPONDYLOARTHRITIS

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Background: TNF blocking agents ameliorate inflammation in spondyloarthritis (SpA) and while their impact on new bone formation remains unclear their impact on other structural lesions such as erosion has not yet been studied in SpA because this lesion is not commonly observed on radiography. Bone erosion is more easily discerned on T1-weighted (T1W) MRI at vertebral corners (VC) and affecting the vertebral endplate (non-corner bone erosion).
Objective: To assess the impact of TNF blocking agents on the evolution of bone erosions.
Method: MRI scans were performed at baseline and 2 years in 61 AS patients of whom 28 received TNF blocking agents in open label follow up of clinical trials while 33 received either TNF blocking agents (n=16) or standard therapy (n=17) in an observational cohort. A bone erosion on MRI was defined as full-thickness loss of the dark appearance of cortical bone at its anticipated location and loss of the normal bright appearance of adjacent bone marrow on T1W scans. Lesions were independently recorded on anonymized MRI scans dichotomously (present/absent) from lower C2 to the upper sacrum of the spine by 2 readers blinded to treatment and time point. The primary analysis was based on concordant data and compared the resolution of lesions according to treatment.
Results: Complete resolution of corner erosions was recorded significantly more frequently in the TNF blocker treatment group (11 of 13 erosions (84.6%)) whereas this was not observed in a single erosion in patients on standard therapy (0/8) (p=0.0002). Non-corner erosions were more frequent than corner erosions but showed minimal resolution after 2 years regardless of treatment (2/42 anti-TNF vs 0/17 standard).
Conclusion: Our data supports a beneficial effect of TNF blocker treatment on the resolution of VC erosions. The lack of impact on non-corner erosions may reflect greater time dependency or pathophysiological differences.

P 89

THE DIAGNOSTIC UTILITY OF MRI IN EARLY SPONDYLOARTHRITIS: VALIDATION OF THE ASAS DEFINITION OF A POSITIVE MRI BY THE MORPHO STUDY GROUP

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Background: The Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial SpA include a positive MRI demonstrating sacroiliitis defined according to consensus opinion as the presence of two bone marrow edema (BME) lesions on the same coronal slice or a single BME lesion on two consecutive slices. Structural lesions are not included in this definition.
Objective: To assess the diagnostic utility of MRI in early SpA according to the ASAS definition and to determine the value of including structural lesions.
Method: Five readers blinded to patient and diagnosis independently assessed MRI scans from the following subjects <45 years of age: 75 with AS, duration <10 years; 26 with mechanical low back pain, duration <10 years; 27 with pre-radiographic inflammatory back pain (IBP), mean duration 29 months); and 59 healthy controls. MRI scans were read systematically according to an online training module and data entry system. Sensitivity, specificity, and likelihood ratios for concordant data were calculated.
Results: We recorded a high frequency (48%) and specificity (95%) of erosion in IBP and formulated a proposal for a modification to the ASAS definition of a positive MRI that incorporates the presence of erosion (MORPHO proposal). For IBP, sensitivity of the ASAS definition was greater while specificity was less than that determined by overall assessment of the MR scan. The addition of erosion (MORPHO proposal) improved the sensitivity of each reader even further with minimal change in specificity so that overall diagnostic utility was better.

	Global			ASAS			MORPHO		
	Sen/Spec	LR+	LR-	Sen/Spec	LR+	LR-	Sen/Spec	LR+	LR-
AS	99/95	18.6	0.01	85/88	7.1	0.2	96/88	8.0	0.05
IBP	52/95	9.8	0.5	67/88	5.7	0.4	81/88	6.9	0.2

Conclusion: The ASAS definition has comparable diagnostic utility to overall assessment of MR scans by expert readers. It is possible that diagnostic utility may be further enhanced by including assessment of erosions.

P 90

RADIOGRAPHIC PROGRESSION IN PATIENTS WITH ACTIVE NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS TREATED WITH ADALIMUMAB OVER 2 YEARS IN COMPARISON TO A HISTORICAL CONTROL GROUP

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Purpose: To evaluate the baseline radiographic changes and long-term effects of adalimumab on radiographic progression in patients with active axial spondyloarthritis (SpA) not yet fulfilling the modified New York Criteria who showed a good clinical response (1).
Methods: Radiographs of the SI-joints (SIJ), lateral cervical and lateral lumbar spine were obtained at baseline and at year 2 in patients treated with adalimumab. Results were compared with baseline and 2-year follow up radiographs from a historical cohort (GESPIC) of axial SpA patients naïve to TNF-antagonist therapy and matched for disease activity and gender. Radiographs from the GESPIC cohort and the adalimumab study were combined and read in 1 batch by 3 independent assessors (all blinded to origin of cohort and sequence) using the modified New York criteria for the SIJ and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).
Results: For the GESPIC cohort 13 radiographs of the SIJ, the cervical and lumbar spine were scored. Twelve pairs of radiographs of SIJ, 12 of cervical and 14 of lumbar spine were available from the adalimumab group. Patients in this analysis were 53 % male for the GESPIC cohort and 52% males for the adalimumab study with a mean age of approximately 43 years for the GESPIC group and 32 years for the adalimumab study. Baseline disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 5.5 (± 1.3) for the GESPIC patients and 4.8 (± 1,68) for the adalimumab group. The baseline mSASSS score for the cervical spine (SD)/ lumbar spine (SD) was 1.22 (1.94) and 0.80 (1.21) for the GESPIC cohort and 0.85 (0.79) and 0.76 (0.88) in the adalimumab patients. After two years follow up there was no clear change in the scores for both groups. The mean changes are listed in table I.
Conclusions: Both in the intervention and in the non intervention group no significant radiographic changes in SI joints and spine could be observed for both groups after two years in patients with early non-radiographic axial SpA, which is different from patients with established AS (2-4). Longer follow ups are necessary to answer the question whether TNF-blockers can inhibit radiographic progression if axial SpA patients are treated early.

Table I: Mean Changes in the mSASSS and the sacroiliitis score* in patients with active axial Spondyloarthritis treated with adalimumab over two years in comparison to a historical cohort (GESPIC)

	Cervical Spine	Lumbar spine	SI-Joints
GESPIC	0.04	0.00	0.04
Adalimumab	0.01	0.25	0.03

(*according to the modified New York criteria)

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P 91

EFFECTS OF ETANERCEPT VS. SULFASALAZINE ON ACUTE INFLAMMATORY LESIONS AS DETECTED BY WHOLE BODY MRI IN EARLY AXIAL SPONDYLOARTHRITIS - A 48 WEEK RANDOMIZED CONTROLLED TRIAL

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Purpose: To evaluate the potential of etanercept (ETA) versus sulfasalazine (SSZ) to reduce active inflammatory lesions on whole-body magnetic resonance imaging (wb-MRI) in active axial spondyloarthritis (SpA) of symptom duration of less than 5 years.
Methods: Patients were randomized to ETA (n=40) or SSZ (n=36) treatment over 48 weeks. All patients showed active inflammatory lesions (bone marrow edema) on wb-MRI in either the sacroiliac joints (SIJ) or the spine. Wb-MRIs were performed at weeks 0, 24 and 48 and were scored for active inflammatory lesions in SIJ, spine including posterior segments, peripheral enthesitis and synovitis by two radiologists, blinded for treatment arm and MRI time point. The primary endpoint was the reduction of active inflammatory lesions on wb-MRI.
Results: Patients' baseline characteristics were similar between both groups. At baseline, 95% of the patients showed active inflammatory lesions in the SIJ, 47% in the spine, but only 5% in the spine but not in the SIJ. In the ETA group, the reduction of the SIJ score (from 7.7 at baseline to 2.0 at week 48) was significantly (p=0.003) larger compared to the SSZ group (from 5.4 at baseline to 3.5 at week 48), similar to the reduction in the spine: 2.2 to 1.0 in the ETA group vs. 1.4 to 1.3 in the SSZ group between baseline and week 48, respectively (p=0.0024). Enthesitis improved also significantly (p=0.027) better in the ETA (26 sites at baseline to 11 sites at week 48) compared to the SSZ group (24 sites at baseline to 26 sites at week 48). Peripheral synovitis and inflammation on the posterior segments showed no significant difference between the two treatment groups. 50% of the patients reached ASAS clinical remission and 70% ASAS 40 response in the ETA group vs 19% and 31% in the SSZ group at week 48.
Conclusion: In patients with early axial SpA active inflammatory lesions detected by wb-MRI improved significantly better in ETA- versus SSZ-treated patients. This effect correlated with a good clinical response in the ETA group.

P 92

MEASUREMENT OF HLA-B27 (B27) TURNOVER IN PRIMARY ANTIGEN-PRESENTING CELLS FROM PATIENTS WITH ANKYLOSING SPONDYLITIS (AS)

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Compared with other class I alleles, AS-associated subtypes of B27exhibit misfolding in the ER, delayed maturation of folded molecules, and aberrant formation of heavy chain (HC) dimers. The relative contributions of these abnormalities to AS pathogenesis remain unknown. We hypothesise that each proposed mechanism alters the synthesis and turnover of distinct B27 conformations, in proportion to their relative contributions to AS. To test this, methods were sought for comparing turnover of B27 and other alleles in HLA heterozygotes. We have developed techniques for measuring protein biosynthesis and turnover by heavy water (^2H_2O) labelling and peptide mass spectrometry. This approach was applied here to B27. B-LCL or monocyte-derived dendritic cells (MoDC) were labelled with ^2H_2O. Folded HLA-ABC molecules were immunoprecipitated and class I HC excised from SDS gels. Tryptic digests were analysed by LC/MS/MS. Identified peptides were assigned to specific MHC alleles or isotypes based on HLA genotype. The relative abundances of mass variants of allele-specific peptides were quantified, reporting on ^2H incorporation, and protein synthesis and turnover rates were calculated. Measured abundances of peptide mass variants were accurate, as shown by their close match to model calculations. HLA-B turnover was slow in LCL ($t_{1/2}$ > 48 h) but readily detectable in healthy donor MoDCs ($t_{1/2} \approx$ 15-20 h). LPS stimulation of MoDCs 24 hours before ^2H_2O labelling shut down HLA-DR turnover but had little effect on class I dynamics. Turnover of folded B27 and control alleles in MoDC from AS patients and healthy donors exhibited inter-individual variation. This work demonstrates that allele-specific quantification of HLA-ABC turnover, including B27, is feasible in primary cells from AS patients and controls. This will be invaluable for dissecting the dynamics of distinct B27 conformations and for exploring genetic, cellular, and clinical variables that influence MHC class I turnover.

P 93

IN VITRO STUDIES DEMONSTRATE THAT ERAP1 IS NOT A CYTOKINE RECEPTOR CLEAVASE

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Ankylosing spondylitis (AS) is a highly heritable inflammatory arthritis characterized by progressive fusion of the spine and sacroiliac joints of the pelvis. The aetiopathogenesis of AS is poorly understood but recent advances in our lab have identified a number of genes associated with AS. AS is strongly associated with the MHC I molecule HLA-B27, but the mechanism by which it causes the disease is unknown. Several genes contribute to the disease, and to identify these we undertook a genomewide-association study, which identified *ERAP1 (endoplasmic reticulum aminopeptidase 1)* to be involved in AS pathogenesis. We and others have confirmed this in several studies and in different ethnic groups since.
ERAP1 has been speculated to be involved in either processing peptides for presentation on MHC I molecules such as HLA-B27, or in shedding of cytokine receptors (IL-1R2, IL6R, TNF-R) from cell surfaces. Here we investigated the role of ERAP1 in cytokine receptor shedding. Spleen cells from ERAP-/- or wild type control mice were activated in vitro and levels of soluble IL-6R and TNF-R in the supernatant were determined by ELISA after 24 hours. No differences were seen in IL-6R or TNF-R levels in culture supernatants from ERAP1-/- or wild type controls. This demonstrates that ERAP1 does not play a role in cytokine receptor shedding and suggests that ERAP1 operates in AS pathogenesis by a mechanism involving antigen 'trimming' for presentation on MHC I molecules such as HLA-B27, providing a major clue as to how HLA-B27 itself causes AS.

P 94

TARGETING MONOCYTE-EXPRESSED HLA-B27 HOMODIMERS IN ANKYLOSING SPONDYLITIS

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Background: Possession of HLA-B27 is strongly associated with development of Spondyloarthropathies including Ankylosing Spondylitis (AS). The mechanism by which HLA-B27 confers this susceptibility is unclear. HLA-B27 forms both heterotrimers (B27) associated with peptide and beta-2-microglobulin, and also heavy chain homodimers ($B27_2$). A pathogenic role for these homodimers has been proposed. However lack of a specific detection reagent has hampered elucidation of $B27_2$ expression. We generated an antibody to $B27_2$ using phage display technology, to investigate the role of homodimers in AS.
Methods: Phage display technology was used to generate monoclonal antibodies specific for $B27_2$. Biotinylated recombinant $B27_2$ complexes were used for positive selection and heterotrimeric B27 for negative selection of a phage fAb library. One clone selected for further characterisation, HD6, was then sub-cloned to generate a chimeric antibody comprising human fAb_2 and murine IgG1 Fc. ELISA was used to confirm its specificity for $B27_2$ complexes. For recognition of cell-expressed $B27_2$, the human B cell lines LBL721.220 (.220), C1R stably transfected with HLA-B27 or control HLAs, and AS patient and control peripheral blood mononuclear cells were used and results analysed by FACS. Inhibition of the interaction of $B27_2$ with the immunoreceptors KIR3DL1, KIR3DL2 and LILRB2 was determined using transfected and FACS-sorted cell lines.
Results: 1) HD6 specifically recognised recombinant $B27_2$ in ELISA, but not HLA-A2, B7 or B27 heterodimers. 2) HD6 bound in FACS to LBL721.220 cells transfected with HLA-B27, which express $B27_2$ cell surface homodimers, but not to LBL721.220 B7 or to B27 with Cys 67 mutated to serine (which do not express $B27_2$). 3) HD6 bound in FACS to peripheral blood monocytes from AS patients but not controls. 4) HD6 inhibited the interaction of $B27_2$ with the immunoreceptors KIR3DL1, KIR3DL2 and LILRB2.
Conclusions: A novel phage display-derived monoclonal antibody has been generated that recognises both recombinant and cell-expressed $B27_2$ by ELISA and FACS. HD6 stains monocytes of AS patients. HD6 will be a powerful tool to understand the role of $B27_2$ in the pathogenesis of SpA and may additionally have therapeutic potential.

Author Index