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Abstracts

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Opening Talks

INV 1

INTERPLAY BETWEEN PATHOGENIC EFFECTOR TH17 AND REGULATORY T CELLS IN AUTOIMMUNITY AND TISSUE INFLAMMATION

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Upon activation, T cells undergo distinct developmental pathways, attaining specialized properties and effector functions. T-helper (TH) cells are traditionally thought to differentiate into TH1 and TH2 cell subsets. TH1 cells are necessary to clear intracellular pathogens and TH2 cells are important for clearing extracellular organisms. Recently, a subset of interleukin (IL)-17-producing T cells (TH17) distinct from TH1 or TH2 cells has been described and shown to have a crucial role in the induction of autoimmune tissue injury including Rheumatoid Arthritis (RA). In contrast, CD4+CD25+, Fox-P3+ regulatory T cells (T-regs) inhibit autoimmunity and protect against tissue injury. TGF-b1 is a critical differentiation factor for the generation of T-regs and using Foxp3-GFP "knock-in" mice we show that IL-6, an acute phase protein induced during inflammation, completely inhibits the generation of Foxp3+ T-reg cells induced by TGF-b1. On the other hand, we demonstrate that IL-23 is not the differentiation factor for the generation Th-IL-17 cells, instead IL-6 and TGF-b1 induces differentiation of pathogenic Th-IL-17 T cells from naïve T cells. Th17 cells produce maximal amounts of IL-21 that further amplifies the Th17 differentiation by acting together with TGF-b1. Consistent with these observations, immunization of inducible TGF-b1 transgenic mice with myelin antigens in complete Freund's adjuvant induces a severe and lethal experimental autoimmune encephalomyelitis (EAE) with massive production of IL-17.
Our data suggests a reciprocal relationship in the generation of pathogenic (Th-IL-17) T cells that induce autoimmunity and regulatory (Foxp3+) T cells that inhibit autoimmune tissue injury.

INV 2

THE APPLIED ANATOMY OF ENTHESES IN RELATION TO THE PATHOGENESIS OF SPONDYLOARTHRITIS

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Entheses are inherently regions at risk of mechanical damage and evidence of degeneration is characteristic of numerous attachment sites studied by the author in dissecting room cadavers. The anatomy of entheses reflects the need to dissipate stress concentration near the anchor site. Thus, many insertions that are known targets in spondyloarthritis (SpA) are characterized by fibrocartilage at the bony interface. Uncalcified fibrocartilage creates a gradual change in mechanical properties between soft tendon/ligament and hard bone, and the calcified fibrocartilage/bone interface contributes to anchorage and provides resistance against shear.
Insertional angle changes that accompany joint movement are minimized by pulleys and retinacula, and stress is dissipated onto the area adjacent to the enthesis by the formation of 'enthesis organs' and the fact that many tendons/ligaments have fascial expansions. Enthesis organs typically occur at sites where the immediately-adjacent tendon/ligament presses on the bone and their existence emphasizes the importance of viewing enthesopathies as potentially multifocal pathologies. A key component of a classic enthesis organ such as that of the Achilles tendon is a bursa. Its presence means that a highly vascular and pro-inflammatory, synovium (that may be independent of that of any synovial joint) is juxtaposed to what in a healthy enthesis, is a poorly vascularised and essentially anti-inflammatory dense connective tissue. The term 'synovio-entheseal complex' has been coined to emphasise the importance of recognizing local joint-specific factors in relation to SpA. It is possible that mechanical damage at entheses in genetically-susceptible individuals (and in the presence of appropriate microbes) could trigger the inflammatory changes characteristic of SpA. On the bone side of entheses, stress is dissipated via a network of trabeculae that characterize spongy bone. The mechanical integration of these spicules as part of the enthesis itself, provides a basis for understanding why osteitis and enthesitis are frequently linked.

INV 3

POPULATION GENETICS AND SPONDYLOARTHRITIS

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Most current archaeological data suggest that *homo sapiens* originated in Eastern Africa about 200,000 years ago. After local expansion, small migratory waves left Africa between 50,000 and 80,000 years ago via the Sinai peninsula and across the lower Red Sea, populating the rest of the planet, most recently in the Americas between 15,000 and 30,000 year ago. Initial population expansion was slow, due the hostile environmental challenges but the development of agriculture (first in the Middle East, where both grains and animals were uniquely available that allowed planting and domestication, which spread over time elsewhere) saw rapid population expansion, settlement and the appearance of city states and eventually complex societies and empires. The domestication of the horse in Central Asia allowed pastoral nomad societies to invade these agricultural societies and influence their genetic structure. Generally these influences on the local gene pools were greatest earlier when the populations were small or where the local population were extinguished by the invaders (Mongols) or by diseases brought by the invaders (colonization of the Americas-smallpox and measles). However, in the Americas, a complex gene pool has developed by recent migrations of disparate populations from Europe, Africa and Asia.
The processes of autoimmunity and autoinflammation are greatly influenced by genetic polymorphisms whose initial role was to protect against hostile environmental influences. In the case of HLA-B27, natural immunity is conferred to certain classic (influenza and possibly malaria) and novel (hepatitis C and HIV) infectious influences. Population demographics suggest that HLA-B27 originated in antiquity in Africa in its parent subtype *B*2705*, and the 37 protein subtypes currently recognized developed along three distinct geographic pathways, with varying disease association. Other genes that have been validated in AS (such as HLA-B60, ARTS1) as well as other spondyloarthritis (inflammatory bowel disease, psoriasis and uveitis) susceptibility (i.e. IL23R) are now seen to cross ethnic boundaries in their influences and likewise reflected response to infectious triggers. Nevertheless, their discovery can be confounded by stratification errors in large "mixed" populations such as those seen in the Americas, which can be prevented by the careful selection of patients and controls and using Ancestry Informative Markers (AIMs).
Recent refinements in genetic technology (such as the use of automated gene chips for genomewide association studies and rapid throughput resequencing) and analysis (i.e. correction for population stratification and novel network theories) as well as the realization the complex genetic diseases ensue from the interaction of a number of genes whose individual contributions are small, requiring extremely large discovery and replication cohorts of patients (>1,000 in each) are rapidly unraveling the genetic puzzle that only recently seemed so daunting. The future will focus on the individual contributions of those genes and how they can be altered for disease prevention and outcome modification.

Invited Lectures

INV 4

SpA DIAGNOSTIC/CLASSIFICATION CRITERIA

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Introduction: The diagnosis and classification of axial SpA in patients without definite radiographic sacroiliitis has been a challenge in the past. Moreover, none of the available criteria contain magnetic resonance imaging (MRI) which proved to be highly important in early sacroiliitis.
Materials and Methods: Within the Assessments in Spondyloarthritis (ASAS) International Society candidate criteria for axial SpA were developed by means of paper patients who were assessed by 20 ASAS experts. In a second step, an international validation study was conducted: consecutive patients were included if they suffered from chronic back pain of unknown origin and had an age at onset <45 years. Using a standardized case report form, the clinical, laboratory, and imaging information was documented. The final clinical diagnosis by the local rheumatologist served as gold standard.
Results: A total of 650 patients fulfilling the entry criteria was included in the study. The ASAS candidate criteria for axial SpA performed well in terms of sensitivity and specificity. The specificity could be improved even further upon minor changes. The resulting ASAS classification criteria for axial SpA are fulfilled if either definite sacroiliiitis on radiographs or MRI is present together with one clinical SpA feature (imaging part, specificity 97%) or if HLA-B27 plus two further clinical SpA features are present (clinical part, specificity 84%).
Conclusion: In a joint effort, the ASAS group has generated new classification criteria for axial SpA which for the first time have incorporated MRI of the sacroiliac joints. Depending on the purpose the new ASAS classification criteria can be used in a flexible way with either a rather balanced sensitivity and specificity for the whole set of criteria or with a very high specificity of 97% for the imaging part of the criteria which requires definite sacroilitiis.

INV 5

DISEASE ACTIVITY IN SpA

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ASAS has defined various domains to cover the entire spectrum of disease impact including specific assessments for each domain. These include measure for disease activity, but also function, spinal mobility and structural damage on radiographs. Assessment of disease activity in Spondyloarthritis (SpA) can be done by using single disease activity measures such as pain or morning stiffness, or by combined indices such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). All these are patient reported outcomes. However, it is known that also acute phase reactants are valuable in the assessment of disease activity.
ASAS has undertaken a project to define a disease activity score as a continuous measure based on a statistical approach to best discriminate between patients with high and low disease activity taking all the possible disease activity assessments into account (including patient reported outcomes, acute phase reactants, tender and swollen joint counts). This resulted in 4 possible ASDAS (ankylosing spondylitis disease activity score) scores.
Remarkably, one or both of the acute phase reactants are included in each of the ASDAS scores. These are subsequently validated in large groups of patients. All scores proved to be valid with respect to discrimination between high and low disease activity, sensitivity to change and discrimination between groups based on change over time. The performance of the 4 ASDAS scores are similar and in most instances better as compared to the BASDAI and always better as compared to the single variables. The final selection of the preferred ASDAS was made by the ASAS members. The development and validation process of the ASDAS will be detailed in the presentation.

INV 6

STRUCTURAL DAMAGE IN ANKYLOSING SPONDYLITIS

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The cornerstones of treatment are physical therapy and drug therapy with non-steroidal anti-inflammatory agents (NSAIDs). The pros and cons of these agents in the therapy of AS have recently been discussed. Patients in whom the disease activity cannot be adequately controlled by conventional means require and may be treated with biologic agents targeting TNF-α. As many as 40% of the ASAS patients in Belgian rheumatological offices were reported to be in need for anti-TNF therapy if recent international recommendations were followed. Anti-TNF therapy with currently 3 approved agents, infliximab, etanercept and adalimumab, has clearly been shown to improve signs and symptoms, function and spinal mobility on both a short-term and a long-term basis of until now up to 5 years, as recently reported. In general, about half of the patients gain about 50% improvement of disease activity as assessed by the Bath Ankylosing Spondylitis Activity Index (BASDAI), about 30-40% show an increase in function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI). Applying the Assessment in Spondyloarthritis International Society (ASAS) outcome criteria usually more than 60% reach ASAS 20 and more than 40% the ASAS40 criteria, while 20-30% even achieve ASAS partial remission. Furthermore, AS patients treated with TNF blockers report an improved quality of life and reach higher productivity scores.
In contrast to the rather dramatic improvement of clinical and imaging parameters reflecting inflammation, structural damage, which manifests in AS mostly as growing syndesmophytes and ankylosis seems not to be inhibited by anti-TNF therapy. However, regarding these studies there are some unresolved methodological issues such as the inability to assess the thoracic spine by standard radiography, the study design (comparison only with historical cohorts) and the low sensitivity of the currently used mSASSS scoring method, the best currently available tool to quantify radiographic changes in AS. Furthermore, the degree of damage that has been reported to occur in AS is not impressive over 2 years with less than 1 (mean) new syndesmophytes developing in the whole spine.
Reasons for the possible lack of an influence of anti-TNF therapy on syndesmophyte formation are that (i) inflammation and new bone formation are, at least in part, uncoupled in AS, and/or (ii) that anti-TNF therapy by inhibiting osteoclast and promoting osteoblast activity even triggers ankylosing processes by interfering with the wnt and/or the RANKL pathway. This may be different for NSAIDs which, by inhibition of COX-2, may affect bone healing, prevent heterotopic ossification and even decelerate pathologic bone growth in AS.
Clearly, this situation is different in rheumatoid arthritis (RA) and psoriatic arthritis where structural damage has been regarded as the most important outcome parameter and where all anti-TNF agents were shown to inhibit radiographic progression characterized by erosions. The situation in AS is likely to be different since new bone formation (in contrast to bone destruction) is the main factor to influence the structure of affected patients. New bone formation might be prevented in AS when inflammation is suppressed before erosive structural damage has occurred. However, any ongoing new bone formation as part of partly possibly physiological repair mechanism may just not be stopped by blocking TNF.

INV 7

FUTURE OF HUMAN GENETIC STUDIES

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Following the advent of genome-wide association analysis during the last year, there has been unprecedented success in the identification of common genetic variants underlying many complex diseases. In this session I will discuss some of the challenges that lie ahead for human genetics research both from the perspective of gene identification and also in terms of translating this basic research into clinical interventions. Topics discussed will include genome-wide sequencing and prospects for identifying rare variants contributing to complex disease risk; epistasis and the identification of gene-gene interactions using genome-wide association; Mendelian Randomization and its use to inform the relationship between modifiable environmental risk factors and disease etiology; and Genomic profiling, utilizing individuals' genotypes to assist diagnosis and predict risk of future illness.

INV 8

ANKYLOSING SPONDYLITIS GENETICS IN 2008

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The history of studies of the genetics of common diseases has until recently been one of much toil and little reward. All that changed in 2007, with the advent of the genomewide association study approach, pioneered by the Wellcome Trust Case Control Consortium (WTCCC). In AS, this study in collaboration with the Australo-Anglo-American Spondyloarthritis Consortium (TASC), identified two new genes involved in AS, *IL23R* and *ARTS1*. This study scanned probably only 10-15% of human genetic variation, and thus more comprehensive genomewide association studies are likely to be even more productive. The mechanisms by which the genetic variation at *IL23R* and *ARTS1* cause AS are unclear, and must now be the focus of hypothesis-driven research by the AS research community. Further research aimed at identifying the key associated variant(s) is ongoing and will be presented.
The experience of the WTCCC and other gene-mapping groups is that sample sizes for gene-mapping studies need to be much larger than previously considered 2-4 years ago, and that the best approach is for groups to collaborate internationally, as few individual groups have sufficient cohort sizes to be able to perform adequately powered studies. The AS genetics community need to be encouraged to operate similarly.
Most disease-associated polymorphisms identified in common human diseases have been associated with odds ratios of 1.1-1.3. This should not be surprising, as we knew from previous linkage studies that the genes involved in common diseases were likely to be common variants with small effect. A common misconception is that these genes are unimportant to find. The effect size of the genetic association in a population does not however directly correlate with the importance of the gene to a disease, as the genetic association depends on the extent and functional significance of the genetic polymorphisms present. The small effect sizes do impact on the utility of the genetic studies as diagnostic or prognostic tests. However even in these early days of such research, examples do exist where genetic findings are clearly of value in diagnosis, particularly in AS.
The era of the genomewide association study may not crack all genes or all diseases, but its impact will affect us all.

INV 9

GWAS IN INFLAMMATORY BOWEL DISEASE: MULTIPLE HITS, OVERLAPPING PATHWAYS

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The last 2 years has seen an explosion in interest in complex disease genetics. The new technology of genome-wide association scanning (GWAS) is being applied across a range of diseases and traits, and nowhere more successfully than in Crohn's disease (CD). Individual scans have identified a total of 10 validated CD-associated genes and loci, and a recent meta-analysis by our international consortium has identified and replicated 20 more. In particular the interleukin 23 pathway has been highlighted by multiple hits, as has the process of autophagy. GWAS has also identified a number of loci common to more than one disease. It is thus beginning to shed light on the aetiological relationships between Crohn's disease and ulcerative colitis as well as ankylosing spondylitis. Details of these overlaps and the lessons learned will be discussed.

INV 10

GENETICS OF PSORIATIC ARTHRITIS

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Introduction: The genetic contribution to psoriatic arthritis (PsA) is estimated to be much larger than to the overlapping diseases of psoriasis and inflammatory arthritis that contribute to it. Whilst enormous progress has been made in recent months in the identification of susceptibility genes for both psoriasis and inflammatory arthritis, identification of unique PsA susceptibility factors has been slower.
Methods: Several approaches have been undertaken in order to identify PsA susceptibility factors: firstly, confirmed rheumatoid arthritis (RA) susceptibility genes have been tested for association with PsA; secondly, confirmed psoriasis susceptibility loci have been studies and, finally, putative PsA susceptibility loci have been investigated directly based on candidate gene approaches.
Results: Neither of the two major RA susceptibility loci, the shared epitope or the *PTPN22* gene, have been associated with PsA susceptibility or severity. Single nucleotide polymorphism (SNP) markers mapping to the confirmed psoriasis susceptibility genes, *IL23R* and *IL12B* have also been found to be associated with PsA but the primary association appears with psoriasis. These findings confirm that the psoriasis observed in patients with PsA appears genetically and clinically identical to the uncomplicated psoriasis treated by dermatologists. Candidate gene studies of PsA have highlighted the TNF-α gene as a putative susceptibility gene, but results of other reported associations have not yet been validated in independent data sets.
Conclusions: Hypothesis-free genome wide association studies have either been completed or are underway for both RA and psoriasis. A similar approach in PsA would have a high likelihood of success in identifying disease genes, given the larger genetic contribution to PsA, and would provide an exciting opportunity to dissect out both unique and shared susceptibility factors between PsA, psoriasis and RA.

INV 11

FUNCTION IN ANKYLOSING SPONDYLITIS

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Ankylosing spondylitis (AS) is a frequent chronic rheumatic disease that affects the axial skeleton by inflammation and new bone formation, it starts most often in the 3rd decade of life. The health problems most frequently reported by AS patients are: interrupted sleeping, turning head when driving, carrying groceries, and having energy for social activities. Although it is more likely for male patients to develop syndesmophytes and ankylosis, female patients usually report more physical limitations than men, and their reduced mobility results in more restrictions of activity and participation. However, many social, structural, and attitudinal barriers influencing activity and participation in patients with AS have not yet been identified.
The International Classification of Functioning, Disability and Health (ICF) provides an excellent common framework for the comparison of disease specific instruments for AS. One hundred twenty-seven ICF categories represent the comprehensive classification of functioning in AS from the patients' perspective. Within each of the four components of the ICF, at least one-third of the categories are impaired or restricted for more than 50% of the patients. The instruments most frequently used to assess function and mobility in AS are the Bath AS functional (BASFI) and the metrology index (BASMI).
The natural course of AS as studied in cohorts shows that disease activity remains relatively constant over time but function declines over time. High initial BASFI values were shown to predict a more severe disease course. Patients with peripheral arthritis are more functionally impaired, but deteriorate less than those with spinal disease alone.
Radiological damage of the cervical and lumbar spine, thoracic wedging, and disease activity are determinants of hyperkyphosis in patients with AS. There is an association between spinal mobility measures and radiographic damage for the individual AS patient. Lateral spinal flexion and BASMI can discriminate between patients with and without structural damage.
Lateral spinal flexion predicts the absence, and a modified Schober test the presence of radiographic damage. However, spinal mobility cannot be used as a proxy for radiographic evaluation in an individual patient. In addition, the function of AS patients can be much impaired due to increased disease activity. This can be substantially improved by potent anti-inflammatory agents such as those targeting TNF-α.
To treat AS patients physically, individual home-based or supervised exercise programs are better than no intervention, supervised group physiotherapy is better than home exercises; and combined inpatient spa-exercise therapy followed by group physiotherapy is better than group physiotherapy alone (Cochrane review). AS patients who underwent a 3-week intensive rehabilitation programme and subsequent home exercises achieved an ASAS 20 response in 89% at the end of the rehabilitation, and in 60% and 33% patients at 6 and 12 weeks follow-up, respectively. Importantly, a combination treatment with anti-TNF agents and occupational therapy was very beneficial for patients with AS, with synergistic effects on pain, function and disability.

INV 12

ASSESSMENT OF FUNCTION AND SPINAL MOBILITY IN SpA

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Several instruments for assessment of function in SpA have been developed but increasingly consensus favours the use of the BASFI based on feasibility and responsiveness to change. The approach to the assessment of function in SpA is undergoing re-appraisal to conform to the framework of the World Health Organization International Classification of Functioning and Disability. A brief ICF Core Set has now been proposed that includes a total of 19 second-level categories: 6 on body functions; 4 on body structures; 7 on activities and participation; 2 on environmental factors. Domains not previously addressed in function instruments include sleep, emotional functions, family relations, and driving. Advances in spinal mobility evaluation have addressed the importance of standardization of assessment and have shown which measures are reliable. Data from phase III clinical trials indicates that lateral lumbar flexion and cervical rotation are most responsive and discriminate best between treatment groups. Cervical rotation using a goniometer has now been added to the core set of mobility measures recommended by ASAS. The responsiveness of the BASMI composite is limited when scored nominally (0, 1, 2) but improves significantly with a 0-10 scoring method or when based on continuous data, with a linear assessment-to-score conversion in the range 0-10, as in the linear BASMI. The responsiveness of the EDASMI is improved when cervical rotation is measured using the goniometer rather than a tape-based approach. Recent adaptations to the assessment of spinal mobility show that this domain is highly responsive to anti-TNF therapy.

INV 13

THE SIGNIFICANCE OF THE ICF FOR RHEUMATIC DISEASES

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A patient's diagnosis alone provides limited information. It tells little about what patients can do, what their prognosis is, what they need, etc. Because functioning is a central dimension in working with patients with rheumatic diseases, concepts, classifications, and measurements of functioning and health are important to clinical practice, research, and teaching in this field (1). The approval of the International Classification of Functioning, Disability and Health (ICF) by the World Health Assembly in May 2001 can be considered a landmark event in establishing a new era of patient-oriented clinical practice, research, and teaching (2,3).
The ICF offers information about how people live with their health conditions. It is based on an integrative bio-psychosocial model of functioning, disability, and health developed by the World Health Organization (WHO) (2). Rehabilitative medicine also places an emphasis on functioning and disability. It targets functioning, the environment, and modifiable personal factors because functioning is seen as being in close interaction with the environment and the person's characteristics (4). Moreover, functioning represents not only an outcome, but also the starting point of the clinical assessment, development of a treatment plan, and evaluation and quality assessment of the plan.
The ICF has the potential to enhance the care of patients by providing a universal language of functioning and disability. It provides a framework to guide treatment and coordinate care among the health care team. The ICF can be applied regardless of the culture or health condition, and is applicable to all health professionals. Use of the ICF in clinical settings has the potential to significantly increase the quality of care by providing a common language and understanding of functioning and disability.

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INV 14

DEVELOPMENT OF THE ICF CORE SET FOR AS

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To assess health outcome in ankylosing spondylitis (AS), experts selected the ASAS/OMERACT core set of domains and instruments to measure them. These domains represent the *minimum* to be assessed in clinical trials or for record keeping. The ICF Core Set, on the other hand, aims represent the *comprehensive* view on the impact of the disease on functioning and health. Moreover, it includes not only the perspective of experts, but also the perspective of patients.
Recently, the ICF Core Set for AS has been defined, following a standard approach that also enables to compare impact of functioning. Altogether 79 categories were included in the Large ICF Core Set with 23 categories representing *body functions*, 19 *body structures*, 24 *activities and participation*, and 13 *environmental factors*. In addition, 'posture' was identified as an impairment but could not be linked to the ICF.
Comparison of the ICF Core Set of domains with the ASAS/OMERACT outcome domains makes clear which aspects of functioning and health will be missed when restricting outcome assessment to the minimal approach. Also when including other disease specific instruments in the comparison, several aspects of the impact of health are not represented by any disease specific instrument.
The ICF Core Set for AS broadens our view on functioning and health and poses challenges to improve existing instruments or develop new instruments to more comprehensively describe and measure the impact of AS.

INV 15

INTRODUCTION: INFLAMMATION AND NEW BONE FORMATION IN ANKYLOSING SPONDYLITIS

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Based on histological, immunohistological and MRI studies it is evident that ankylosing spondylitis starts with inflammation in the sacroiliac joints and spine at the cartilage/bone interface. Symptoms such as pain, morning stiffness and fatigue are caused by inflammation.
However, long-term outcome and disability is predominantly determined by new bone formation and ankylosis of the spine. Function is determined by both inflammation and ankylosis. Inflammation is the major determinant for function early in the disease while ankylosis is the more relevant component later on. The question of how inflammation and new bone formation are linked is of major importance for understanding part of the pathogenesis and for the development of optimal treatment strategies in AS. We have recently proposed that inflammation causes erosive structural damage first (1). Fibrous repair tissue will then subsequently be ossified, a process which is even stimulated when inflammation is suppressed, either spontaneously or by treatment, because inflammatory cytokines such as TNF-alpha inhibit the wnt- pathway of new bone formation. Once structural damage has occurred further ossification of the fibrous repair tissue cannot be inhibited by TNF-blockade.
On this background it is not surprising that growth of syndesmophytes have been observed in AS patients treated successfully, as judged by improvement of signs and symptoms, with TNF-blockers. Thus, it is the crucial question for the near future whether new bone formation can be prevented when inflammation is suppressed early enough before structural damage has occurred or whether new bone formation can occur completely independent from inflammation. In the first case early diagnosis and early therapy of inflammation would be the optimal treatment strategy while therapeutic intervention would have to target both inflammation and new bone formation in the latter case.

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INV 16

WHAT DRIVES THE INFLAMMATION IN SpA?

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Over the past years, it has become clear that TNF is a key player in the pathogenesis of spondyloarthritis but the mechanisms by which this occurs are only partially known.
Particularly, the cellular targets sufficient to mediate the articular and extra-articular manifestations of spondyloarthritis remained to be defined, as well as the cellular constituents capable of modulating this TNF driven inflammation. Recently, we reported a peculiar role for mesenchymal cells in a mouse model of spondyloarthritis, characterized by enhanced TNF mRNA stability, resulting in Crohn's like ileitis as well as peripheral arthritis. Hence, TNF-R1 expression on mesenchymal cells was sufficient to mediate combined gut and joint pathologies in this model of murine spondyloarthritis. However, it remained unclear whether regulatory T cell subsets could modulate this inflammation. More recently, we uncovered that a particular regulatory T cell lineage, invariant NKT (iNKT) cells, are natural regulators of TNF driven inflammation by modulating maturation and differentiation of antigen presenting cells in a pathway that is strictly dependent upon TNF. Altogether, these observations provide new insights in the regulatory as well as the effector mechanisms of spondyloarthritis.

INV 17

ANIMAL MODELS OF ENTHESITIS AND ANKYLOSIS

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Ankylosing enthesitis is a hallmark feature of the human spondyloarthritides (SpA). The enthesis defines an anatomical zone in which tendons, ligaments and capsules insert into the bone. Entheses can be part of the joint organ but are also recognized as extra-articular disease locations. New cartilage and bone formation originating from the entheseal sites are typical for SpA both in the axial and the peripheral skeleton. Ankylosis causes loss of function leading to disability.
Spontaneous arthritis in aging male DBA/1 mice is triggered by grouping male mice from different litters. This model is characterized by entheseal cartilage and bone formation in the proximal and distal interphalangeal joint of the toes in the hind paws and more rarely the ankles. Other features of this model similar to SpA are periosteal new bone formation, dactylitis and destructive onychoperiostitis (Lories *et al*., Ann Rheum Dis 2004). Other models of entheseal ankylosis are ANK-ENT mice and late stages of proteoglycan induced arthritis.
We have characterized the DBA/1 model extensively and demonstrated that ankylosis in this model is dependent on bone morphogenetic protein signaling (Lories *et al*., J Clin Invest 2005). Further studies have also demonstrated that new tissue formation and inflammation are probably largely independent processes as ankylosis is not inhibited by anti-TNF therapy (Lories *et al*., Art Rheum 2007). Recent data further suggest that bone erosion is not necessary to trigger new tissue formation (Lories *et al*., Rheumatol 2008; McGonagle *et al*., Art Rheum 2008). New data also support a role for Wnt signaling in ankylosing enthesitis.
As clinical cohort data seem to confirm the hypothesis that inflammation and joint or spine ankylosis are at least partially independent processes, further animal model studies, in particular using complex or targeted genetic approaches, are important to understand the molecular mechanisms underlying this important feature of SpA and to develop targeted therapeutics.

INV 18

LINKS BETWEEN INFLAMMATION AND NEW BONE FORMATION

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Structural damage in ankylosing spondylitis is essentially different from rheumatoid arthritis. Whereas both diseases share trabecular bone loss leading to major osteoporosis, the local changes along joints and intervertebral spaces (in case of AS) are contrary. In RA, progressive destruction of bone is observed leading to local bone erosion, which is thought to be a direct consequence from inflammation mediated osteoclast formation and tissue destruction. A large proportion of local bone damage starts at the outer side of the joint based on chronic synovitis and resorption of cortical bone at the periosteal sites. In contrast, AS is characterized by bone proliferation and the deposition of mineralized tissue along periosteal sites close to joints or intervertebral spaces. Thus, AS is characterized by a dissociation of trabecular and cortical bone changes- with a negative balance in the former one and a positive balance in the latter one. Understanding of periosteal bone proliferation in AS is essential to explain the clinical picture of disease. Although it is currently not entirely clear whether syndesmophyte formation has a pivotal role in patients' symptoms. In fact, the efficacy of TNF blocking agents to control signs and symptoms of AS but syndesmophyte formation suggest a different picture. Still, these lesions warrant attention because they reflect the progressive disease process in AS. Despite there is no final explanation, why AS leads to periosteal bone proliferation and RA does not, there are several hypotheses which could explain these differences. (i) Joint remodelling in RA and AS occurs at different sites, RA preferentially at at peripheral joints, AS at axial joints and intervertebral spaces. Presence of fibrocartilage could determine the sites, which are prone to enhanced bone proliferation. However, these sites are also present in peripheral joints and thus differences in the distribution of the disease may not or only partially explain the different patterns of joint remodelling among RA and AS. (ii) There is a profound difference between RA and AS with respect to the origin of inflammation. RA is synovial driven inflammation, whereas AS is predominantly an osteitis, evident by an inflammation of the bone marrow as observed in MRI scans. In fact, the link between osteitis and subsequent formation of syndesmophytes at the same sites becomes more and more evident. (iii) RA and AS have a profoundly different kinetics of disease, with RA resembling a chronic inflammatory disease process, which is characterized by a continuous synovitis, whereas AS is a more flare like disease process with phases of lower disease activity. These phases of lower activity could thus enable a regenerative response leading to osteophyte formation. (iv) Differences among structural remodelling in RA and AS could be based on entirely different molecules, which are turned on during joint inflammation.
Obviously in RA there is an active suppression of osteoblasts and skeletal repair, which is partially linked to active suppression of bone formation by induction of negative regulators of bone formation such as DKK-1 or noggin, which suppress the WNT and BMP pathway, respectively. On the other hand, formation of osteophyte is linked to genes, which drive the differentiation from mesenchymal cells into osteoblasts. This process requires activation of the bone morphogenetic protein and WNT signalling pathways. In fact, activators of these pathways lead to bony proliferations in animal models of arthritis.
Understanding of the mechanisms, which lead to syndesmophyte formation in AS are essential for a better understanding of the disease process. We are currently in a phase, where we begin to understand the molecules driving osteophyte formation and this knowledge will also give us a better insight into the disease process of AS.

INV 19

EARLY DIAGNOSIS AND THERAPY IN SpA – THE MAASTRICHT EXPERIENCE

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The concept of spondyloarthritis (SpA) has gained importance in the light of the availability of effective clinical treatments including the TNF-blocking drugs. If axial SpA is considered an early form of AS – and there is some argument to underscore that thesis - it may be possible to shorten the delay between the onset of complaints and the diagnosis of AS with 5 to 10 years on average. It is therefore mandatory that the disease is recognised before definite radiographic changes of the sacroiliac joints have occurred, and several sets of criteria and algorithms have been proposed for early diagnosis and classification.
The Maastricht Early Spondyloarthritis Cohort (ESPAC) has been established to investigate the concept of early diagnosis, and its consequences with regard to long term outcome.
Magnetic resonance imaging (MRI) of the SI joints, performed over time, has a prominent place in this cohort.
In this lecture, the cohort will be described, as well as the performance of several criteria sets with regard to early diagnosis. Additionally, the role of MRI in making a diagnosis of SpA will be highlighted.

INV 20

REFERRAL PATTERNS FOR EARLY AXIAL SPONDYLOARTHRITIS, AND SELECTION CRITERIA FOR AND RESPONSE TO ANTI-TNF THERAPY

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Introduction: Early axial SpA is the attributable cause of back pain in about 5% of chronic back pain patients. The identification and referral to rheumatologists of these patients remains a challenge in primary care. The ASAS recommendations on initiation of anti-TNF therapy in ankylosing spondylitis have proven useful in daily practice. Nonetheless, certain patient characteristics may allow to predict the response to anti-TNF agents.
Materials and Methods: A standardized local referral programme was initiated to test the feasibility of screening for axial SpA. Patients with chronic back pain and age at onset below 45 years of age could be referred to rheumatology if in addition either inflammatory back pain (IBP) was present or HLA-B27 was positive. The potential of patient characteristics to predict a good clinical response (BASDAI 50) was tested in clinical trials with anti-TNF agents.
Results: The local referral programme turned out to be highly effective. Among 350 referred chronic back pain patients 43% had axial SpA, either ankylosing spondylitis or non-radiographic axial SpA. The symptom duration of the latter group was 4 years, and about 30% had a duration of less than 1 year. Both, IBP and HLA-B27 performed well as screening instruments, however, the rate of positive diagnoses (i.e. axial SpA) was expectedly higher in HLA-B27 positive patients than in patients who were referred because of IBP. Significant predictors of a good response to anti-TNF agents in axial SpA were younger age/ short disease duration, elevated CRP, better functional status, positivity for HLA-B27 and extended inflammation on MRI.
Conclusion: Screening for axial SpA using standardized referral programmes is feasible and highly effective. Certain patient characteristics may help to estimate which patient with axial SpA is likely to achieve a great clinical benefit from anti-TNF therapy.

INV 21

EARLY STUDIES OF SpA: THE LEEDS EXPERIENCE

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Inflammatory back pain (IBP) perceived in the sacroiliac joint (SIJ) region is often the earliest harbinger for the development of axial SpA including AS. Radiographic changes of sacroiliitis are uncommon in early disease and may take several years to develop. In a clinical and imaging study, 54 patients with IBP1 of recent onset were investigated. Baseline MRI showed that 85% had bone marrow oedema (BMO) at the SIJs and lumbar spine consistent with active disease. BMO was also found in 40% of subjects in a control group with mechanical back pain and asymptomatic volunteers, however its severity differed between the groups with severe inflammation (grade 2 and 3) found solely in the inflammatory group but not in the controls and associated with HLA-B27. Follow-up MRI at one year showed that subclinical disease (persistence of BMO) was present in the majority of patients (73.5%) despite clinical improvement and was associated with HLA-B27. Radiographic follow-up of this cohort at 8 years identified predictors of poor prognosis with severity of MRI sacroiliitis (BMO grade 3) at baseline and HLA B27 showing a high specificity for the future development of AS (LR=8.0).
In a parallel study, 40 patients within 3 years of onset of symptoms and identified as having a high risk of developing AS (all HLA B27 positive, with IBP1 and SIJ BMO on MRI) were randomised to 4 infusions of infliximab or placebo with MRI at baseline and 16 weeks with the aim to assess the impact of early intervention in this poor prognosis group. Results showed that infliximab was effective in suppressing inflammatory lesions on MRI as well as on clinical, functional and quality of life outcomes in this time. Longer follow up of this cohort will look at the possible impact of this drug on altering disease progression.

Reference:

1 CALIN A, PORTA J, FRIES J, SCHURMAN J: Clinical history as a screening test for ankylosing spondylitis. *JAMA* 1977; 237(24): 2613-4.

INV 22

JUVENILE ONSET SPONDYLOARTHRITIS: WHAT IS THE PROGNOSIS AND ROLE OF ANTI-TNF THERAPY?

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Juvenile-onset spondyloarthritis (SpA) comprise a group of HLA-B27 associated disorders characterized by peripheral arthritis and enthesitis. At onset, most cases correspond to undifferentiated SpA, but within the following 10 years, ~75% of the patients may develop sacroiliac joint and spinal symptoms and the diagnosis of ankylosing spondylitis (AS) should then be considered.
The frequency of juvenile-onset SpA (including psoriatic arthritis) may surpass that of juvenile rheumatoid arthritis. On the long term, the probability of remission five years after onset is only 17%; nearly 60% – particularly those with disease activity for >5 years – had moderate to severe functional limitations by ten years despite remission in 47%. In children with enthesitis related arthritis, CHAQ scores are higher than those of children with oligo or polyarticular JIA and their physical functioning lower; their physical health is poorer and bodily pain higher. In contrast, it has been also reported low level disability, including sexual activities after a mean of 27 years disease duration. Compared with adults, juvenile-onset AS required more hip replacements and more patients were in functional classes III and IV and their mean BASFI score was higher.
The therapeutic approach of juvenile-onset SpA is only aimed to reduce disease activity. Yet, case-series of juvenile-onset SpA treated with infliximab and etanercept have reported excellent results with no significant adverse events. Our double-blind, 12-week, infliximab vs placebo trial have shown superior clinical efficacy with infliximab in controlling the signs and symptoms of active juvenile-onset SpA. The 52-week-extension phase showed infliximab sustained efficacy, safety, and tolerability.
Infliximab and perhaps other TNF-α blockers are the best alternative for treating juvenile-onset SpA. Because TNF-α blockers were indicated for arthritis and enthesitis – the earliest manifestations of juvenile-onset SpA – it is expected that this therapy would prevent late structural damage, particularly spinal.

INV 23

THE ROLE OF INFECTION IN SpA

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Infection plays a role as a triggering event in reactive arthritis (ReA) ReA is triggered by Chlamydia trachomatis, Yersinia, Salmonella, Shigella and Campylobacter in about 10-14% of the infected subjects. Ureaplasma urealyticum and Mycoplasma hominis, Clostridium difficile, Escherichia coli O157:H7, even Helicobacter pylori have also been suggested as triggering microbes.
Does persistent infection lead to chronic SPA? About 10-20% of patients with enteric triggered ReA have a prolonged course, which is more common in Chlamydia ReA. Persistent or recurrent urogenital infection or chronic gut inflammation are good candidates for chronicity. There is evidence of persisting microbial antigens in synovium, gut, or lymph nodes. Persisting microbial structures (cell-wall deficient bacteria and bacterial biofilms) may also contribute to chronicity. Psoriatic arthritis (PsA) patients have streptococcal infections, but also chronic viral infections (e.g. hepatitis C and HIV) more frequently compared with subjects with psoriasis.
Do infections cause ankylosing spondylitis (AS)? Acute ReA (especially in HLA-B27+), can proceed to chronic SPA and about 20-40% of patients have AS 10-20 years later. Klebsiella has been proposed to be involved in SPA and in AS, especially in association with peripheral arthritis. Klebsiella belongs to normal gut flora, thus linking AS with gut. AS occurs in between 5 and 10% of patients with inflammatory bowel disease (IBD), those positive for HLA-B27 having a especially high risk. Although IBD cannot be seen as a bacterial infection, stimulation of the immune system by local gut bacteria because of mucosal lesions serves most probably a similar purpose. Asymptomatic or uncomplicated enteric or urogenital infection have been linked to the development of AS. Thus an infection might be able to trigger pathogenic mechanisms which later manifest itself as 'primary AS'. Probably in most, if not all, of the AS patients a bacterial trigger is essential in the pathogenesis.

INV 24

PSORIASIS – RECENT DEVELOPMENTS IN PATHOGENESIS AND TREATMENT

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Psoriasis is a chronic inflammatory skin disease which now is regarded as a systemic disease primarily mediated by activated T-cells. Although several systemic drugs are available for the treatment of moderate to severe plaque psoriasis they frequently are associated with significant limiting side effects. Recent developments in our understanding of the pathophysiology of psoriasis and advances in biotechnology have permitted to develop targeted highly active agents. Since key cytokines such as tumor necrosis factor alpha (TNF alpha), interleukin-23 (IL-23), IL-17, endothelial cell and T-cell activation as well as a novel T-cell subset (Th17 cells) have been implicated in the pathogenesis of psoriasis several biological medications (biologics) targeting these pathways have been developed or are currently under investigation. Accordingly, anti-TNF-alpha molecules such as infliximab, adalimumab and etanercept as well as biologics targeting surface molecules involved in T-cell stimulation or endothelial cell activation such as efalizumab and alefacept have been proven to be highly effective with safety concerns focussing on infections. Antibodies targeting IL-12/23, p40 such as ustekinumab and ABT873 in Phase I and III clinical trials demonstrate a very significant and dose dependent efficacy with only a few adverse events. New strategies including small molecules, angiogenesis inhibitors and compounds targeting intracellular messenger targets such as tyrosine kinase inhibitors are currently being investigated in Phase I and II clinical trials. In the future developments in pharmacogenetics may provide predictive markers to optimize the response to treatment and to minimize adverse events.

INV 25

ANTERIOR UVEITIS: CURRENT STRATEGIES TO IDENTIFY THE CAUSE AND IMPROVE THE OUTCOME

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Introduction: Recurrent, acute anterior uveitis is commonly associated with spondyloarthritis. Factors responsible for this association remain incompletely understood.
Materials and Methods: Intravital microscopic and histologic evaluation of mouse eyes in the animal model of aggrecan-induced sacroiliitis and arthritis. Characterization of IL-23 receptor polymorphisms. Microarray analysis of gene expression in patients with ankylosing spondylitis with and without active uveitis. Data base analysis of reports of uveitis secondary to the use of TNF inhibitors.
Results: Immunization of TCR-transgenic BALB/c mice (which overexpress the T cell receptor specific for a dominant arthritogenic epitope of the aggrecan G1 domain) with aggrecan in DDA adjuvant induces an anterior uveitis as detectable by intravital microscopy and confirmed by histology. The eye inflammation begins as early as one week after immunization, well before the onset of joint disease, and may follow a waxing and waning course. The antigenic G1 domain of aggrecan, is detectable within the eye by Western blotting. Patient studies indicate that IL-23 receptor polymorphisms predispose to recurrent, acute anterior uveitis, even in patients who do not have clinical evidence for spondyloarthritis.
Microarray studies confirm that patients with AS differ from controls with regard to gene expression in peripheral blood. The impact of uveitis on this gene expression is still under analysis. Although TNF inhibitors prevent uveitis in patients with spondyloarthritis, etanercept might provoke uveitis in a rare individual based on a survey of reports to a database for ocular adverse events.
Conclusions: Uveitis is a frequent association with spondyloarthritis. The pathogenesis of the uveitis involves shared genetic factors with ankylosing spondylitis, as well as presumed distinguishing genetic and environmental contributors.

INV 26

INFLAMMATORY BOWEL DISEASES – NOVEL ASPECTS FOR PATHOGENESIS - DIAGNOSIS AND THERAPY

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Introduction: Certain forms of spondylarthropathy are associated with a high prevalence of ileal inflammation. Histologically this inflammation is almost identical to that of Crohn's disease. It has been suggested that this inflammation represents a sub-clinical form of Crohn's disease. However most studies have been carried out in patients on NSAIDs where it is difficult to dissociate the findings from the effects of NSAIDs. Here I review some recent studies that provide an insight into the pathogenesis of then ileitis of spondylarthropathy.
Material and Methods: Data was obtained from the authors files.
Results: Studies involving asymptomatic first degree relatives of patients with Crohn's disease (n=151) and AS (n=124) in Iceland show that between 40 and 50% have intestinal inflammation (judged by a faecal calprotectin test). Variance components analyses suggest that the inheritance pattern of this inflammation is affected by a similar and major additive gene in both groups of relatives. The importance of this inflammation was assessed in the relatives of AS patients where HLA B27 status, faecal calprotectin levels and CT abnormalities of the sacroiliac joints were correlated.
Relatives with increased faecal calprotectin had significantly greater CT changes that were suggestive of early AS; suggesting a causal relationship. A large gaenology study showed that patients with AS or inflammatory bowel disease in Iceland are significantly more related to each other than are randomly sampled control subjects, in terms of an increased risk of either or both conditions developing in third-degree relatives.
Conclusion: These findings suggest that one or more undiscovered genetic variants may underlie the risk of both AS and Crohn's disease and that the intestinal inflammation plays a pathogenic role in AS. Further studies in these relatives may yield important data on the early pathogenic events in Crohn's disease.

INV 27

LONG-TERM SAFETY OF TNF-BLOCKERS

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The use of TNF-antagonists has become a mainstay of therapy for patients with severe and refractory forms of the inflammatory diseases of the axial and peripheral joints such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and other spondyloarthropathies (SpA). In most instances, such therapy is initiated with the intention to continue the use of the agent, if successful in controlling disease manifestations, for very long periods of time if not indefinitely. Therefore, considerations regarding the long-term safety of such agents become of paramount importance to practicing clinicians. However, data regarding the safety of medications that are derived from randomized clinical trials or initial longer-term systematic follow-up cohorts are primarily used for establishing sufficient safety and tolerability with regards to registration of the medication and are limited to follow-up times of one or a few years, at most. Therefore, additional data from longitudinal observational registries are needed to provide information on the true very-long term safety of these agents. A number of registries, mostly in Europe, have addressed this need, including the BSRBR in the UK, RABBIT in Germany, BIOBADASER in Spain, and ARTIS in Sweden. Analyses based on these registries have focused mostly on patients with RA, but additional analyses of patients with other diagnoses have not, to date, pointed at specific safety issues for individuals non-RA diagnoses. The main areas of investigation have been 1) infections; 2) tuberculosis; 3) malignancy; 4) autoimmunity and immunogenicity. Published results from the clinical trials and registries addressing these issues will be reviewed. It can be concluded that the risk of infections with anti-TNF agents is somewhat elevated compared to the baseline case for the relevant patient groups, with an absolute risk increase of severe infection of 1-4 per 100 patient-years of exposure. Tuberculosis is an infection of special concern, because its prevalence is clearly increased in patients with RA – even without anti-TNF treatment – and the risk is considerably higher when these agents are used. Meticulous screening can, thankfully, reduce the risk considerably. Concern over an increase in the risk for malignancies, raised by some of the randomized trials, was not confirmed in the largest registry-based analyses. Autoimmune manifestations such as ANAs and anti-DNAs are noted in patients treated with anti-TNFs, but appear to be of limited clinical significance. In summary, the safety profile of anti-TNF agents, as analyzed in several very large registries, continues to be very satisfactory and supportive of the use of such agents in appropriately selected patients.

INV 28

CYTOKINES AS TARGETS IN INFLAMMATORY RHEUMATIC DISEASES

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Despite the successful development of a variety of novel therapeutic agents, unmet clinical needs exist in the treatment of inflammatory arthritis and spondyloarthropathy. Therapeutic intervention should address inflammation, articular damage, comorbidity and functional decline, all attendant to uncontrolled inflammatory processes. Several data now suggest that the kinetics of intervention are important – in principal earlier intervention leads to improved outcome regardless of the therapeutic agent employed. This is evident in comparing primary with subsequent DMARD interventions and in particular in comparing the clinical responses to TNF blockade in early versus later disease cohorts. Pathologic studies of synovial biology have not revealed particularly striking phenotypic differences in appearances over time – there are however limitations in the extent and rigor of sequential analyses in individual patients' biopsies and in the functional nature of such studies by necessity. This raises important issues in the design of optimal management strategies. (i) Upon clinical presentation, the inflammatory response should be limited rapidly to minimise the onset of damage to tissues that could provide an environment conducive to chronicity. There may be cytokines (in addition to TNF) that are effective as targets in this respect by virtue of their broad roles at early stages of inflammatory responses. (ii) Cytokines (e.g. IL-12, IL-23, IL-35) that regulate critical T cell, dendritic cell and B cell interactions remain relatively poorly understood in the context of inflammatory synovitis but may facilitate interventions that can promote tolerance induction. Moreover, novel cytokine activities such as IL-33 are emerging that implicate other cellular lineages in the inflammatory synovial responses e.g. mast cells. Similarly the pathways that lie upstream of cytokine release are now being recognized and offer targeting potential in their own right. (iii) A variety of models now exist that facilitate analysis of such possibilities in particular *in vivo*. These will in turn instruct appropriate target selection – we should not at this stage assume that the same targets will be valid across the kinetics of an immune response and therefore a disease state.

INV 29

POSSIBLE NEW AGENTS TO TREAT ANKYLOSING SPONDYLITS AND OTHER SPONDYLOARTHRITIDES

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The introduction of TNF-blockers for the treatment of patients with active ankylosing spondylitis (AS) over the last 5-10 years has meant a major breakthrough in the management of this chronic inflammatory disease. How early AS patients should be treated with a TNF-blocker, whether the remission rate can be increased or whether even a drug free remission can be achieved if treated early enough and whether early therapy can prevent long-term structural damage are open and important questions which have to be addressed and solved in the near future. NSAIDs are potent anti-inflammatory agents which are still the first line of treatment. Recent evidence even indicates that NSAIDs might inhibit the growth of syndesmophytes, possibly through a prostaglandin-mediated inhibition of osteoblasts. Thus, the exact role of the two established therapies for AS, TNF-blockers and NSAIDs, in treatment strategies has still to be determined. Nonetheless, is has become clear by clinical experience but also through many studies which have been performed with the two kind of drugs over the last years that not all patients show a major response if treated. Future research will focus on new agents which can inhibit inflammation in patients who are TNF-failures but also in direct comparison to TNF-blockers and on drugs which can inhibit new bone formation. An ideal drug for the treatment of AS would suppress inflammation and prevent new bone formation. Based on experience in animal models, on the treatment of other chronic inflammatory diseases and on histological and functional studies in AS treatment directed at the following targets are currently already tested or should be tested in the near future: B cells (rituximab), T cells (abatacept), IL-6R, IL-17, IL-23, regulatory T cell (Treg). Regarding new bone formation several molecules of the wnt pathways could be targeted such as 'bone morphogenic proteins' (BMP). Obviously, a better understanding of the pathogenesis will allow to investigate further targeted therapies.

INV 30

BIOLOGY AND ROLE IN AUTOIMMUNITY OF TRIMMING AMINOPEPTIDASES

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Peptide ligands for MHC class I molecules are produced through the action of one or several intracellular proteases. Initial antigen degradation by cytosolic proteasome complexes is frequently followed by aminoterminal peptide trimming. Trimming can occur in the cytosol, before peptide transport into the endoplasmic reticulum (ER) by the transporters associated with antigen processing (TAP). However, available evidence suggests that trimming after TAP transport, by aminopeptidases of the ER, plays a larger role in HLA class I antigen processing. In human cells, two related ER aminopeptidases with complementary specificities, ERAP1 and ERAP2, have been shown to trim epitope precursors. The two enzymes can form dimeric complexes, with a possible effect on enzyme activity and/or specificity. Analysis of mice deficient for ERAAP, the only known ER trimming peptidase in that species, demonstrated that formation of a substantial percentage of pMHC complexes requires peptide trimming in the ER. Cell surface MHC class I molecules in these mice display reduced stability, presumably because of a dearth of optimal peptides in the ER, and of MHC class I loading with N-terminally extended peptides. ERAAP ko mice mount only slightly altered T cell responses to several viruses, demonstrating that peptide trimming is not essential for priming of antiviral CD8+ T cells. However, ERAAP ko antigen presenting cells are highly immunogenic in ERAAP sufficient mice and elicit vigorous T and B cell responses. It is therefore conceivable that local changes in expression of human ERAP enzymes, as well as altered ERAP specificity due to coding sequence polymorphism, might render affected tissues immunogenic, and underlie the recently reported association of ERAP1 polymorphism with ankylosing spondylitis.

INV 31

THE BIOLOGICAL AND PATHOGENETIC ROLE OF HLA-B27-BOUND PEPTIDES: TOWARDS A GLOBAL PERSPECTIVE

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The basis for the association of HLA-B27 with ankylosing spondylitis (AS) and chronically evolving reactive arthritis remains unknown. Several hypotheses, each one emphasizing the pathogenetic potential of a particular feature of HLA-B27, attempt to explain the mechanism of these diseases and the differential association of B27 subtypes to AS. Stable transfection of bacterial protein constructs into human cells was used to demonstrate that HLA-B27 presents endogenously processed peptides from the arthritogenic bacteria Chlamydia trachomatis with a high level of sequence identity to self-derived HLA-B27 ligands and other human protein sequences. This finding provides molecular support for a pathogenetic role of HLA-B27 based on mimicry between foreign and self-B27 epitopes. Folding and other biological features do not correlate with the differential association of HLA-B27 subtypes to AS. As an alternative to single-feature based mechanisms, HLA-B27 can be analyzed from a more global perspective of its biology, emphasizing the inter-dependency of multiple molecular features and the influence of other disease-modifying genes. From this viewpoint, peptide binding emerges as the cornerstone of HLA-B27 biology and pathogenetic role, as it determines not only the antigenic features of the molecule, but also its folding and stability.

INV 32

PEPTIDE HANDLING/MISHANDLING IN AS MODELS

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Animal models have provided important insights into molecular mechanisms of pathogenesis in inflammatory arthritic diseases. Rodents that overexpress the MHC class I molecule HLA-B27, a major predisposing factor for ankylosing spondylitis (AS) and other human spondyloarthritides (SpA), have been shown to develop spontaneous SpA-like disease. Although these animals do not provide a precise phenocopy of AS, they have been useful for defining the cellular requirements for disease, and further dissection of pathogenic mechanisms is likely to provide insights into the precise role of HLA-B27.
In my presentation I will review the role of handling and mishandling of peptides by HLA-B27 in animal models of SpA. Peptides, along with β_2m, constitute the cargo that MHC class I molecules deliver to the cell surface for display to CD8+ T cells. Peptides play a crucial role in self, non-self discrimination, and in marking cells for destruction when infected with certain microorganisms. Both peptides and β_2m are critical for the proper assembly of MHC class I complexes. Peptide-induced conformational changes stabilize MHC class I heavy chains during their assembly in the endoplasmic reticulum (ER), thereby preventing the rapid degradation of unassembled heavy chains. The requirement of HLA-B27 for higher concentrations of peptide to induce stabilization suggests that mishandling of peptides may be a factor in its tendency to misfold and form aberrant disulfide linked and BiP-bound heavy chain complexes in the ER. Recent results from whole genome association studies implicating *ARTS-1* (also known as ERAAP) as a predisposing factor in AS, raise the possibility that additional events occurring in the ER, and influencing the immunobiology of HLA-B27, are involved in pathogenesis. However, the protein encoded by *ARTS-1* is bifunctional, serving as a cytokine receptor 'sheddase' as well as an ER-associated aminopeptidase, and therefore the role of this gene product may be complex.
Considerable evidence generated in the 1990s using HLA-B27 transgenic mice deficient in β_2m suggested that peptides generated in the cytosol and transported into the ER were not involved in the development of spontaneous arthritis. However, these results have not been reproduced in other laboratories, perhaps due in part to complex background strain differences, making it difficult to draw definitive conclusions about the role of peptides in mouse SpA. Nevertheless, in the rat model there is indirect evidence from CD8$\alpha\beta$ T cell depletion studies to support the idea that classical T cell recognition of HLA-B27-restricted peptides is not required for disease. However, if peptides are important for stabilization of heavy chains in the ER and peptide 'mishandling' contributes to heavy chain misfolding, then they may be critical players in pathogenesis. This raises important possibilities for ARTS-1/ERAAP and peptide trimming in the ER as a factor in the pathogenesis of AS.
Recent results from our laboratory suggest that HLA-B27 misfolding in the rat model of SpA may be linked to disease through the unfolded protein response (UPR), rather than peptide presentation to CD8+ T cells. Macrophages undergoing an HLA-B27-induced UPR produce more IL-23 than IL-12 in response to certain pattern recognition receptor (PRR) agonists. Interestingly, there is dramatic overexpression of IL-17 and expansion of IL-17-producing CD4+ T cells in the colon of HLA-B27 transgenic rats that correlates with development of colitis. These data implicate a novel mechanism to explain the role of HLA-B27 misfolding in Th17-driven inflammation in this animal model with implications for human disease.

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Oral Presentations

O 1

LOCAL AND SYSTEMIC LEVELS OF IL-23 ARE STRONGLY ASSOCIATED WITH DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS BUT NOT SPONDYLOARTHRITIS

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Background: T-helper 17 (Th17) cells are a T-cell population that play a pivotal role in several inflammatory conditions and are dependent on interleukin-23 (IL-23) for their survival and expansion. More recently, a genetic association was discovered between polymorphisms in the gene coding for the IL-23 receptor and spondyloarthritis (SpA). Also, targeting IL-23 has been shown to be of clinical benefit in Crohn's disease and psoriasis, two conditions that are closely related to SpA. Our aim was to evaluate the potential role of Th17 associated cytokines in SpA pathogenesis by measuring their levels in the joints and circulation of SpA patients as well as correlating them with disease activity parameters.
Methods: Paired synovial fluid (SF), serum and synovial biopsies were obtained from 53 SpA and 23 rheumatoid arthritis (RA) patients. Interleukin-17, IL-23 and CCL20 were measured by ELISA in the SF and serum of the patients and correlated with systemic and local parameters of disease activity.
Results: SF IL-17 levels were as high in SpA as in RA patients and correlated with neutrophil numbers in the synovial fluid of these patients. In contrast, the levels of IL-23 and CCL20, a major Th17 attracting chemokine, were higher in joints of RA than in SpA patients despite a similar degree of local and systemic inflammation. In addition, there was a remarkable association between the expression of the Th17 cytokine system and the presence of intimal lining layer hyperplasia in RA. Also in the serum, IL-23 levels were higher in RA and correlated strongly with disease activity parameters.
Conclusion: Th17 related cytokines are abundantly expressed in joints of SpA as well as RA patients. IL-23 levels, however, are higher in RA patients than in SpA patients and correlate with disease activity parameters in RA. These results point to a potential differential regulation of the Th17 cytokine system in SpA compared to RA. Overall these data warrant further investigation into the Th17 cytokine system as a promising therapeutic target in chronic arthritis.

O 2

ASSOCIATION OF IL-23R WITH AS GENETIC SUSCEPTIBILITY AND INFLAMMATION RELATED WITH ELEVATED EXPRESSION OF IL-23 AND IL-17 IN CHINESE POPULATION

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Background: To explore the association between IL-23R and AS in Chinese and the significance of IL-23 and IL-17 in AS.
Methods: 138 Chinese Han cases and 129 ethnically matched controls were involved.
Rs11209026, rs1343151, rs11209032 and 3 nearby SNPs of IL-23R were genotyped by sequencing. Hardy-Weinberg equilibrium, genotypes and allele differences were evaluated using SPSS13.0. Linkage disequilibrium and haplotype analysis were carried out by SHEsis software. IL-23R and IL-23p19 mRNA expression was detected with RT-PCR and Western blot. 57 AS patients and 38 healthy controls were involved. Serum and supernatants of cultured PBMCs levels of IL-23 and IL-17 were detected by ELISA.
Results: Allele and genotype frequency between cases and controls were significant for rs11209032 and rs6677188 ($p<0.001$). They are in strong linkage disequilibrium ($D' = 0.925$, $r2 = 0.561$). IL-23R expression in PBMCs of patients was elevated at mRNA and protein level ($P <0.001$). IL-23 and IL-17 levels in patients' serum before etanercept therapy (1159.71 ± 139.45; 172.21 ± 73.81 pg/ml) were significantly higher than those in controls. IL-23 and IL-17 elevation in patients was positively correlated with BASDAI, total back pain and nocturnal pain and morning stiffness duration. At 6w and 12w, serum levels of IL-23 (494.45 ± 103.00, 444.45 ± 90.49 pg/ml) and IL-17 (71.44 ± 16.74, 69.95 ± 16.97 pg/ml) were lower than those before therapy ($P<0.001$). IL-23 levels were lower at 12w than at 6w ($P<0.001$). IL-23 and IL-17 levels in supernatants of cultured PBMCs of patients (108.63 ± 34.53; 134.59 ± 38.32 pg/ml) were higher than that of controls ($P<0.001$).
Conclusion: IL-23R is associated with AS in Chinese. IL-23 may relate with AS inflammation through inducing IL-17 production. IL-23 and IL-17 can be down-regulated by etanercept.

O 3

ENHANCED TNF-DRIVEN CROSSTALK TO INVARIANT NKT CELLS FAVOURS REGULATION OF MURINE SPONDYLOARTHRITIS

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Introduction: Natural killer T (NKT) cells represent a highly conserved glycolipid reactive immunoregulatory T cell lineage with features of innate and adaptive immunity. The most abundant NKT cell subset is characterized by an invariant T cell receptor (TCR) alpha chain and is referred to as invariant NKT cells (iNKT cells). Upon CD1d-mediated antigen presentation, these cells have the capacity to produce large amounts of both TH1 and TH2 cytokines and therefore modulate other immune cells. It has been suggested that these cells have an ambivalent role in experimental arthritis, depending on the model used. In patients suffering from chronic arthritis (rheumatoid arthritis or ankylosing spondylitis) or Crohn's disease, TNF blockade has proven to be a valuable treatment. However, the role of iNKT cells in TNF driven inflammation has not been appraised yet.
Materials and Methods: We assessed the role of iNKT cells in TNFΔARE mice, which are characterized by an enhanced TNF mRNA stability. TNFΔARE mice are considered a suitable mouse model for Crohn's disease associated arthritis because they develop peripheral arthritis, sacroiliitis, spondylitis and Crohn's like ileitis.
Results: When these mice were backcrossed onto an iNKT cell deficient (Jα18-/) background, we observed accelerated disease progression. Conversely, transferred purified iNKT cells from healthy controls into TNFΔARE x Jα18-/- mice partially restored this enhanced disease severity. Furthermore, we noticed that antigen presenting cells, especially dendritic cells, were enriched in inflamed regions, and expressed a semi-matured phenotype, with upregulation of CD1d. The endogenous presentation of glycolipids to iNKT cells was strongly promoted, and required lysosomal processing.
Conclusions: These findings indicate that iNKT cells can regulate TNF driven inflammation by a mechanism of chronic TNF-α induced maturation of antigen presenting cells, leading to marked enhancement of endogenous glycolipid presentation by CD1d. This leads to activation of iNKT cells to exert their regulatory role.

O 4

GENOMEWIDE ASSOCIATION STUDY IN ANKYLOSING SPONDYLITIS IDENTIFIES MAJOR NON-MHC GENETIC DETERMINANTS OF DISEASE SUSCEPTIBILITY

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Purpose: Ankylosing spondylitis (AS) susceptibility is primarily genetically determined, with heritability >90% and HLA-B27 the primary susceptibility allele. This study aimed to identify other AS-associated genes beyond HLA-B27.
Methods: 2108 Australian, British and North American AS cases of white European descent were enrolled, fulfilling modified New York Criteria. Control genotypes were obtained from the Wellcome Trust Case-Control Consortium study of the 1958 British Birth Cohort (n=1500) and from the Illumina iControlDB database of North American healthy controls.
Cases were genotyped for 317,000 SNPs using Illumina HumHap300 microarray genotyping slides. Cases and controls of non-white European ancestry were identified using Eigensoft principle components analysis approaches and excluded, and related individuals identified by IBS analysis using PLINK, and excluded. Case-control analysis was then performed by Cochrane-Armitage test. In addition, a replication cohort of 711 North American and 1129 U.K. AS patients and 1022 North American and 1436 U.K. Controls was examined for 144 SNPs showing highest significance in the initial GWAS and 48 Ancestry Informative Markers (AIMs) using SNPplex and Taqman genotyping. Genomewide significance (GWS) was defined at $P<10^{-7}$, and suggestive genomewide significance (sGWS) as $P<10^{-5}$.
Results: The MHC association with AS was confirmed (rs7743761, odds ratio (OR)=4.5, $p<10^{-267}$), as were associations with ARTS-1 (rs30187, OR=1.3, $P=7x10^{-10}$), IL23R (rs11209026, OR=0.55, $P=1.5x10^{-9}$), and around IL-1R2/R1 within the IL-1 gene complex, (rs12619383, OR=1.3, $P=1.9x10^{-4}$). Two regions not previously reported achieved GWS, on chromosome 21q22 (rs2242944, OR=1.3, $P=2.6x10^{-10}$) and on chromosome 2p15 (rs10865331, OR=1.4, $P=1.1x10^{-14}$). In both regions no gene is known to be transcribed. 21 unique regions achieved sGWS, including SNPs in the gene TNFR1 (rs4149576, OR=1.2, $P=4.8x10^{-6}$), overexpression of which has been shown to cause sacroiliitis in mice, and near TRADDD, which interacts with TNFR1 (rs9033, OR=1.2, $P=3.2x10^{-5}$). Preliminary analysis of the replication cohorts found all of these regions to maintain GWS or sGWS.
Conclusions: The associations reported here suggest that ARTS-1 may induce AS by its known capacity to cleave proinflammatory cytokine cell surface receptors such as TNFR1 and IL-1R1. The strong association of two 'gene deserts' with AS suggests the involvement of non-coding RNA variants in AS etiology. Further replication of these findings is near completion.

O 5

A META-ANALYSIS OF IL23R ASSOCIATIONS WITH ANKYLOSING SPONDYLITIS

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Background: The heterodimeric receptor of IL23 is formed by the beta 1 subunit of IL12R and an IL23 specific subunit encoded by the *IL23R* gene. Both subunits are required for IL23 signaling. In a study by the Wellcome Trust Case Control Consortium (WTCCC) and the Anglo-Australo-American AS consortium (TASC), it has been shown that *IL23R* variants are associated with ankylosing spondylitis. Two further smaller studies have shown limited associations of *IL23R* variants with AS. To reduce the impact of lack of power in the assessment of the association between *IL23R* polymorphisms and AS, we undertook a meta-analysis of published studies and included unpublished data on additional 730 AS cases from the UK. The size of the effect and the primary causal variants in *IL23R* remain to be identified precisely.
Methods: In total, 3597 cases and 3150 controls from 4 different studies have been combined in the meta-analysis of association. Populations were from Canada, Spain, UK and USA. Data were analysed using STATSDIRECT software. DerSimonian-Laird test was used to calculate random effects pooled odds ratio with 95% confidence intervals and p-values.
Results: Statistically significant associations have been found between various *IL23R* polymorphisms and AS. *IL23R* SNP rs11209032 showed a strong association with AS ($P<0.0001$). SNPs rs10489629, rs1343151 and rs1495965 showed marginal associations with AS ($P<0.0007$, $P<0.0002$ and $P<0.0004$ respectively).
Conclusions: *IL23R* polymorphisms may be associated with either increased or decreased susceptibility to AS. In order to confirm these results, more polymorphisms covering the whole gene and its regulatory sequences should be tested. Functional consequences should also be investigated.

O 6

SEVERITY OF HIP DISEASE IS COUPLED WITH SEVERITY OF SPINAL DISEASE IN ANKYLOSING SPONDYLITIS

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Introduction: In ankylosing spondylitis (AS) chronic inflammation in the sacroiliac joint and spine is followed by ankylosis. In the hip, it is followed by cartilage erosion and joint destruction. The frequency and predictors of hip disease in AS have not been fully elucidated. We address these issues in the current study.
Methods: AS patients were divided into the presence (HIP+) or absence (HIP-) of hip disease by radiographic evidence of joint space narrowing or by total hip replacement (THR). Means (±SD) were calculated for various clinical variables and compared using the student's *t*-test.
Results: Amongst 220 patients, 47 (21.4%) had radiographic evidence of hip disease, and of these, 15 patients (12 males), 6.7% of the cohort, had had THR (8 bilateral, 7 unilateral). Mean age (±SD) was 42.8 (±14.7) in the HIP+ group and 38.9 (±12.9) in the HIP- group ($p=0.08$). There was a statistical difference in disease duration between the HIP+ (19.3 years ±11.6) and HIP- (15.6 years ±11.3) groups ($p=0.05$), but not in HLA-B27 positive patients, 75.7% (HIP+) and 82.3% (HIP-), or proportion with juvenile onset AS, 25.5% (HIP+) and 24.9% (HIP-). There was a trend towards more males in the HIP+ group (89.4% versus 78.6%) ($p=0.10$). There was no statistical difference in BASDAI, ESR or CRP between the 2 groups. Mean mSASSS (±SD) was 32.4 (±27.7) in the HIP+ and 16.1 (±22.0) in the HIP- groups ($p<0.001$). Mean BASMI (±SD) was 4.9 (±2.7) in the HIP+ and 2.7 (±2.4) in the HIP- groups ($p<0.001$). We analyzed a modified BASMI in which the intermalleolar distance score was excluded (BASMI – IMD), and this too was significantly different, HIP+ (3.9±2.5) and HIP- (2.2±2.1) groups ($p<0.001$).
Conclusion: Hip disease is a frequent finding in AS and is associated with clinically and radiographically more severe spinal disease. The occurrence and severity seem to be linked and suggest common pathogenic mechanisms.

O 7

EVALUATION OF POWER DOPPLER ULTRASONOGRAPHY (PDUS) FOR THE DIAGNOSIS OF SPONDYLARTHROPATHY (SpA) IN PATIENTS WITH UNCERTAIN DIAGNOSIS CONSULTING FOR CLINICAL SYMPTOMS SUGGESTING OF SpA: THE ECHOSPA PROSPECTIVE MULTICENTER FRENCH COHORT

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Recently, PDUS proved to be a highly sensitive tool to assess enthesitis in SpA. In patients with a suspicion of SpA, diagnosis could be improved by detecting enthesitis with PDUS.
Objectives: To constitute a French cohort suited for assessing the diagnostic performance of PDUS for the diagnosis of SpA.
Methods: Prospective, multicenter French cohort study. Outpatients consulting for symptoms suggestive of SpA (inflammatory back pain (IBP), arthritis or inflammatory arthralgia (IA), enthesitis or dactylitis (ED), uveitis with HLA-B27 positivity (B27+U), familiarity for SpA (Fam)) were recruited. At entry, patients were submitted to clinical examination, pelvic x-ray, MRI and CT scan of sacroiliac joints, HLA-B typing. PDUS of 16 entheses was performed by an independent examiner blind to subject's identity and symptoms. Diagnosis of SpA will finally be retained or excluded by an experts' committee, blind to PDUS results, after 2 yrs of follow up. Sample size was set to 500 patients (estimated prevalence of SpA of 30% after 2 yrs).
Results: Between January 2005 and September 2007, 489 patients were included (96% of target). Mean age was 40 yrs, mean duration of symptoms was 4+2 yrs; 42% of patients were HLAB27+ and 62% were female. Primary inclusion criterion was IBP in 49%, IA in 28%, ED in 10%, B27+U in 9% and Fam in 4%. At inclusion, the opinion of the referral rheumatologist with regard to the suspicion of SpA was "probably yes" in 45%, "probably not" in 7%, and "doubtful" in 48 %. Regarding the 250 patients who have yet completed the study (2% of patients were lost to follow-up); a diagnosis of SpA was made by the referral rheumatologist in 32%, whereas SpA was excluded in 21% and a doubt persisted in 37% of them.
Conclusion: If the value of PDUS is confirmed, the consequences will be multiple, such as an improvement of diagnostic procedures and therapeutic management of SpA, and a reduction of diagnostic costs.

O 8

THE LOWER PART OF THE THORACIC SPINE ADDS IMPORTANT INFORMATION IN ASSESSMENT OF RADIOGRAPHIC PROGRESSION IN PATIENTS WITH ANKYLOSING SPONDYLITIS (AS)

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Background: The modified Stokes AS spinal score (mSASSS), the most reliable instrument to evaluate structural outcomes, assesses the cervical and the lumbar spine in patients with AS and is important for the outcome in studies with such patients. Magnetic resonance imaging studies have shown that the lower thoracic spine shows the most inflammatory lesions in AS.
However, this part of the spine not included in the mSASSS.
Objectives: To assess the contribution of the lower thoracic spine to radiographic outcomes in AS.
Methods: Standard conventional radiographs of the cervical and lumbar spine of 80 AS patients were quantified for radiographic progression within 2 years by using the mSASSS.
All vertebral edges (VE) of the lower part of the thoracic spine segment (Th-9 to Th-12) that were assessable on lumbar spine radiographs were additionally scored ('adjusted mSASSS') and compared to the original mSASSS.
Results: In comparison to the original mSASSS, additional vertebral edges (VE) could be seen in 70/80 patients (88%), from segment Th-12 to Th-9. However, only data up to the lower segment of Th-10 added significantly in depiction of radiographic progression, with 3.1±1.0 additional vertebral edges per patient. The mean change in mSASSS units after 2 years was 0.9±2.8 with the original mSASSS, and 1.7±3.1 with the adjusted mSASSS ($p<0.001$). Syndesmophytes/ankylosis were seen in 1.4±2.9 VEs per patient in the cervical and lumbar spine and in 0.6±1.2 VEs per patient in Th10-Th12.
Conclusions: The lower part of the thoracic spine is not included in the mSASSS but is usually visible in standard conventional radiographs in clinical practice. Its inclusion adds substantial information on additional syndesmophytes per patient. Further studies will prove the usefulness of inclusion of the thoracic spine in the outcome of treatment in AS patients.

O 9

MAGNETIC RESONANCE IMAGING (MRI) OF THE ANTERIOR AND POSTERIOR SPINAL SEGMENTS DURING ADALIMUMAB (HUMIRA®) THERAPY FOR ACTIVE ANKYLOSING SPONDYLITES (AS)

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Objectives: To analyze the ability of facet joint scoring of the spine, in addition to an established MRI scoring method, to detect adalimumab effects on spinal inflammation.
Methods: MRIs were performed for 58 patients from the open-label RHAPSODY trial. AS patients with BASDAI ≥4 received adalimumab 40 mg every other week for 12 weeks. Axial skeleton MRIs were performed at baseline and after 12 weeks. Active spinal inflammation was scored according to the Berlin MRI spine score (0–69). Facet joints of each spinal segment were scored for inflammation (0=inactive, 1=probable, 2=definite/active).
Results: Mean (SD) MRI baseline spine score was 6.0 (7.8) and decreased to 3.2 (4.6) after 12 weeks of adalimumab ($p<0.001$) (47% reduction in spine inflammation). Mean MRI score of the facet joints decreased from 5.9 (7.8) at baseline to 2.0 (3.1) after adalimumab ($p<0.001$). Eight patients had no reduction in MRI score, but a reduction in facet joint score: two patients (3%, Reader 1) and six patients (10%, Reader 2). Inter-reader agreement was good-to-excellent for Berlin MRI spine score (baseline ICC=0.94, Week-12 ICC=0.69) and facet joint scores (baseline ICC=0.93, Week-12 ICC=0.71).

Improvements in Berlin MRI Scores and Facet Joint Scores with Adalimumab

	Reader 1		Reader 2	
	Week 0	Week 12	Week 0	Week 12
Mean Berlin MRI spine score (SD) [range]	5.5 (7.5) [0–43]	2.0 (2.6) [0–2]	6.9 (8.8) [0–41]	4.4 (7.0) [0–34]
Mean posterior segment MRI score (SD) [range]	5.3 (7.4) [0–42]	1.1 (2.0) [0–8]	6.6 (8.7) [0–40]	2.8 (4.5) [0–20]

Conclusions: Adalimumab significantly reduced active inflammatory lesions of the spine. Facet joint scores detected change of inflammation in up to 10% of patients with no change in the anterior segment of the spine. Addition of facet joint scoring may increase the overall sensitivity to change in MRI assessments.

O 10

ANKYLOSING SPONDYLITIS AND THE RISK OF FRACTURE: RESULTS FROM A LARGE PRIMARY CARE-BASED NESTED CASE CONTROL STUDY

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Background and Aims: Ankylosing spondylitis (AS) is associated with bone loss in the vertebrae and an increased prevalence of vertebral fractures, but literature about the magnitude of the risk of fracturing is limited. One retrospective cohort study provided evidence of an increased risk of clinical vertebral fractures but not for non-vertebral fractures. This study further explores the risk of clinical vertebral and non-vertebral fractures in a large population database.
Methods: In a primary care-based nested case-control study, 231,778 fracture cases and 231,778 age- and sex-matched controls were recruited. A history of AS was assessed from the medical records. AS was diagnosed in a total of 758 people. Odds ratios (OR) and 95% confidence intervals (CI) were calculated after adjustment for medication, other illnesses, smoking and body mass index whenever known.
Results: The prevalence of AS was 0.18% in fracture cases and 0.15% in controls. Patients with AS had an increased risk of clinical vertebral fracture (OR: 3.26; CI: 1.51-7.02). The risk for forearm and hip fracture was not significantly increased (OR: 1.21 [CI: 0.87-1.69] and 0.77 [CI: 0.43-1.37], respectively). The risk of any clinical fracture was increased in AS patients with a history of inflammatory bowel disease (IBD) (OR: 2.79, CI: 1.10-7.08), whereas it was decreased in AS patients taking non-steroidal anti-inflammatory drugs (NSAIDs) (OR: 0.65, CI: 0.50-0.84). The risk was not associated with recent back pain, psoriasis, joint replacement therapy and use of sulfasalazine.
Conclusions: Patients with AS have an increased risk of clinical vertebral fracture, but not of non-vertebral fractures, while in patients with concomitant IBD the risk of any clinical fracture is increased. The mechanism by which intake of NSAIDs reduces the risk of any clinical fracture warrants further research.

Poster Presentations

P 1

ER STRESS MODIFIES THE IL-23 RESPONSE TO TOLL-LIKE RECEPTOR AGONISTS AND INTRACELLULAR BACTERIA INFECTION

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The secretion of IL-12 and IL-23 by dendritic cells plays a key role in co-ordinating protective and pathological immune responses. We have previously shown that LPS activation of monocytic cell lines induces the unfolded protein response (UPR); we wished therefore to determine the contribution of the UPR to the induction of proinflammatory cytokine production following TLR activation or intracellular bacterial infection.
The ER stress inducing agent thapsigargin (TP) was added to monocyte derived dendritic cells isolated from the peripheral blood of healthy individuals, in the presence or absence of TLR agonists, to simulate micobiological infection. TP in combination with TLR2,3,4 and 8 stimulation synergistically enhanced TNF-α, IL-23 p19 but not IL-12 p35 mRNA.
Furthermore, UPR activation in combination with TLR agonists only enhanced TNF-α, IL-23 but not IL-12p70 secretion. Using lentiviral delivery of short hairpin RNAs to reduce the expression of the ER stress signalling molecule, XBP-1, in U937 cells, we were able to demonstrate that UPR signalling was a critical component of this synergistic response.
Activation of the UPR by the addition of TP also induced phenotypic changes in immature dendritic cells and enhanced their ability to stimulate the differentiation of naïve $CD4^+$ T cells.
Infection of the monocytic cell line U937 with the obligate intracellular bacterial pathogen Chlamydia trachomatis resulted in a significant increase in ER stress activation, again knockdown of XBP-1 in infected cells decreased the expression of IL-23p19mRNA. This suggests that UPR induction is an important component of the IL-23 response to intracellular infection. This work identifies a novel pathway of IL-23 activation that results in the super-induction of IL-23 mRNA in monocyte and dendritic cells. This study has demonstrated that the UPR can have significant affects on the function of immune cells that orchestrate proinflammatory immune responses.

P 2

MICROARRAYS IDENTIFY RGS1, A REGULATOR OF G-PROTEIN SIGNALING, AS A HIGHLY SENSITIVE AND SPECIFIC SpA BIOMARKER

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Aim: To discover blood-based biomarkers for SpA patients with inflammatory back pain, but lacking psoriasis, IBD, active uveitis, or reactive arthritis.
Method: Genome-scale microarray analysis was carried out on PBMC from 20 healthy and 49 SpA subjects. Genes with *t*-test p-values < 0.000002 were evaluated by measuring their ROC area under the curve (AUC). An AUC > 0.8 indicates high sensitivity and specificity.
Results: The gene expression pattern of SpA as a whole was heterogeneous. Correlation matrix of microarray data against 19 clinical variables unmasked existence of two uniform subsets: patients with radiological sacroiliitis score of < 2 (classified as USpA) showed 135 differentially expressed genes, whereas in patients with sacroiliitis > 3 (classified as AS), only 6 of these same USpA genes were differentially expressed. 5 PCR-validated genes discriminated AS from normal subjects with an AUC > 0.8: RGS1, CAMP, defensin-alpha, MIP-2alpha and plasminogen activator inhibitor (PAI). 21 additional validated genes discriminated USpA from normal subjects with an AUC > 0.8. The highest was again RGS1.
The others with AUC > 0.9 were NR4A2, FosB, ATF3, IL-1alpha, IL-6, IL-8, MIP-1alpha, MIP-2alpha, PAI and HB-EGF. When all SpA patients were considered a group, RGS1 again showed high sensitivity of 84.3% and specificity of 95% (p=0.0001). These biomarkers were also evaluated by combining them into a single score. A combination of RGS1 plus NR4A2 provided for USpA almost perfect sensitivity of 93.3% and specificity of 100% (p<0.0001).
Conclusions: (1) RGS1 (a modifier of chemokine receptor signaling) and the transcription factor NR4A2 (a known modifier of arthritis inflammation) are highly sensitive and specific SpA biomarkers. (2) SpA patients with or without radiological sacroiliitis displayed drastically different gene expression profiles. The surprising lack of correlation to the duration of disease questions whether USpA and AS are necessarily longitudinally overlapping entities.

P 3

HETEROGENEOUS MICRORNA PATTERN OF AS PATIENTS: ELEVATED MIR-27A AS A NEW BIOMARKER SIGNIFICANTLY DOWNREGULATED BY ENBREL TREATMENT

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Background: To investigate whether microRNA (miRNA) expression altered in AS and the effect of Enbrel treatment.
Methods: PBMCs from 10 healthy controls and 10 active AS patients before and after Enbrel treatment (50mg qw. Subcutaneously) were included in miRNA microarray with 428 miRNA probes. MiRNA expression profile differences between any two of the 3 groups were tested by calibrated value. Candidate miRNAs were performed with Beacon Probe miRNA real time PCR in a larger sample size (n=40 for each group). A fold change of >2 was considered significant. Spearman correlation analysis between miRNAs expression before Enbrel treatment and 16 clinical parameters of patients (BASDAI, BASFI, ESR, CRP, etc) was performed using SPSS13.0.
Results: The miRNA expression pattern of microRNA microarray in AS patients as a single group was heterogeneous. Results discovered 19 significantly differentially expressed miRNAs: 14 expressed higher in AS group than those in controls; 5 expressed lower in AS group than those in controls. 4 most significantly altered miRNAs (>5 folds) miR-17-5p, miR-29a, miR-126-3p and miR-27a were validated by miRNA real time PCR. Four miRNAs miR-17-5p, miR-29a, miR-126-3p and miR-27a expression were significantly higher in patients (Ct value: 7.83±3.67, 7.26±5.18, 3.52±3.76 and 10.97±1.38, respectively) than that in healthy controls (Ct value: 10.68±1.42, 11.06±0.54, 4.61±1.34 and 8.71±3.30, respectively).
Matched fold changes were 7.21, 13.93, 2.13 and 4.76, respectively. Three miRNAs miR-17-5p, miR-29a and miR-126-3p expression were again dramatically downregulated after 12 weeks' Enbrel treatment (Ct value: 9.82±3.62, 8.93±4.73 and 4.88±3.72). Matched fold changes were 3.97, 13.93 and 2.57, respectively). Moreover, elevated mir-27a expression was positively correlated with ESR (r=0.370, P=0.02) and CRP (r=0.358, P=0.02).
Conclusions: AS pathogenesis involved abnormal miRNA contribution. Mir-27a was a valuable biomarker to evaluate inflammation and disease activity in AS patients.

P 4

DISTINCT PROTEOMIC PROFILE IN ANKYLOSING SPONDYLITIS PATIENTS: TALIN1 IS A NEW VALUABLE BIOMARKER FOR DIAGNOSIS AND TREATMENT

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Background: To identify special proteins in peripheral blood mononuclear cells (PBMCs) and sera in AS patients.
Methods: Twenty patients were recruited: AS group (n=8), healthy individual group (n=6) and RA goup (n=6) including their protein and mixed sera respectively. They were age and sex-matched. Proteins were separated from PBMCs by 2-Dimenstional Electrophoresis (2-DE) and analyzed by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) and TOF-TOF mass spectrometry. Real-time RT-PCR was used to validate the proteins in enlarged age- and sex-matched samples of AS (n=30), RA (n=20) patients and healthy individuals (n=30).
Results: Among 1200 protein spots detected on the gels, 10 up-regulated and 3 down-regulated protein spots were found in AS group compared to other groups. Six proteins including Talin1, which were 5-fold up-regulated in AS patients, was identified by MALDI-TOF and TOF-TOF MS. Western blot showed Talin1 in AS, HC and RA group are 1.1411±0.4292, 0.4686±0.2139 and 0.3805±0.1590, respectively. Its expression is higher in AS group than that in HC and RA group (P<0.05). Furthermore, the results of mRNA relative quantity showed that Talin1 expression was significantly increased in AS patients compared to that in healthy individuals and RA patients (9.36±2.20 in AS,1.00±0.24 and 0.97±0.20 respectively, P<0.01). In sera, 10 differentially expressed protein spots were detected. ELISA verified result of CP showed its expression in AS, HC and RA group are 0.2963±0.0650, 0.2035±0.0374 and 0.3295±0.1125 mg/ml, respectively. Transthyretin expression in AS, HC and RA group is 0.0993±0.0197, 0.1544±0.0431 and 0.1077±0.0219 mg/ml, respectively. CP and transthyretin expression is significantly higher in AS and RA group than that in HC group (P<0.05).
Conclusions: Proteomic profile of AS is distinct and talin1 can be used as a useful biomarker for diagnosis and treatment.

P 5

ABNORMAL HIGH-EXPRESSION OF CD154 ON T CELLS OF AS PATIENTS IS DOWN-REGULATED BY THE ENBREL TREATMENT

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Background: To evaluate the expression of costimulatory molecule CD154 on T-cells in peripheral blood from patients with ankylosing spondylitis (AS) and their changes after treatment with Enbrel in a randomized, double-blind, placebo-controlled trial.
Methods: Sixty-six patients with AS (39 cases at active stages and 27 cases at inactive stages; According to the clinical features, they were divided into two groups: 35 cases with axial and peripheral joint involvement and 31 cases with axial involvement alone), 30 patients with rheumatoid arthritis (RA) and 30 healthy volunteers were recruited in this study. The expression of CD154 on CD3+ T cell as well as T-cells subsets were evaluated using flow cytometry.
Results: (1) The CD154 expression on CD3+T cells in peripheral blood in AS patients was significantly higher than that in healthy volunteers and RA patients ($P<0.05$). Frequency of CD3+CD4+ T cell in AS and RA patients was respectively significantly higher than that in healthy volunteers, and frequency of CD3+CD8+ T cell in AS and RA patients were significantly lower than that in healthy volunteers ($P<0.05$). (2) The expression of CD154 on CD3+T cells in peripheral blood in active AS cases or cases with peripheral joint involvement was respectively significantly higher than that in inactive cases or cases with axial involvement only ($P<0.05$), which was positively correlated with tender joint count and swollen joint count ($P<0.05$). (3) Compared with AS patients treated with placebo at 6-week, CD154 expression on CD3+T cells decreased in patients treated with Enbrel ($P<0.05$).
However, there was no significant difference between patients with treatment of Enbrel and healthy volunteers at 6-week ($P>0.05$).
Conclusions: We initially reveal the abnormal high expression level of costimulatory molecule CD154 on CD3+T cells in AS patients and CD154 may be used as a biomarker to assess AS disease activity and the effect of Enbrel.

P 6

SOLUBLE LIGHT: A NOVEL CYTOKINE IN SPONDYLOARTHRITIS

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Introduction: The lack of sensitive biomarkers remains a problem in AS. LIGHT (TNFSF14) is a newly identified member of the TNF superfamily that recruits TRAF2 and TRAF5 leading to release of NFκB and AP-1. By microarray, we have shown that infliximab results in significant reduction in the gene expression of LIGHT in peripheral blood. We estimated the serum level of soluble LIGHT (sLIGHT) in patients with AS and the effect of infliximab treatment on sLIGHT.
Methods: Thirty-six patients and 5 normal controls were studied. The patients had AS (n=15), IBD associated AS (n=16) or PsA (n=5). All AS patients met the NY criteria. All 15 patients with AS received infliximab and were followed up regularly with BASDAI, CRP and ESR. Seven of these patients had received placebo as part of a RCT and were observed for 14 weeks before starting infliximab. Serial serum samples obtained before and after 2 weeks of initiation of infliximab treatment were used for estimating change in sLIGHT (ELISA).
Results: The mean (±SD) sLIGHT values for patients and normal controls were as follows; AS 243.95 (±144.5) pg/ml, IBD/AS 332.47 (±155.7) pg/ml, PsA 430.2 (±252.4) pg/ml and controls 91.62 (±31.2) pg/ml. The sLIGHT level in all spondyloarthritis was significantly higher than controls. sLIGHT was highest in PsA. There was significant ($p=0.001$) decrease in BASDAI, CRP and ESR with infliximab but not with placebo. sLIGHT decreased following infliximab (p=ns). There was strong correlation of the fold-change in sLIGHT with the fold-change in CRP ($R=0.664$; $p=0.007$) and ESR ($R=0.722$; $p=0.002$). There was no correlation with the fold-change in BASDAI.
Conclusion: sLIGHT is elevated in patients with spondyloarthritis. The change in objective markers of inflammation following infliximab is strongly correlated to the change in sLIGHT.

P 7

LINKAGE ANALYSIS OF FAMILIAL ANKYLOSING SPONDYLITIS CONFIRMS A ROLE FOR ARTS1 BUT THE CANDIDATE EXONIC VARIANT K528R IS NOT RELATED TO CYTOKINE RECEPTOR SHEDDING PROFILES

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Introduction: A recent genome-wide association scan reported that ARTS1 is a major non-MHC locus associated with ankylosing spondylitis (AS). ARTS1 has two known functions: (i) promoting shedding of cytokine receptors such as TNFRI, IL-1RII and IL-6R; (ii) trimming peptides for MHC class I-mediated antigen presentation.
Objectives: 1. To assess whether there is excess transmission of ARTS1 alleles in multiplex families with AS. 2. To assess whether the 528R variant correlates with cytokine receptor shedding profiles.
Methods: We genotyped 231 multiplex AS families with two ARTS1 exonic SNPs (rs30187 and rs27044), and performed family-based association analyses. Sera from 80 AS patients (not on biologic treatments) were assayed for sTNFRI, sIL-1RII and sIL-6R by ELISA.
Results: FBAT analysis on our AS families revealed that the exonic variant (rs30187[G]) is associated with AS (dominant model; p-value = 0.012). There was no significant association of the exonic variant rs27044 with AS. The AS cohort for the functional analysis (n=80) had a mean age of 42.31 ± 10.6 years. In this cohort, the ESR (mean 18 ± 15.6 mm/hr); CRP (mean 14.8 ± 18. 8 g/dL); BASDAI (mean 5.3 ± 2.4) had no correlation with the major or minor alleles of rs30187 and rs27044. In terms of serum levels of sTNFRI, sIL1R, and sIL6R, there was no relationship to the respective ARTS1 alleles. There was a significant correlation of sIL-6R with sIL-1RII ($R=0.49$; $p<0.0001$) and with sTNFRI ($R=0.31$; $p=0.007$) but there was no correlation between sTNFRI and sIL-1RII.
Conclusion: This is the first report showing excess transmission of rs30187[G] in multiplex AS families, confirming population studies on the association of rs30187 with AS. However, we observed no relationship between the AS-associated ARTS1 K528R variant and cytokine receptor shedding profiles. Our results suggest that the functional relevance of the ARTS1 K528R variant might relate more to peptide trimming for antigen presentation.

P 8

THE INFLAMMATORY MILIEU AND HLA-B27 EXPRESSION IN ANKYLOSING SPONDYLITIS – IMPLICATION FOR DISEASE PATHOGENESIS

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Introduction: HLA-B27 is strongly linked with the pathogenesis of Ankylosing Spondylitis (AS) and increasing evidence suggests that a minimum threshold of gene expression is necessary to cause the disease. The aim of this study was to outline the influence of the inflammatory milieu in modulating B27 gene expression.
Methods: Twenty different cytokines were used as stimuli on CD14+ PBMNCs from HLA-B*2705+ ASs and NCs, and on HLA-B*2709+ NCs in culture for 72 hours. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, M-CSF, GM-CSF, IP10, MCP-1, MIP-1, IFNs, TGF-b, TNF-α were tested at optimal concentration. HLA-B27 whole molecules were determined at the surface of CD14+ PBMCs by means of ME1 mAb and a cytofluorimetric quantitative technique in Antibody Binding Capacity (ABC) units. Data were expressed as mean ratio of stimulated versus unstimulated cultured cells (TCM only).
Results: A significant increase in B27 expression was observed for IFN-γ (2.9±1.2 p=0.002), IFN-α (1.9±0.3 p=0.041), IFN-β (2.6±0.8 p=0.015), IL-12p70 (2.1±1.2 p=0.041), IL-7 (2.1±0.8 p=0.026), and IL-15 (3.2±1.7 p=0.002). AS B*2705+ PBMNCs showed a trend to major increase in B27 expression compared with B*2705+ and B*2709+ NC. Low variation of B27 expression was observed with the other stimuli (less than 1.5 fold of controls), including TNF-α (p=0.69), even at high concentration (20ng/ml – 360ngl/ml range).
Conclusions: The first steps of transcription are mainly controlled at the promoter region and cytokines are known to be able to activate transcription factors. An initial (infectious? mechanical?) stimulus may trigger the up-regulation of B27 determining more favourable condition for disease onset (antigen driven? unfolded protein response?, others?). The role of TNF-α in the pathogenesis of disease, which is likely to be linked also to individual genetically-determined functional characteristics, may be not directly determinant in modulating B27 expression.

P 9

ANTIGEN SPONDYLITIS MONOCYTES SHOW UPREGULATION OF PROTEINS INVOLVED IN ANTIGEN PRESENTATION

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Introduction: Ankylosing Spondylitis (AS) is an autoimmune inflammatory disease of unknown aetiology. Transgenic rat studies have implicated Monocytes. We wished to quantify differences in protein expression in monocytes between patients with Ankylosing Spondylitis (AS), Rheumatoid Arthritis (RA) and healthy controls.
Methods: The protein expression of CD14 bead purified AS, RA and control monocytes was studied by 2D gel electrophoresis and by quantitative label-free expression profiling. Tryptic digestion of monocyte proteins was followed by nano ultra-performance liquid chromatography coupled to ESI MS/MS mass spectrometry. Data sets were analysed using Waters Expression Profiling System (WEPS) and Ingenuity Pathway Analysis (IPA). *In vitro* proteasomal digests of extended HLA-B27 epitopes were carried out in the presence or absence of the proteasome activator complex PA28.
Results: 2D gel electrophoresis identified the immunoprotasome prtein PA28 as upregulated in some AS patient's monocytes compared to healthy controls. AS and RA monocytes differed in protein expression the healthy controls using IPA. The most significant pathways for both the AS and RA pools, based on numbers of differentially expressed proteins were the Vascular Endothelial Growth Factor (AS:25, RA:24), leukocyte extravasation (AS:39, RA:35), NF-κB (AS:27,25), Integrin (AS:32, RA:36), Jak-Stat (AS:15, RA:16) and Toll-like Receptor signalling pathways (AS:11, RA:10). The only pathway in which a marked difference was observed in the number of differentially expressed proteins between the AS and RA patients was the Proteasome Ubiquitin Pathway. PA28 enhanced generation of HLA-B27 peptide epitopes *in vitro*.
Conclusions: We have combined quantitative label-free proteomics with Ingenuity Pathway Analysis to characterize differential protein expression in AS monocytes. AS monocytes shows significant changes in protein expression compared to matched RA and healthy controls. Our results support a role for proteasome-dependent proteolysis in AS monocytes.
We further demonstrate the utility of novel proteomic techniques in investigating inflammatory rheumatic diseases.

P 10

IL-23 IS NOT ELEVATED IN THE SERUM OR UPREGULATED IN THE PERIPHERAL BLOOD MONOCYTES (PBMCS) OF ANKYLOSING SPONDYLITIS (AS) PATIENTS

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Background: IL-23 has been implicated in the pathophysiology of Psoriasis and Psoriatic Arthritis. However its role in AS has not been clearly determined. A IL-23 receptor polymorphism has been reported to associate with AS and the purpose of this study was to define the role of IL-23 in AS.
Methods: 22 AS patients classified by the modified New York criteria were assessed clinically and 10mls of heparinised blood and 5 mls of serum was collected from each patient.
RNA was extracted from PBMCs and IL-23 expression analysed by Taqman QRT-PCR. Il-23 levels in the serum were measured by ELISA. Standard acute phase response was assessed by measuring CRP. 25 Healthy subjects acted as controls. The study was approved by the local ethics committee.
Results: Detection of IL-23 in PBMCs was considerably lower in the AS pats. compared with controls (p=0.001).Soluble IL-23 was detected in only 2 out of 22 AS patients and 3 out of 11 control subjects. There was no correlation between the IL-23 levels detected and clinical parameters of disease activity in the AS patients or with drug therapy.
Conclusions: In this small group of AS patients, IL-23 does not seem to be upregulated and there is a suggestion that IL-23 expression may be down-regulated when compared with controls. Il-23 may therefore not be a major component of the inflammatory response in AS.

P 11

FREQUENCY AND PHENOTYPE OF TH17 CELLS IN AS PATIENTS AND HEALTHY CONTROLS

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Introduction: T helper cells that produce IL-17 (Th17 cells) have been described as a new lineage of CD4+ T cells and are thought to have key roles in inflammatory arthritis.
Ankylosing spondylitis (AS) is a chronic inflammatory disease in which elevated serum levels of IL-17 have been reported. This study, we compared the frequencies of Th17 cells in AS and healthy controls, and studied the phenotype, chemokine receptor expression and other cytokines produced by Th17 cells.
Materials and Methods: 8-color flow cytometry was used to analyze surface phenotype, cytokine production, and chemokine receptor expression of PBMC-derived T cells from 20 AS and 16 healthy people. We also measured by ELISA secretion of IL-17 into culture supernatants by PBMC.
Results: (1) The percentages of IL-17+CD4+ T cells and IL-22+CD4+T cells were increased in PBMC of AS as compared with healthy controls. The ratio of IL-17+CD4+ T cells to IFN-γ +CD4+ T cells was much higher in AS than in healthy controls ; conversely, the ratio of IL-10+CD4+T cells to IL-17+CD4+ T cells in AS was much lower. (2) IL-17 concentrations in AS supernatants were significantly higher in compared to healthy controls by ELISA. There was a correlation between the percentages of IL-17+CD4+T cells and the amounts of IL-17 in culture supernatants. (3) All Th17 cells were CD4+ and CD45RO+. Most of the Th17 cells expressed both CCR6 and CCR4. However, not all of the Th17 cells expressed the IL-23 receptor. (4) A significant proportion of cells that produced IL-17 also produced IL-22 and IFN-γ but not IL-10.
Conclusions: This study has shown that Th17 cells are significantly more prevalent in PBMC in AS. This supports the hypothesis that IL-17 producing cells contribute to the pathogenesis of AS.

P 12

INTERLEUKIN 17 ACTIVATION IN SMALL INTESTINE IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

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Introduction: The purpose of the study was to investigate the involvement of interleukin 17 (IL-17) in rheumatoid arthritis (RA).
Methods: We studied IL-17 mRNA expression and the number of IL-17 positive cells in duodenal biopsy samples from 12 patients with RA with real-time reverse transcriptase polymerase chain reaction and immunohistochemistry, respectively. 3 duodenal and 3 ileal biopsy samples from patients with ankylosing spondylitis (AS) were analysed for IL-17 mRNA expression. We also measured IL-17 mRNA expression in synovial fluid and peripheral blood derived cells as well as soluble IL-17 concentration in synovial fluid and peripheral blood in patients with RA.
Results: The expression of IL-17 mRNA in duodenal biopsy samples from patients with RA was increased ($p<0.05$). In a subset of biopsy samples from AS patients IL-17 expression was elevated compared to samples obtained from control patients, and the medians in RA and AS patients were equal. We found elevated levels of IL-17 in serum samples taken from early RA patients, but no association with disease activity was seen. Soluble IL-17 was also detectable in 5 of 6 synovial fluid samples studied. The levels of IL-17 mRNA in peripheral blood or synovial fluid derived cells were low or undetectable in both the patients with early or chronic RA.
Conclusion: Our results here support the role of IL-17 in human RA and suggest intestinal activation of IL-17 pathway in both RA and AS. We demonstrate that increased production of IL-17 is seen locally in the synovial fluid from inflamed joints and also in serum from untreated patients with early RA. The source of IL-17 in RA is not the circulating leucocytes, but IL-17 is secreted most likely from the immune cells infiltrating synovium or other inflamed tissues, such as small intestine.

P 13

IDENTIFICATION OF PEPTIDES FROM CHLAMYDIA TRACHOMATIS PROCESSED AND PRESENTED IN VIVO BY HLA-B27 WITH PUTATIVE RELEVANCE IN THE PATHOGENESIS OF REACTIVE ARTHRITIS

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The association of HLA-B27 with spondyloarthropathies, including ankylosing spondylitis and reactive arthritis is one of the strongest between an MHC molecule and a disease.
Chlamydia trachomatis, an obligate intracellular parasite, is a known pathogenetic agent in reactive arthritis. Several bacterial sequences have been proposed as putative HLA-B27-restricted epitopes in the CTL responses of patients with reactive arthritis or have been shown to have high homology with constitutive self-ligands of HLA-B27. In this study we have set up an experimental system to address the issue of whether relevant sequences from individual bacterial proteins can be processed and presented by HLA-B27 *in vivo*. The method is based on the transfection of GFP-bacterial protein constructs into HLA-B27-positive cells, followed by mass spectrometry-based comparison of the HLA-B27-bound peptide repertoires from cells transfected or not with the bacterial protein. Using this approach we have identified Chlamydial peptides which are endogenously processed in a proteasome-dependent way, are presented *in vivo* by HLA-B27 and show molecular mimicry with known self-ligands of this molecule. These findings validate this approach for the mapping of bacterial HLA-B27 ligands with putative relevance in the pathogenesis of reactive arthritis.

P 14

HLA-B27 POLYMORPHISM IN CHINESE HAN POPULATION: A DISTINCTIVE DISEASE SUSCEPTIBILITY OF B*2715 FOR ANKYLOSING SPONDYLITIS

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Background: To investigate the distribution of B27 subtypes in AS patients of Chinese Han population and the association with disease phenotype by using the update B27 subtypes data.
Methods: One hundred AS subjects were recruited randomly from the spondyloarthritis patients' data bank of our department. All the subjects should be independent individuals, and the duplicated sample in the same family would be excluded. Diagnosis of AS was based on the modified New York criteria (1984). Salt fractionation was used to prepare genomic DNA.
Luminex liquid array combining PCR-SSOP was conducted for low resolution of HLA-B genotype typing (AccuPlex™, Dynal-Invitrogen, USA). PCR-SSP was performed for high resolution B27 typing in B27 positive subjects (PEL-FREEZ, Dynal-Invitrogen, USA).
Results: Ninety-eight independent AS patients were recruited by randomization, of which 93 were B27 positive. Therefore the overall positive rate was 94.9%, while in family patients it reached 96%. Three kinds of subtypes were detected in this population: B*2704 (n=76, 81.72%), B*2705 (n=12, 12.9%) and B*2715 (n=5, 5.38%). The mean age at onset for B*2704, B*2705 and B*2715 group was 20.45±4.50 years, 26.67±9.95 years and 17.8±11.12 years, respectively, with a significant difference among groups (c2=7.888, p=0.019). No distinct clinical feature differences were found among these three groups, such as gender, family history of AS, the initial involved joint (axial or peripheral), peripheral joints involved or not, and being sporadic or not. However, the age at onset for B27 negative group and positive group was 28±7.9 years and 21.1±6.2 years respectively, with a significant difference between these two groups (c2=-2.047, p=0.041) and there were no distinct clinical feature differences between them.
Conclusions: A novel subtype B*2715 associated with AS was first identified in Chinese population in our study, which might correlate with age at onset in AS patients. B*2704 is the predominant subtype in AS patients of Chinese Han population, and then, B*2705.

P 15

FURTHER INVESTIGATION OF THREE NON-MHC LOCI ASSOCIATED WITH ANKYLOSING SPONDYLITIS

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Introduction: A whole genome association scan by the Wellcome Trust Case Control Consortium (WTCCC) in ankylosing spondylitis (AS), using 14,500 non-synonymous single nucleotide polymorphisms (nsSNPs), confirmed the strong MHC association and identified two novel associations (ARTS1 and IL-23R). An additional 130 nsSNPS showed at least nominal association and were tested in an independent AS sample to confirm the most significant associations.
Methods: We genotyped 730 unrelated UK AS cases for 93 non-MHC, ARTS1 and IL23R nsSNPS by iPLEX technology (MassArray, Sequenom). Genotype frequencies were compared to the 1958 birth cohort and non AS cases from the WTCCC. nsSNPs in four genes were significant at P<0.0001. For three of these genes we identified tagging SNPs in the gene region using HapMap data. Genotyping of these SNPs in a large number of cases and controls is performed by iPLEX technology to confirm and refine the original associations.
Results: SNPs in SNAPC4, CLSTN3, JARID1A and LNPEP showed association with AS at P<0.0001. Fifty six SNPs, tagging a further 132 in SNAPC4, CLSTN3 and JARID1A gene regions have been selected for genotyping in cases and controls. No further genotyping in LNPEP was done as this gene is in linkage disequilibrium with ARTS1 and the association is likely to be secondary to that of ARTS1. The results of this further genotyping will be presented.
Conclusion: The WTCCC genotyping of 14,500 nsSNPs identified many potential new SNPs outside the MHC for association with AS. We have genotyped a large number of these in an independent sample of AS cases and have replicated the association seen with ARTS1 and IL23R and with a further 4 SNPs. We have investigated the region around these SNPs to confirm and refine the associations.

P 16

LINKAGE TO CHROMOSOME 2Q36 IN AUTOSOMAL DOMINANT ANKYLOSING SPONDYLITIS IN TWO CHINESE PEDIGREES

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Background: To identify genetic mode and candidate region of AS in Han Chinese population.
Methods: We conducted genome wide scans in 8 pedigrees of Han Chinese origin with at least three generations using 384 fluorescent microsatellite markers. Genotyping was performed on an ABI 3700 automated DNA sequencer. Gene mapper 3.0 was used for data collection and microsatellite allele analysis. Pairwise LOD scores were calculated using LINKAGE package. All genotypes were checked for Mendelian segregation in pedigrees. An autosomal dominant model was assumed and the frequency of the abnormal allele was set at 0.003 in view of the prevalence of the disorder, and 85% penetration was assumed. High-resolution mapping was performed based on markers with significant LOD scores. Haplotype was constructed based on crossovers in each family.
Results: Clinical data and genotyping results in 8 pedigrees showed that the inheritance pattern of AS is autosomal dominant. Initial linkage analysis revealed a positive linkage LOD score of 2.07 at marker D2S126 (θ=0) in one pedigree. Fifteen additional markers with heterozygosity >0.75 were selected to conduct fine mapping and narrowed the region to 2q between D2S377 and D2S159. By replicating these markers in 8 pedigrees, positive LOD scores were achieved in another pedigrees and the maximum combined LOD score was 6.44 at marker D2S2228 (θ=0) in two pedigrees. AS patients had axial involvement alone in one pedigree and had both axial and peripheral joint involvement in the other pedigree. By analyzing individuals in which recombination had occurred in both families, haplotype analysis narrowed down the candidate region to a 6-Mb region on 2q36.1-2q36.3 which was shared by these two pedigrees.
Conclusions: This is the first report to confirm a new genetic mode of transmission-autosomal dominance in AS. Linkage to 2q36.1-2q36.3 in two pedigrees may reveal the new disease-causative gene for AS.

P 17

ASSOCIATION OF IL-1 SINGLE NUCLEOTIDE POLYMORPHISMS WITH ANKYLOSING SPONDYLITIS IN THE CHINESE HAN POPULATION

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Background: To investigate polymorphisms of IL-1 complex with AS in the Chinese Han population and to determine whether they were associated with susceptibility/clinical manifestation to AS.
Method: One hundred and three Chinese Han AS patients and 117 ethnically matched healthy controls were genotyped for five single nucleotide polymorphisms (SNPs) (IL1β-511, β+3953, F10.3, RN.4, RN.6/1) and the IL1RN.VNTR, markers previously associated with AS. Allele, genotype, and haplotype frequencies were compared between patients and healthy controls using SHEsis software. The distribution difference of IL-1 gene polymorphisms was also compared in AS patients with different clinical manifestations (coxitis, peripheral arthritis, tendonitis, acute anterior uveitis, BASDAI and age at onset).
Results: We observed significant association of alleles and genotypes of the SNP IL1F10.3 with AS (p=0.008 and p=0.028, respectively). Strong linkage disequilibrium was identified between IL1β-511,IL1β+3953 and RN.4 (D'>0.95). Haplotype construction analysis (6 markers) identified two haplotype TCCTA1C and TCTTA1T could increase disease risk significantly (p=3.32*10-5, OR=4.41, 95%CI=2.1~9.3 and p=0.04, OR=2.16, 95%CI=1.02~4.60, respectively). Two haplotype TCTTA1C and CCTTA1C had a negative correlation to disease risk (p=1.4×10-4, OR=0.23, 95%CI =0.19~0.51 and p=0.005, OR=0.32, 95%CI =0.14~0.74, respectively). Clinical data analysis found RN2.VNTR A2 as a risk factor of peripheral arthritis (p=0.025), and a deviation in the genotype distributions of F10.3 and RN.6/1 was observed in patients with different disease severity (p=0.046 and p=0.02, respectively). No significant association was observed between other polymorphisms and clinical manifestations of patients.
Conclusion: The present study demonstrates that IL-1 gene cluster appears to be a genetic susceptible gene to AS in the Chinese Han population. It also implies IL-1 gene may be involved in the special clinical phenotypes such as disease severity and peripheral arthritis. It is valuable to verify these by extending samples size.

P 18

TWO SYNONYMOUS SNPS IN ARTS1 ARE ASSOCIATED WITH ANKYLOSING SPONDYLITIS IN CHINESE POPULATION

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Background: To ascertain whether ARTS1 is associated with AS in Chinese population.
Methods: The promoter region (3000bp upstream of the first exon), exonic region and exon-intron junctions of ARTS1 gene were sequenced in 30 patients and 30 healthy controls to identify original potential candidate SNPs associated with AS. 203 Han Chinese AS patients and 210 ethnically matched healthy controls were recruited to verify candidate SNPs by PCR-RFLP. Genotype and allele frequencies were tested for Hardy-Weinberg equilibrium.
Genotype and allele differences between cases and controls were evaluated using Fisher's exact test. Linkage disequilibrium test and haplotype analysis were carried out by SHEsis.
Multiple regression was used to evaluate the correlation between associated SNPs and patients' clinical parameters (sex, age, age at onset, sausage-like toes, peripheral arthritis, hip joint involvement, ophthalmia, B27, family history, BASDAI, BASFI, ESR, CRP, etc) using SPSS13.0.
Results: Fourteen potential candidate SNPs were identified in preliminary sequencing. Six SNPs (rs26653, rs27434, rs27640, rs27529, rs26510 and rs27582) were considered in RFLP. Results showed association of 2 SNPs in ARTS1 with AS: (1) rs27434: OR=1.650083, 95%CI: 1.246682~2.184016, MAF: 0.497 in patients vs. 0.375 in controls; P=0.000450; (2) rs27529: OR=0.711462, 95% CI: 0.532491~0.950587, MAF: 0.405 in patients vs. 0.487 in controls; P=0.021170. These two SNPs are in linkage disequilibrium (D'=0.731, r2=0.332). Haplotype analysis noted a higher proportion of GATGTA in cases (OR=1.581 95%CI: 1.115~2.240, P=9.93e-4) and a higher proportion of GGTGTA in controls (OR=0.273, 95%CI: 0.130~0.573, P=2.79e-4). No significance in allele and genotype frequency between cases and controls were observed for other 4 SNPs\. Multiple regression indicated that rs27434 was correlated with age at onset (P=0.015).
Conclusion: An association of ARTS1 gene and AS was observed in Chinese population, with 2 newly identified SNPs. And rs27434 was correlated with age at onset in AS patients.

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ARTS1 VARIANTS ASSOCIATED WITH ANKYLOSING SPONDYLITIS

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Introduction: A strong association between ARTS1 and ankylosing spondylitis (AS) was first reported by the Wellcome Trust case control consortium (WTCCC). ARTS1 is known to be highly polymorphic, therefore we have conducted a series of experiments to identify the primary genetic association(s) arising from this gene. These involve replication and refinement of the original observations, resequencing of ARTS1 to define the full extent of allelic variation and further testing of these alleles in extensive association studies.
Materials and Methods: First, we genotyped 730 unrelated AS cases for 5 ARTS1 SNPs using iPLEX technology. For comparison we used 2879 individuals with unrelated diseases, genotyped for the same SNPs as part of the WTCCC. These results were combined with the WTCCC study for analysis. Statistical significance was tested using the Cochrane-Armitage test of trend. Second, we sequenced the coding regions of ARTS1 in 48 AS cases by dye-terminator direct sequencing. Finally these variants were tested for strength of association with AS in 1500 patients and controls.
Results: All SNPs in the combined replication analysis achieved significance, with rs30187 producing the most significant association (p=4.9x10-9). Thirteen previously recognised exonic SNPs, 8 known SNPs located near exon boundaries and 1 SNP in the 3'UTR were identified in AS patients. In addition we identified 7 novel polymorphisms (3 nsSNPs) in the gene. Thus a total of 29 SNPs were assessed in the extended ARTS1 case-control genotyping study.
Conclusions: We have replicated the association of 5 nsSNPs in ARTS1. We have also identified 7 novel variants in the gene exhibiting a range of associations with AS which will help to identify the primary ARTS1 association(s) in this disease.

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ASSOCIATION OF IL23R AND ARTS1 GENES WITH SUSCEPTIBILITY TO ANKYLOSING SPONDYLITIS AMONG A MEDITERRANEAN/PORTUGUESE POPULATION

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Introduction: Association between ankylosing spondylitis (AS) and two genes, ARTS1 and IL23R, has recently been reported in North-American and British populations. The population attributable risk fraction for ARTS1 in this study was 25%, and for IL23R, 9%. This indicates the reduction in the population prevalence of AS that would occur if the effect of the association concerned were removed from the population. Confirmation of these findings in other ethnic groups has not yet been demonstrated. We sought to test the association between single nucleotide polymorphisms (SNPs) in these genes and susceptibility to AS among a Mediterranean/Portuguese population.
Material and Methods: The study was conducted on 360 AS patients and 284 ethnically matched Portuguese healthy controls. AS was defined according to the modified New York Criteria. Genotyping of IL23R and ARTS1 allelic variants was carried out with TaqMan allelic discrimination assays. Association analysis was performed using the Cochrane-Armitage test as implemented in PLINK, with odds ratios calculated from allelic counts.
Results: A total of 14 nsSNPs markers (8 for IL23R, 5 for ARTS1, 1 for LN-PEP) were analysed. Four markers (2 for IL23R and 2 for ARTS1) showed significant single-locus disease associations, confirming that the association of these genes with AS in the Portuguese population. The strongest associated SNP in IL23R was rs1004819 (OR=1.45, 95% CI=1.14-1.85; p=0.0042), and in ARTS1 was rs27044 (OR=1.29, 95% CI= 1.02-1.63; p=0.032). No association was seen with an SNP in LN-PEP, which flanks ARTS1 and was associated with AS in the British population. The population attributable risk fractions in the Portuguese population for these SNPs are 11% and 8% respectively.

Conclusion: These results show that IL23R and ARTS1 genes are also associated with susceptibility to AS among this Mediterranean/Portuguese population, and that they contribute a significant proportion of the population risk for this disease. (CORPOREA Study Group participation).

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CHARACTERIZATION OF HLA GENETIC POLYMORPHISM IN A PORTUGUESE POPULATION WITH ANKYLOSING SPONDYLITIS

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Introduction: The aim of this study was to characterize the distribution of gene B alleles and B*27 subtypes in Ankylosing Spondylitis (AS) patients from mainland Portugal. Variants from MHC class I and class II were also analysed.
Material and Methods: Patients with AS and healthy controls were matched according to ethnicity. Individuals from both AS and control groups that were positive for HLA-B*27 were defined at allelic resolution by sequence-based typing of exons 2 and 3 of the HLA-B gene. In a randomly chosen sub-group of 43 AS patients and 96 controls, HLA multi-locus A/B/Cw/DRB1/DQB1 haplotype frequencies were estimated using the iterative expectation-maximization (EM) algorithm PyPop.
Results: AS (n=335) patients: 211 males; mean age: 44.5±13 years; mean disease duration: 19.9±12.2 years; healthy controls (n=174). Positivity for B27 was 82% in AS patients; the equivalent figure for the healthy controls was 9.2%. The distribution of B27 alleles is shown in table 1. In the AS group, HLA-ABDRB1 haplotype frequencies were: A*02, B*27, DRB1*01 (5.68%); and A*24, B*27, DRB1*04 or A*02, B*27, DRB1*13 (4.55%). For the control group, we found a frequency of 3.1% for A*01, B*08, DRB1*03 as the most frequent haplotype. The first to be associated with B*27 was A*02, B*27, DRB1*01 (0.31%).
Conclusion: The prevalence of HLA-B*27 in both the AS cohort and in the healthy controls was higher than previously described for a Southern European population. The distribution of B*27 allele subtypes is different in AS patients and healthy controls. This is the first study to perform high-resolution B*27 genotyping in a mainland Portuguese population and therefore can be useful in comparative populational studies. CORPOREA study Group participation.

Table I. Distribution of B27 alleles in Portugal.

	AS (n=130)	Healthy controls (n=16)
B*2705	83.7%	81.2%
B*2702	14.7%	6.3%
B*2704	1.6%	0%
B*2707	0%	12.5%

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DISPARATE FOLDING AND STABILITY OF THE ANKYLOSING SPONDYLITIS-ASSOCIATED HLA-B*1403 AND B*2705 PROTEINS

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Introduction: HlA-B*1403 is associated to ankylosing spondylitis (AS) as B*2705. The latter presents unusual folding properties. The purpose is to investigate the folding, assembly, maturation and stability of HLA-B*1402 (non AS associated) and B*1403, and the relationship of these features with (AS).
Methods: Stable transfectants expressing B*1402, B*1403 and B*2705 were used. Folding rates were estimated from the ratio of unfolded-to-folded heavy chain (HC), immunoprecipitated with specific antibodies, in pulse-chase experiments. HC misfolding was measured as the half-life of Endoglycosidase H (Endo H)-sensitive β2-microglobulin-free HC. Maturation/export rates were measured by acquisition of Endo H resistance. Association with calnexin or tapasin was analyzed by co-precipitation with chaperone-specific antibodies.
Surface expression of HLA heterodimers and free HC was estimated by flow cytometry.
Thermostability of HLA/peptide complexes was assessed by immunoprecipitation with a heterodimer-specific antibody after incubation at various temperatures. HC expression was quantified by Western blot.
Results: B14 folding was faster and more efficient than for B*2705, and similar for B*1402 and B*1403, but some unfolded HC from both B14 subtypes remained in the endoplasmic reticulum with a long half-life. The export rate of B*1402 and B*1403 was slow, and the heterodimers partially dissociated after exiting the endoplasmic reticulum, as revealed by significant amounts of Endo H-resistant and surface-expressed free HC. Both interaction with tapasin and thermostability decreased in the order: B*2705>B*1402>B*1403, suggesting that the B*1402 and, specially, B*1403-bound peptide repertoires were less optimized than that of B*2705.
Conclusion: The folding, maturation and stability of B*1403 differ more from B*2705 than from B*1402. Thus, these features cannot account for the association of only the two former allotypes with AS.

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HLA-B27 HEAVY CHAIN ACCUMULATES IN THE ENDOPLASMIC RETICULUM SELECTIVELY IN DISEASE ASSOCIATED SUBTYPES AND BIND SUBOPTIMAL PEPTIDE REPERTOIRES

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The role of HLA-B27 in the pathogenesis of ankylosing spondylitis (AS) is unknown. HLA-B*2705 shows "aberrant" folding characteristics, being prone to misfold, and this property may be responsible for the association to disease. Since not all B27 subtypes associate with AS susceptibility, we analyzed the effect of subtype polymorphism on the maturation kinetics of HLA-B27 subtypes in an attempt to explain their differential association with AS. The formation of fully assembled B27 complexes was analyzed in C1R cells transfected with HLA-B27 subtypes and mutants mimicking B27 polymorphism by pulse-chase analysis and immunoprecipition either with the monoclonal antibody HC10, wich recognizes MHC class I free heavy chains (HC), or with the conformation-sensitive monoclonal antibody ME1. N-linked glycosylation of heavy chains, was monitored by treatment with Endoglycosidase H (Endo H). The association of B27 heavy chain with tapasin was analyzed by pulse-chase analysis and co-immunoprecipition with the monoclonal antibody PaSta-1, which recognizes human tapasin. Optimization of peptide repertoires was analyzed by thermostability assays.
Although 2m proceeds with β the rate of HC synthesis and the assembly of HC/ similar kinetics in B27 subtypes, they were heterogeneous in their maturation phenotype, some subtypes exiting rapidly the ER, while others remained in a transport-incompetent state.
However the rate of maturation did not correlate with disease association. Only in disease-associated subtypes, except B*2707, most of the heavy chain 2m and subtype polymorphism determined the assembly β failed to bind efficiency. This failure in folding or assembly leads to the retention of B27 HC in the ER and correlates with higher tapasin binding and the presence of suboptimal peptide repertoires.

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HLA-B27 TRANSGENIC RAT OX62+ DCS EXHIBIT MULTIPLE CELLULAR DEFICIENCIES AND THE TOLERIGENIC CD4- SUBSET SUFFERS REDUCED VIABILITY

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Background: Several lines of rats transgenic for HLA-B27 and human β2-microglobulin develop an inflammatory disease that strikingly resembles human SpA. It is hypothesized that disease in HLA-B27-transgenic rats arises as a consequence of interaction between antigen-presenting cells expressing high levels of HLA-B27 and peripheral T lymphocytes, and may result from a rupture of tolerance towards gut bacteria.
Methods: We used 2D PAGE and iTRAQ to compare the protein expression profile of HLA-B27 dendritic cells (DCs) to that of healthy HLA-B7 expressing and nontransgenic (NTG) rat DCs. MHC II surface expression and apoptotic sensitivity were quantified using flow cytometry.
Results: Three protein sets from the proteome analysis were indicative for aberrant cellular processes. First, all proteins involved in protein processing and MHC I assembly were upregulated in B27 DCs, illustrating the higher pressure on the ER due to misfolding of the HLA-B27 heavy chain. Second, all proteins directly influencing actin-dynamics were downregulated. We showed earlier that this not

only influences motility, but also plays an important role in deficient immunological synapse formation. Third, the key thiol protease Cathepsin S involved in MHC II synthesis was downregulated, which led us to quantify RT1-B and RT1-D surface expression. Downregulation concerned both CD4+ and CD4- OX62+ HLA-B27 DC subpopulations and maturation enlarged differences in both population bias and expression intensity. Deficient actin dynamics could also contribute to this lower MHC II surface expression. Study of sensitivity to MHC class II-mediated apoptosis by antibody stimulation showed that compared to NTG, both B7 and B27 CD4+ DC were more prone to apoptosis but did not mutually differ. In contrast, overnight culturing resulted in a higher cell death in B27 than in control CD4- DC, even without antibody stimulation. Interestingly, decreased actin dynamics could also be involved in DC apoptosis.
Conclusion: DCs suffer greatly from HLA-B27 expression, with probable major physiologic implications.

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LEUKOCYTE SIGNALLING PROFILES IN HEALTHY SUBJECTS WITH A HISTORY OF YERSINIA-TRIGGERED REACTIVE ARTHRITIS

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Objective: Reactive arthritis (ReA) is a disease that manifests as a sterile joint inflammation. It is triggered by an extra-articular bacterial infection such as salmonella and yersinia infections in the gastrointestinal tract or chlamydia infections originating from the urogenital or respiratory tract. ReA is in general self-limiting, and most patients will recover within a year. The majority of ReA patients are HLA-B27-positive. However, the precise mechanisms that account for this genetic disease susceptibility are not known. We therefore examined whether there are differences in intracellular signalling in selected signalling pathways in ten HLA-B27-positive healthy subjects who had completely recovered from yersinia-triggered ReA compared with ten HLA-B27-positive and ten HLA-B27-negative healthy individuals.
Methods: Phosphorylation levels of NF-κB p65 and p38 in fresh leucocytes stimulated with TNF (0-100ng/ml) for 1 to 10 min, LPS (0-1000 ng/ml) for 5 to 20 min or MDP (0-1000ng/ml) for 10 to 40 min at 37°C, were determined using phosphospesific monoclonal antibodies in whole blood flow cytometric assay. Similarly, phosphorylation levels of STAT1, STAT3, STAT5, STAT6 and ERK1/2 in fresh leucocytes stimulated with IFN-γ (0-0,5 ng/ml), IL-6 (0-100 ng/ml), GM-CSF (0-5 ng/ml), IL-2 (0-100 ng/ml), IL-4 (0-100 ng/ml) or 5 μM PMA and Ca-ionophore for 5 min at 37 °C were determined. Areas under curve (AUC) values for dose response and time course of NF-κB and p38 phosphorylation and RFU values of STAT1, STAT3, STAT5, STAT6 and ERK1/2 were used in comparison of patients and controls (Mann-Whitney U test).
Results: Phosphorylation levels of the different intracellular signalling molecules in monocytes, lymphocytes and neutrophils did not differ significantly between the subjects with previous ReA and the healthy controls.
Conclusions: The findings demonstrate that the intracellular immune cell signalling profiles of HLA-B27-positive healthy subjects with the history of ReA and those of HLA-B27-positive and –negative healthy subjects are comparable.

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ASSOCIATION OF MARKERS OF BONE- AND CARTILAGE DEGRADATION WITH RADIOLOGICAL CHANGES AT BASELINE AND AFTER 2 YEARS FOLLOW-UP IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: There is a lack on knowledge of factors that reliably can predict radiological changes in patients with ankylosing spondylitis (AS).
Objective: to investigate whether urinary C-terminal cross linking telopeptide of type I (CTX-I) and type II (CTX-II) collagen, as specific biochemical markers of bone and cartilage degradation respectively, are associated with radiological damage and progression, and with bone mineral density (BMD) in patients with AS.
Methods: Eighty three patients with AS (mean (SD) age: 50.4 (12) years, 65% male, mean (SD) disease duration after diagnosis: 16.7 (10) years) who participate in an ongoing cohort study of patients with AS (OASIS: Outcome in Ankylosing Spondylitis International Study cohort) were assessed for urinary CTX-I and –II. Results of both biochemical markers were compared with baseline scores for radiological damage (modified SASSS, primarily reflecting syndesmophyte formation and -growth), and with scores for radiological progression after 2 years follow-up. Markers were also associated with disease activity parameters and bone mineral density (BMD).
Results: Mean duration of complaints was 28.6 years. At that time 54% of patients had signs of radiological damage, and 35% of them showed radiological progression after 2 years. Baseline radiological damage ($\leq$=0.24; $\rho \leq 0.05$) correlated with CTX-II, but not with CTX-I. CTX-II correlated with serological markers of inflammation (ESR ρ=0.29 and CRP ρ=0.30; $p \leq 0.01$), but not with baseline BASDAI or BMD. There was a negative correlation between CTX-I and BMD of the trochanter ($\leq$=-0.31; $p \leq 0.01$) In multivariate analyses CTX-II significantly and independently contributed to explaining variation in radiological damage (standardized $\beta = 0.27$; $\rho = 0.03$) and progression (st. $\beta = 0.27$; $\rho = 0.05$).
Conclusion: In AS, cartilage degradation plays a role in explaining radiological damage and -progression in the spine.

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DKK-1 LEVELS ARE COMPARABLY INCREASED IN PATIENTS WITH AS AND RA, SHOW SIMILAR DECREASES WITH ANTI-TNF THERAPY, AND ARE NOT ASSOCIATED WITH MARKERS OF BONE REMODELING

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Introduction: Preliminary data in patients with AS show that levels of DKK-1 are low compared to RA and healthy controls suggesting that this might account for the propensity to new bone formation in AS. We aimed to 1. Compare DKK-1 levels in a large population of patients with AS compared to controls and active RA. 2. Evaluate correlations between DKK-1 and markers of bone remodeling in AS. 3. Examine the effects of anti-TNF alpha therapy on DKK-1 in AS.
Methods: We studied 126 patients with AS (mean BASDAI 4.3), 41 patients with RA (mean DAS 5.1), and 74 controls. We also assessed DKK-1 in 38 AS patients and 21 RA patients at baseline and 3 months after initiating anti-TNF alpha therapy (etanercept = 17, infliximab = 42). DKK-1 was assayed by ELISA. We evaluated biomarkers of bone formation (C-terminal Pro-peptide of Collagen Type-I (CICP), bone-specific alkaline phosphatase) and resorption (C-terminal telopeptide of type I collagen (Cross-Laps), N-terminal telopeptide of type I collagen (Ntx)) by ELISA. Groups were compared using the unpaired t-test. Pearson correlation was used to analyze associations between DKK-1, bone biomarkers, and clinical indices of disease activity.
Results: Mean serum DKK-1 levels (ng/ml) were similar in AS (24.5) compared to RA (22.0) and significantly greater than in controls (13.0) ($p<0.0001$ for both). Levels were non-significantly higher in female (14.5) than in male (11.2) controls, and in female (23.2) versus male (20.2) RA patients. This was not observed in AS patients (female (24.3) vs male (24.7). Non-significant reductions in DKK-1 levels were noted after treatment with anti-TNF alpha that were comparable for RA (mean change: -1.06) and AS (mean change: -1.8) with no significant difference between anti-TNF alpha therapies. No significant correlations were observed between DKK-1 and bone biomarkers, BASDAI, nocturnal pain, morning stiffness, and CRP.
Conclusions: In contrast to a previous report we show increased DKK-1 in AS that is comparable to RA. Our data does not support a role for DKK-1 in the pathogenesis of new bone formation in AS.

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UTILITY OF THE MODIFIED STOKE ANKYLOSING SPONDYLITIS SPINE SCORE (MSASSS)

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Introduction: Objective evaluation of disease severity in ankylosing spondylitis (AS) is of critical importance in defining the phenotype for genetic studies and in evaluating the outcome of treatments. Validated scores of spinal disease progression potentially offer a useful objective measure of disease severity which may be more robust than other indices. The modified Stoke AS spine score (mSASSS) has been developed as an objective radiographic index of the severity of AS in the cervical and lumbar spine. We wished to assess the reproducibility and utility of mSASSS and its relationship to other markers of disease severity.

Methods: We ascertained 73 patients with AS (disease duration 5-36 years) attending a specialist clinic to compare clinical assessments of disease severity. These included the Bath AS indices of disease activity (BASDAI), function (BASFI), metrology (BASMI); lumbar flexion by the modified Schober test and mSASSS. Clinical measurements were made by 2 experienced physiotherapists and each mSASSS was duplicated by 2 blinded readers. Correlation co-efficients and regression analyses were performed in the software programmes STATS DIRECT and SPSS.
Results: In 37 patients for whom full data were available for each of the assessments mSASSS was moderately correlated with BASMI (r=0.50, p 0.001). In contrast no significant correlation was seen in the subsets of patients with data on mSASSS and lumbar flexion (r=0.2, p=0.2), BASDAI (r=0.19, p=0.2), BASFI (r=0.08, p=0.5).
Conclusions: Even objective measurements of severity of AS are quite poorly correlated. Radiographic scoring systems fail to take account of the posterior spinal elements and may therefore be misleading. The development of more robust radiographic scores is desirable.

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AGREEMENT BETWEEN EVIDENCE AND BELGIAN RHEUMATOLOGISTS' EXPERIENCE ON HLA B27 DETERMINATION IN PATIENTS WITH SPECIFIC IMAGING FEATURES IN ANKYLOSING SPONDYLITIS

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Objective: To develop an evidence-based and experience-based recommendation to the question: "Is the determination of HLA B27 useful for the diagnosis of AS in the presence or absence of specific imaging features?"
Methods: A systematic literature search was conducted during August–October 2007.
Different imaging features used in the different stages of sacroiliitis visible on X-ray, MRI, CT, and ultrasound were evaluated. Whenever possible, sensitivities, specificities, and likelihood ratios of HLA B27 for the diagnosis of AS were calculated. The results were presented to 59 Belgian rheumatologists. Based on the evidence in the literature, which was categorized according to the EULAR evidence hierarchy (1,2), a recommendation was made.
The strength of the recommendation (1,2) was assessed by voting on level of agreement.
Results: Through a combination of MeSH terms and keywords, very few relevant publications were found. Moreover, no single study has yet been performed in which the correlation between HLA B27 status and different imaging features had been studied.
Therefore, a recommendation was made based on experts' opinions. The Belgian rheumatologists made the following recommendation: "Conventional imaging should be performed before HLA B27 determination. HLA B27 determination should be considered in case of doubtful diagnosis of AS (e.g., in the case of negative SIJ imaging). In case of doubtful (stage 1) SIJ imaging, a CT scan or MRI should be performed prior to HLA B27 determination." 74% of the attendees agreed with this recommendation. The category of evidence was deemed "IV," and the strength of the recommendation was deemed "D."
Conclusion: A recommendation on the role of HLA B27 determination for the diagnosis of AS in the presence or absence of certain imaging features in AS was developed using a combination of research-based evidence and expert consensus. Because of lack of evidence, the recommendation is based on experts' opinions.

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WRIST AND HAND INVOLVEMENT IN PSORIATIC ARTHRITIS AND RHEUMATOID ARTHRITIS: AN ULTRASOUND COMPARISON

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Introduction: Very little is known about the possible differences in the involvement of joints and periarticular structures in rheumatoid or psoriatic arthritis (PsA). The main pathological features detected by US in rheumatoid arthritis (RA) are synovitis and bone erosion while, in spondyloarthropathies, entheseal inflammation is the common feature. Tendon involvement is particularly frequent and dactylitis is a typical PsA manifestation.
Aim of the Study: To investigate the features of wrist and hand involvement in PsA and RA.
Materials and Methods: Bilateral ultrasound (US) examination of the wrist and hand was performed, by the same physician, in a group of subjects affected by RA (n=15) and PsA (n=15), using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with a linear probe operating at 14 MHz. We examined radiocarpal, intercarpal, metacarpophalangeal, proximal interphalangeal and distal interphalangeal (DIP) joints and flexor and extensor tendons (both in wrist and hand). The patients were recruited on a time-criteria (the last 15 patients for each diagnosis) from the whole number of subjects referring to the US unit of our Clinic.
Results: US examination showed joint wrist synovitis in 7/15 (46.6%) patients (both in RA and PsA), hand synovitis in 9/15 (60%) and in 11/15 (73.3%) RA and PsA patients respectively. We found DIP joint involvement in only 1 PsA patient, as it was for dactylitis (in a different PsA patient). Bone erosions were present in 7/15 (46.6%) and 5/15 (33.3%) RA and PsA patients respectively. Tendon involvement was present in the 4/15 (26.6%) and 3/15 (20%) in the wrist and 5/15 (33.3%) and 6/15 (40%) in the hand respectively.
Conclusion: We did not observe significant differences in wrist or hand involvement (both in joint and tendon structures) between RA and PsA patients, except for a more frequent involvement of PIP joints in PsA group.

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INTERRELATIONS BETWEEN INFLAMMATORY SPINAL MRI LESIONS AND LOCALIZATION OF AXIAL PAIN, BASDAI IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Objective: To compare inflammatory spinal MRI lesions (IL) in patients (pts) with ankylosing spondylitis (AS) with localization of the axial pain and level of BASDAI.
Methods: We studied 36 pts with idiopathic AS fulfilled the modified NY criteria (22 males and 14 females, median age 26 yrs (range 19-55), median disease duration 8 yrs (range 1.8-24); 34 pts were HLA-B27 positive). The majority (58%) of pts had active AS (median BASDAI 4, range 3,0-5.6) and severe pain in the spine [median (100-mm VAS) 45 mm, range 30-50]; night spinal pain had 22 (61%) pts. T2-weighted sequences with fat suppression were used to detect IL. Calculations of IL were undertaken only in 29 patients in whom tomography of spine in sagittal and axial plane was performed.
Results: Overall 50 MRI were performed in 36 AS pts (30 – thoracic, 12- lumbar and 8 – cervical spine). MRI signs of IL were detected in 35 pts (97%). Calculation of IL changes in separate anatomical structures of spine was made on 41 images performed in 29 pts in 2 planes. The IL exactly corresponded to pain localization (26 of 29 patients; 90%). In 3 patients the localization of MRI changes and pain did not correspond. IL were most commonly detected on tomograms of thoracic spine (average number of changes on one image was 7,1). In lumbar and cervical spine IL were revealed more rarely; (3,7 and 2,1 respectively. Median number of IL (25-75% range and extremes) in 12 patients with low AS activity (BASDAI <40) was 4 (1,8-10,3; 0-23) and in 17 patients with high disease activity (BASDAI >40) was 6 (4-16; 2-28), which did not constitute any significant difference between these patients groups (p = 0,35; Mann-Whitney test).
Conclusions: Inflammatory MRI lesions are observed in 90% pts in the localisation of axial pain. More frequently these findings are observed in thoracic spine. We did not observe any relationship between the number of inflammatory MRI changes and AS clinical activity.

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DISSOCIATION OF CLINICAL SYMPTOMS OF BACK PAIN AND IMAGING FOR SPINAL INFLAMMATION IN A PATIENT WITH ACTIVE ANKYLOSING SPONDYLITIS (AS)

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Introduction: The correlation between disease activity and inflammation in patients with AS has recently been a matter of debate.
Objective: We report on a young patient who presented with increasing spinal stiffness but no pain or high disease activity.
Methods: Based on limitation of spinal mobility and radiographically almost fused sacroiliac joints, the diagnosis of AS was established. Clinical, laboratory and imaging data were collected at different time points (see below).
Results: The patient (34-year-old, male, good general health at presentation) noticed impairment of cervical rotation mainly during car driving, swimming and cycling in the last 5-6 months. All clinical measurements for spinal mobility were pathologically reduced.
Laboratory examinations showed increased CRP (3.5 mg/dl) and ESR (41mm/1h) values and a positive HLA-B27. Conventional spinal radiographs revealed several syndesmophytes and some ankylosis in the cervical and lumbar spine. Spinal MRI at BL showed inflammatory lesions in all spinal segments. The BASDAI was 1, the BASFI 1.7 and the BASMI 5 at baseline. He was treated with celebrex 2x200mg/day and physiotherapy over 4-months.
Celebrex was stopped due to a new onset of Crohn's disease. Spinal inflammation (MRI) was already reduced at this time point but the CRP was still elevated. After successful treatment with infliximab for 8 months, no signs of Crohn's disease could be seen shortly thereafter.
Adalimumab treatment had to be started due to allergic reactions to infliximab and is now continued with no change of the clinical situation. MRI examinations show only some inflammatory lesions. The patient did not have any other clinical symptoms of Crohn's disease also after adalimumab treatment.
Conclusions: Although MRI is a reliable tool for assessment of disease specific activity and inflammatory lesions in AS, there are still patients with high dissociation between clinical symptoms and MRI findings. Imaging, especially MRI, is important for identification of such patients and documentation of the course of disease related inflammation.

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THE NATURAL COURSE OF RADIOGRAPHIC PROGRESSION IN ANKYLOSING SPONDYLITIS-DETAILED ANALYSIS OF A LARGE RETROSPECTIVE COHORT

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Objective: To assess and quantify the natural course of radiographic progression in anti-TNF-α naïve AS patients over longer periods of time in detail.
Methods: 146 AS patients (age 54.2±12y, symptom duration 23.6±11y, 81% male) were retrospectively evaluated. All had complete sets of cervical and lumbar radiographs of at least two time points within 6 years which were read by two readers using the mSASSS in concealed time order. Definite damage or progression was based on the occurrence of syndesmophytes. Growth angles between AS specific features such as syndesmophytes and degenerative features such as spondylophytes were retrospectively analysed for detection of differences in progression over time.
Results: In a mean follow-up period of 3.8±1.7 years (1-6y) and a mean number of consecutive x-ray visits of 2.7 (2-6) per patient, the mean mSASSS increased from 20.5±14.4 at baseline to 24.6±15.9 ($p<0.001$). Analysis of status scores showed syndesmophytes in 27.1% and 12.6% vertebral edges at the anterior and the posterior site, respectively, which increased to 32% and 15.7%, respectively, at follow-up (both $p\leq0.05$ between groups). New syndesmophytes were seen in 60.3% patients. Overall, 153 anterior vertebral edges showed radiographic deterioration, while 99 posterior vertebral edges progressed. This means additional information of 40% of the overall amount of new syndesmophytes after 2 years ($p<0.05$). There only were no differences in progression rates between any baseline characteristics with exception of the amount of syndesmophytes. The mean growth angle of syndesmophytes and spondylophytes was 12.8°±11.6° and 83.1°±19.8°, respectively ($p<0.001$).
Conclusions: The mean mSASSS change after 4 years was higher than expected from other comparable large cohorts. Structural changes at the posterior vertebral edges, which are not assessed by the mSASSS, are common in AS patients. Furthermore, 40% of those syndesmophytes show radiographic deterioration after 4 years. Syndesmophytes can be best distinguished from spondylophytes in AS by using a 45° cut-off of growth.

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THE RELATIONSHIP BETWEEN INFLAMMATION AND NEW BONE FORMATION IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: Spinal inflammation is best detected by MRI and new bone formation by conventional radiography in AS and contribute to decreased spinal mobility and functional impairments.
Objectives: To study whether spinal inflammation at baseline is associated with radiographic progression after 2 years in AS patients treated with anti-TNF-α.
Methods: Spinal MRIs and conventional radiographs were available from 39 AS patients treated with infliximab (n=26) and etanercept (n=13) at baseline (BL) and after a 2-year follow-up (FU). By concentrating on development of new syndesmophytes at vertebral edges (VE) we quantified the degree of structural damage in comparison to baseline spinal inflammation and persisting spondylitis at FU.
Results: Overall, 922 VEs of the cervical and lumbar spine of all patients were analysed.
There was no difference in the proportion of VEs with radiographic damage and VEs with (17.6%) and without (15.6%) spinal inflammation at BL. New syndesmophytes occurred significantly more often in VEs with (6.5%) than without (2.1%) inflammation as detected by STIR at BL vs. 2y-FU ($p=0.002$, OR:3.3 (95%CI:1.5 - 7.4) and $p=0.047$, OR:2.7 (95%CI:1.1 - 7.0)), respectively. The results for the T1-post-Gd sequence were similar. On the other hand, radiographic progression based on the development of new syndesmophytes was seen in 26/922 VEs (2.8%) after 2 years. Of those, 10 VEs (38%) had initially shown signs of inflammation as detected by MRI, while the remaining 16 VEs (62%) had no inflammation at BL ($p=0.006$ between groups). The analysis based on the T1-post-Gd MRI sequences revealed similar results.
Conclusions: Even in patients treated with anti-TNF-α, syndesmophyte formation occurred almost 3-fold more often in regions with MRI-proven spinal inflammation at baseline. This suggests at least in part a link between inflammation and new bone formation. More effective suppression of spinal inflammation may lead to a better inhibition of radiographic progression in AS.

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DEMONSTRATION OF ENTHESEAL THICKENING BY US MAY BETTER DISCRIMINATE INFLAMMATION OF THE ACHILLES TENDON THAN TENDON THICKENING IN SPONDYLOARTHROPATHIES

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Background: Although enthesis is the most affected part of the Achilles tendon (AT) in spondyloarthropathies (SpA), the proximal part of the tendon may be also affected by inflammation or mechanical factors. We aimed to define the best point for measuring AT thickness for the diagnosis of enthesopathies using US.
Material and Methods: US of the AT was performed in 55 spondyloarthropathy patients (SpA) and 46 healthy controls (HC) using a MyLab70 US system (Esaote Biomedica, Genoa – Italy) with a linear probe 6-18 MHz. Following measurements were obtained: 1. Antero-posterior thickness of the enthesis measured at the level of the AT deeper margin insertion into the calcaneal bone on longitudinal median scan (ET) 2. Antero-posterior thickness of the AT obtained 3 cm proximal to ET (TT). The ratio of the ET/TT was calculated.
Results: Both ET and TT were significantly increased in males vs females (mean ±SD for ET: 4.6±0.7 vs. 4,0±0,8 mm, $p<0,001$; TT: 4.5±0.6 vs. 4.2±0.6 mm; $p<0.001$). ET was increased in SpA (4.4±0,8 vs. 4.0±0.8 mm, $p<0.001$), but the TT was similar in both groups. In females, only ET was significantly higher in SpA (ET: 4.2±0.8 mm in SpA vs. 3.7±0.6 mm in HC, $p=0.001$; TT: 4.2±0.6 mm in SpA vs. 4.1±0.5 mm in HC, $p=0.5$). In male SpA, both ET and TT was found similar to HC (ET: 4.7±0.6 mm in SpA vs 4.4±0.8 mm in HC, $p=0.07$; TT: 4.6±0.6 mm in SpA vs 4.5±0.5 mm in HC, $p=0,6$). The number of AT with predominantly entheseal thickening (with enthesis/tendon ratio more than or equal to1) was significantly higher in SpA (females: 31/66 vs. 11/58; $p=0.001$; males: 30/44 vs. 13/34; $p=0.008$).
Conclusions: Achilles tendon thickness differences between genders necessitate referral to gender specific normal values. Entheseal thickening was more frequent than tendon thickening in SpA. Enthesis/tendon ratio may have a better diagnostic value for inflammation than entheseal thickening.

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RELIABILITY OF HIGH-RESOLUTION ULTRASONOGRAPHY IN THE ASSESSMENT OF ACHILLES TENDON ENTHESOPATHY IN SERONEGATIVE SPONDYLOARTHROPATHIES

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Introduction: The present study was mainly aimed at investigating the interobserver and intraobserver reproducibility of US in the assessment of Achilles tendon enthesopathy in patients with seronegative spondyloarthropathies (SpA).
Material and Methods: Twenty-eight patients presenting at the Rheumatology Department of the Università Politecnica delle Marche with a SpA diagnosis according to the European Spondyloarthropathy Study Group criteria were included. Patients female/male ratio was 1.8 (18/10), mean age was 42 (range 25–75) years and mean disease duration was 9 (range 1–35) years. Mean (SD) BASDAI BASFI scores were 32.4 (14.5) and 26.3 (9.2) respectively.
Bilateral Achilles tendon US examinations were carried out independently by three investigators using a MyLab 70 XVG (Esaote Biomedica, Genoa – Italy), equipped with a broadband 6-18 MHz linear probe. Each Achilles tendon was scanned for assessing the presence or absence of US findings indicative of enthesopathy according to OMERACT preliminary definition. The same findings were also scored on a 3-grade semiquantitative scoring system on which investigators reached a consensus prior to the study. Total additive scores per Achilles tendon were calculated.
Results: Moderate to excellent interobserver and intraobserver agreements were found for most of the US findings indicative of enthesopathy according to OMERACT preliminary definition (interobserver agreement: weighted kappa values estimating soft tissue inflammation were 0.656-0.671; kappa values for tissue damage were 0.548-0.613). Similar results were obtained using semiquantitative assessments (interobserver agreement: weighted kappa values estimating soft tissue inflammation were 0.669-0.696; kappa values for tissue damage were 0.597-0.711) (intraobserver agreement: weighted kappa values were 0.816 for soft tissue inflammation and 0.901 for tissue damage).
Conclusion: US assessment of Achilles tendon enthesopathy in patients with SpA, using the OMERACT preliminary definition, was found reliable. Bone irregularity and entheseal hypoechogenicity resulted the most difficult abnormalities find agreement.

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ULTRASONOGRAPHIC ASSESSMENT OF ACHILLES ENTHESITIS IN PATIENTS WITH ANKYLOSING SPONDYLITIS: A PROSPECTIVE FOLLOW-UP UNDER ANTI-TNF THERAPY

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Introduction: Enthesitis is considered as the primary anatomical lesion in ankylosing spondylitis (AS). Evidence of imaging changes induced with anti-TNF drugs in enthesitis treatment is still limited to case reports or small trials. We aimed to investigate the effects of anti-TNF therapy on Achilles tendons in AS patients by ultrasonography (US).
Materials and Methods: US was performed in 44 active AS patients by a blinded rheumatologist to physical examination, using a MyLab70 US system (Esaote Biomedica, Genoa – Italy) with a linear probe 6-18 MHz. Scoring system to evaluate Achilles tendon was previously developed by our group. Achilles tendon, enthesis, retrocalcaneal bursa and calcaneus were investigated for hypoechogenicity, thickness, calcifications, calcifications, erosions and power Doppler signal. Each Achilles tendon was assessed using a grey-scale score (GSS) and power Doppler score (PDS) on a 0-2 semi-quantitative scale and total additive scores (TS) per patient were calculated. Follow-up US examinations were performed in 32 patients 2 months after the anti-TNF therapy, by the same investigator.
Results: Physical examination revealed that ten patients were symptomatic for either Achilles enthesitis or retrocalcaneal bursitis (23%), while 82% of these patients had grey-scale changes on US and 21% had power Doppler signal. Patients with symptomatic enthesitis had higher median GSS, PDS and TS vs. asymptomatic patients [6 (2-11) vs. 2 (0-10) for GSS, p<0.001; 3 (0-11) vs. 0 (0-2) for PDS, p=0.006; 9 (2-22) vs. 2 (0-10) for TS, p<0.001]. After two months of anti-TNF therapy, GSS and TS decreased significantly [4 (0-11) vs. 2 (0-6) for GSS, p<0.001; 4 (0-22) vs. 2 (0-12) for TS, p<0.001], while the decrease in PDS was not significant.
Conclusions: Our results indicate that greyscale US may demonstrate early changes in Achilles enthesitis after only two months of anti-TNF therapy in AS patients.

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ENTHESITIS BY US IS UNASSOCIATED WITH ARTHRITIS IN PSORIASIS

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Introduction: Arthritis can be seen in up to 1/3 of patients with psoriasis. Enthesitis is a predominant feature of spondyloarthropathies and an increased prevalence of enthesitis was previously found in psoriasis patients. However, the association of enthesitis with arthritis is controversial. We aimed to investigate enthesitis in psoriasis by US and compare the enthesitis scores according to the presence of psoriatic arthritis (PsA).
Materials and Methods: Forty-seven psoriasis patients were evaluated by a dermatologist for Psoriasis Area and Severity Index (PASI) and by a rheumatologist for the presence of PsA according to CASPAR criteria. US was performed by another rheumatologist blind to physical examination, using a MyLab70 US system (Esaote Biomedica, Genoa – Italy) with a linear probe 6-18 MHz. The scoring system involved the enthesis of the lower extremities as described in Glasgow Ultrasound Enthesitis Scoring System. All findings were graded semi-quantitatively from 0-2 and a grey-scale score (GSS), power Doppler score (PDS) and a damage score (DS) were obtained. Total additive scores of inflammation (TS) were calculated by adding GSS and PDS. The results are given as median (range).
Results: Thirty-nine percent of psoriasis patients had PsA. GSS, PDS, DS and TS were found similar in patients with or without PsA (PsA vs. without PsA: GSS:7(1-19) vs. 5(2-14); PDS:0(0-5) vs. 0(0-5); DS: 6(0-20) vs. 5(0-15); TS: 8(1-19) vs. 6(3-14)). In multiple regression analysis, GSS was significantly correlated to duration of psoriasis and body mass index (BMI) (r=0.57; p=0.004) but not related to age or initial PASI. DS was also significantly correlated to BMI (r=0.51; p=0.003), independent of the psoriatic activity and duration. Comparison of patients under systemic immunosuppressive therapy and topical therapies or PUVA did not show any differences between the groups.
Conclusions: US findings of enthesitis in psoriasis seem unrelated to the presence of arthritis but is associated with the duration of psoriasis and BMI, suggesting common mechanisms of inflammation of the skin and enthesis in psoriasis.

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DETERMINANTS OF AGE AT ONSET AND STRUCTURAL DAMAGE IN AXIAL SPONDYLOARTHRITIS - RESULTS FROM GESPIC

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Introduction: The objective of this study was to analyse determinants of age at onset and structural damage in patients with axial spondyloarthritis (SpA) of short duration.
Materials and Methods: Patients with axial SpA (n=462) including both AS with a symptom duration of <=10 years (n=236) and non-radiographic axial SpA (i.e. patients with axial SpA yet not exhibiting definite radiographic sacroilitiis) with a symptom duration of <=5 years (n=226) were analysed. All patients participate in the German Spondyloarthritis Inception Cohort (GESPIC), a prospective longitudinal multi-centre cohort on patients with early SpA. Radiographs (sacroiliac joints, n=247; spine; n=179) at baseline were scored by 2 independent readers who were blinded for clinical data.
Results: HLA-B27 but not gender determined age at onset of symptoms which was significantly lower in HLA-B27 positives as compared to HLA-B27 negatives in AS (mean age 28.9 vs. 37.4 yrs; p<0.001) as well as in non-radiographic axial SpA (31.6 vs. 37.7 yrs; p<0.001). Multivariate regression analysis revealed male sex (OR 2.38, 95% CI 1.19-4.73; p=0.014) but not HLA-B27, disease activity or symptom duration to be associated with definite radiographic sacroiliitis, and found a trend for elevated CRP (OR 1.85, 95% CI 0.96-3.56; p=0.066). Similarly, male sex (OR 2.40, 95% CI 1.05-5.51; p=0.039) and elevated CRP (OR 2.59, 95%CI 1.23-5.45; p=0.012) were associated with the presence of at least 1 syndesmophyte in the spine. Male AS patients (n=118) had higher mSASSS scores at baseline as compared to female patients (n=61): mean mSASSS 5.8 vs. 3.1; p=0.025. There was neither an influence of HLA-B27 nor of BASDAI on radiographic damage of the SI joints and the spine.
Conclusion: HLA-B27 determines age at onset in early AS and in non-radiographic axial SpA. Male sex and elevated CRP but not HLA-B27 are associated with structural damage in both SI joints and spine.

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REAPPRAISAL OF THE MSASSS: HOW CAN RELIABILITY BE IMPROVED?

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Introduction: We aimed to examine the frequency and reliability of detection of the different features of the mSASSS to determine if reliability can be improved by (i) excluding infrequent and/or less reliable features, and (ii) incorporation of a damage score for facet joints.
Methods: In stage 1, 4 readers scored the mSASSS of 40 AS patients at baseline and 2 years. Facet joints from C2 to T1 were scored 0 = normal, 3 = joint space narrowing, 6 = ankylosis. Films were paired and read blinded to time sequence and patient. A formal training session was then conducted by a musculoskeletal radiologist that included clarification of definitions for the features scored by the mSASSS. A summary of the consensus definition were made available to all readers during stage 2 when the exercise was repeated in 34 AS patients. Reliability of status and change scores was assessed by Cohen's unweighted Kappa and the ICC.
Results: Stage 1. The percentage of abnormal vertebral corners for the features scored in the mSASSS ranged as follows: squaring (4.1-16.0%), sclerosis (1.1-7.6%), erosions (1.0-1.9%), syndesmophytes (3.9-7.2%), bridging (4.7-8.8%). The frequencies of abnormal facet joints ranged from 18.3 to 33.8%. Reliability of status scores was poor amongst all reader combinations for squaring, erosions, and sclerosis (mean kappa <0.30). One reader pair achieved good reliability for syndesmophytes and all reader pairs demonstrated very good reliability for bridging and facet joint damage (mean kappa 0.66-0.84). Stage 2. Similar frequencies of abnormalities in the vertebral corners were noted as for stage 1. Reliability did not improve following training for any feature with the exception of bridging. Reliability of change score for the mSASSS did not exceed 0.80 for any reader pair for the conventional mSASSS as compared to 2 reader pairs (ICC 0.80 and 0.96) when a simplified mSASSS recording only syndesmophytes, bridging, and facet joint damage was used.
Conclusions: Sclerosis and erosions occur very infrequently and together with squaring are not reliably detected. A simplified mSASSS that scores syndesmophytes and bridging together with damage in the facet joints is more reliable.

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INFLAMMATORY LESIONS OF THE SPINE ON MRI PREDICT THE DEVELOPMENT OF NEW SYNDESMOPHYTES IN ANKYLOSING SPONDYLITIS: EVIDENCE FOR COUPLING BETWEEN INFLAMMATION AND NEW BONE FORMATION

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Introduction: We aimed to test the hypothesis that a vertebral corner that demonstrates an active corner inflammatory lesion (CIL) visible on MRI is more likely to evolve into a de novo syndesmophyte visible on plain x-ray than a vertebral corner which demonstrates no inflammation on MRI.
Methods: MRI scans and plain radiographs were performed in 29 patients recruited into randomized placebo-controlled trials of anti-TNF alpha therapy where MRI was conducted at baseline, 12 or 24 weeks, and 2 years, whilst plain radiography was conducted at baseline and 2 years. A validation cohort consisted of 42 AS patients followed prospectively who had MRI at baseline and plain radiography at baseline and 2 years. Anonymized MRI were assessed independently by 2 readers who were blinded to radiographic findings. The following were compared: 1. The proportion of new syndesmophytes developing from a persistent inflammatory lesion at the corresponding vertebral corner; 2. Proportion of new syndesmophytes developing from a resolved inflammatory lesion at the corresponding vertebral corner; 3. Proportion of new syndesmophytes developing where there is no prior inflammatory lesion.
Results: New syndesmophytes developed significantly more frequently in those vertebral corners with inflammation on MRI at baseline (7/48 (14.6%)) as compared to those without inflammation on baseline MRI (14/282 (5.0%)) regardless of whether the lesion persisted or resolved after anti-TNF treatment (p=0.002) (Table). This was confirmed in the analysis of the prospective cohort where 5 of 43 (11.6%) corners with CIL on baseline MRI developed new syndesmophytes as compared to only 12 of 666 (1.8%) without inflammation on baseline MRI (p=0.001).

	Persistent CIL	Resolved CIL	VC without inflammation
No(%) with New Syndesm	3 (8.8%)	4 (28.6%)	14 (5.0%)
No(%) without New Syndesm	31 (91.2%)	10 (71.4%)	268 (95%)

Conclusions: A syndesmophyte is more likely to develop from a prior inflammatory lesion supporting coupling between inflammation and ankylosis.

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INFLAMMATION IN THE SACROILIAC JOINTS AND SPINE IN ACTIVE AXIAL SPONDYLOARTHRITIS WITHOUT RADIOGRAPHIC SACROILIITIS: BASELINE PATIENT CHARACTERISTICS FROM A CLINICAL TRIAL WITH ADALIMUMAB

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Introduction: To investigate sacroiliacal (SI) joint and spinal inflammation in patients with active, axial Spondyloarthritis (SpA) without radiographic sacroiliitis.
Methods: MRIs of Si joints and spine were conducted at baseline in a 12-week, placebo-controlled trial of adalimumab, with a 40-week open-label extension. Patients with BASDAI≥4 and insufficient response to ≥1 NSAIDs were included. Active SI joint inflammation was scored according to Hermann *et al*. (1), with each SI joint divided into quadrants and with modifications for additional points of intensity for each SI joint (0-34).
Active spinal inflammation was scored by Berlin MRI spine score (0-69). Posterior segments were scored (0 = no inflammation, 1 = inflammation).
Results: Of 37 patients with complete MRI data for SI joints at baseline, 81% had SI joint score ≥1; 78% ≥2, and 22% ≥10. Mean score was 5.9 (0-31). Slightly greater scores were observed in Quadrants II and III for the right (0.9, 0.9) and left (0.8, 1.0) SI joint vs. Quadrants I and IV (left SI joint: 0.5, 0.2; right SI joint: 0.5, 0.6). Twelve patients (35%) also had high intensity of inflammatory lesions. Of 9 patients with complete spinal MRI data at baseline, 66.7% had a spine score ≥1; 33% ≥2, and 22% ≥10. Mean scores were 10.7 (0-58) for the spine; 1.6 (0-9) for cervical spine; 3.2 (0-16) for thoracic spine; and 1.1 (0-8) for lumbar spine. Three patients also had involvement of the posterior spine segments.
Conclusions: The majority of patients with active axial spondyloarthritis without radiographic sacroiliits had inflammatory lesions, and many also had extended SI joint inflammation. A lesser majority had spinal inflammation with involvement of posterior segments. In patients with active axial SpA without radiographic sacroiliitis, baseline inflammation was detected by MRI, comparable to what has been observed for patients with active AS.

Reference:
1 HERMANN KG, *et al*. *Radiologe*. 2004; 44: 217-28.

P 43

COMPARISON OF PERIPHERAL ENTHESAL INVOLVEMENT BETWEEN FORESTIER'S DISEASE AND ANKYLOSING SPONDYLITIS (AS): A POWER DOPPLER ULTRASONOGRAPHY (PDUS) STUDY

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Forestier's disease (FD) is a hyperostotic pathology, characterised by an ossification of enthesis of the spine and extraspinal sites. Sometimes it is difficult to distinguish between this disease and ankylosing spondylitis (AS). We have previously shown by using PDUS, a very frequent involvement of peripheral entheses in AS, with a highly specific inflammatory aspect.
Objective: To describe PDUS entheseal involvement in FD, as compared to that observed in AS.
Methods: Eight patients with FD (Forestier and Rotès-Quérol radiological criteria) and 8 patients with AS (modified NY criteria) and "bamboo" spine were included. PDUS of 6 entheses was performed by an independent investigator blinded to subject's identity. Thickness and/or hypoechogenicity (yes/no), calcifications, enthesophytes and erosions (semiquantitative grading 0 to 3) as well as Doppler signals (PD) at bone insertion (0-3) were recorded.
Results: 96 entheses were examined in each group. In FD 82 of 96 (85%) entheses were abnormal vs. 49 of the 96 entheses (51%) in AS (p<0.001). The most frequent abnormal findings in FD were enthesophytes (54% of entheses vs. 33% in AS; p<0.001), which were also more severe (50% graded as 3, vs. 0% in AS; p <0.001), followed by calcifications (42%). Three FD patients (38%) presented PD signal in 4 enthesis, vs. 5 AS patients (62.5%) in 10 enthesis (grade 2). Among FD with positive PD, 2 had a psoriasis; and in all 3 cases, a diagnosis of AS had been suspected, but not confirmed.
Conclusions: PDUS morphological abnormalities are very frequent in FD, even more than in axial AS, and that severe enthesophytes seem to be a distinctive PDUS feature of FD. A vascularized pattern was also observed in some FD patients, even though not as frequently as in AS, a finding which raises the possibility that some patients could have been misclassified.

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EVALUATION AND IMPROVEMENT OF THE INTRA- AND INTER-OBSERVER RELIABILITY OF POWER DOPPLER ULTRASONOGRAPHY (PDUS) FOR DETECTING, SCORING AND SCANNING ENTHESITIS IN SPONDYLARTHRITIS (SPA) PATIENTS: DEVELOPMENT OF A MULTI-STEP METHODOLOGICAL APPROACH

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Enthesitis is a distinctive feature of SpA, which can be detected by using PDUS (1). However PDUS is considered as an imaging technique highly dependent of operator experience.
Objectives: To develop a multi-steps methodological approach, for improving the reliability of detecting, scoring and scanning enthesitis in SpA patients among a group of sonographers with different level of PDUS experience.
Methods: The study was divided in 3 steps. In step 1, we evaluated the standard reliability of 6 sonographers by scanning bilaterally and twice 5 enthesis of 5 patients. Morphological abnormities in B mode (thickness/echogenicity, calcification/enthesophytes, and erosions) as well as Doppler signal at cortical bone insertion were recorded. In step 2, based on disagreements observed during the first part, we worked on consensus by evaluating 90 PDUS images of enthesitis, by using a dedicated website, and by scanning again 5 patients after a period of 1 month of own training session. Finally step 3 was aimed at evaluating if one year of daily practice would improve the reliability of sonographers by scanning 5 more patients.
Kappa values were used to analyze data.
Results: Reliability of images reading was excellent: intra observer kappa ranged from 0.7 to 1 and mean inter-observer kappa was 0.87). Table shows the improvement of the inter-observer reliability on scanning patients along steps.

mean kappa	step 1	step 2	step 3
Thickness/echogenicity (Y/N)	0.25	0.32	0.57
Calcific/enthesophytes (Y/N)	-0.19	0.46	0.61
Erosions (Y/N)	0.43	0.49	0.56
Vascularization (Y/N)	0.46	0.59	0.76
Vascularization (0-3)	0.43	0.55	0.68

Conclusion: This study shows that the standardization of PDUS technique among sonographers with different levels of experience followed by their personal PDUS practice was associated with a strong improvement in inter-observer reliability for detecting enthesitis in SpA patients. This approach can be proposed to standardize PDUS assessment of musculoskeletal disorders.

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WEBSITE – WWW.SPA-IMAGING.ORG – ILLUSTRATING MR FINDINGS IN SPONDYLOARTHOPATHIES

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Background: Magnetic resonance imaging (MRI) is increasingly used to confirm the early diagnosis of ankylosing spondylitis (AS) and other forms of spondyloarthopathy (SpA). MRI is also suitable to monitor these diseases. The value of MRI may improve by a uniform image interpretation in departments performing MR-scanning. To achieve this, there is a need for easy accessible image examples showing typical disease manifestations, normal findings and differentials at MRI. A website which can be regularly updated is suitable for this purpose.
Purpose: The overall objectives are: 1) to illustrate and describe the typical MRI findings in patients with SpA corresponding to different degree of severity and type of disorder, 2) to show MR changes that may be misinterpreted as SpA and normal findings, and 3) to illustrate the findings by other imaging modalities as they sometimes may be preferable.
Content: Since involvement of the sacroiliac joints always occur in AS and in most other forms of SpA, the website focuses on changes in these joints, illustrating various degrees and location of abnormalities. Normal findings, including normal variation, and diseases that can simulate sacroiliitis are shown for comparison. Spinal MRI changes are dealt with in a similar way and changes in other joints are illustrated briefly.
Usability: Doctors who use MRI to diagnose and monitor SpA can easily acquire knowledge that will promote optimal use of MRI. Patients have the opportunity to acquire knowledge about MRI possibilities and can see the changes on which their diagnosis and treatment are based. The website is presented both in English and Danish languages. For the sake of the patients the website is predominantly in layman's terms. Possible doctor's terms are translated in a word directory. The website is supported by the Danish Association of Ankylosing Spondylitis by awarding the Bechterew prize in 2007 to the authors.

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A METHOD FOR ESTIMATING CHRONIC CHANGES OF THE SACROILIAC JOINT BY MRI

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Introduction: A valid method for grading chronic changes of the sacroiliac joint (SIJ) at magnetic resonance imaging (MRI) is generally lacking. The purposes of this study were: 1) to elaborate and test a grading method based on semi-coronal slice orientation and 2) evaluate the validity of the method compared to conventional radiology (CR).
Materials and Methods: A total of 15 males and 22 females (mean age 37 years (range 16-51 years)) were examined by MRI and CR. The MRI sequences encompassed a semi-coronal T1-weighted (T1) and a T1 fat saturated sequence. The chronic changes assessed were: 1) Erosion and 2) Fatty marrow degeneration (FMD). Each joint was analysed separately (a total of 74 joints) and was divided in an upper and lower iliac and sacral part. On every slice each quadrant was scored dichotomously for the presence of abnormality; one point was added to the erosion score if there was partial ankylosis and two points for complete ankylosis.
Similarly, one point was added if the depth of FMD extended more than one cm beneath the joint surfaces covering more than 1 cm2 of the subchondral area. The sum of scores for all slices indicated the degree of severity. The MRI images were assessed by two viewers and the radiographs by one senior radiologist according to the New York criteria.
Results: The inter-observer agreement regarding erosion, FMD, and the total scores was good. For all parameters 36 of 37 patient were within the 95% limits of agreement with ranges of (-3.6 to 3.9), (-5.1 to 4.5) and (-6.5 to 6), respectively. The corresponding kappa values were 0.89, 0.86 and 0.81. The total MRI scores were significantly related to the radiographic scores ($p<0.01$).
Conclusion: The method seems usable for estimating chronic SIJ changes having a high inter-observer agreement.

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COMPARISON OF RADIOGRAPHIC PROGRESSION IN EARLY AND LATE ANKYLOSING SPONDYLITIS

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Introduction: Radiographic progression in Ankylosing spondylitis (AS) has been studied in patients with longstanding disease, only. Whether the rate of radiographic progression is different at certain stages of disease is unknown.
Materials and Methods: Sixty-three AS patients full-filling the modified New York criteria were enrolled to the study for prospective follow-up. Patients with two visits of at least one year interval were included. Radiographs of cervical and lumbar spine were scored according to mSASSS by an independent reader who was blinded for clinical data and time point of the radiographs. Definite radiographic progression (formation of new syndesmophytes, determined by score 2 and 3) and any radiographic progression (worsening of mSASSS >1 point) was recorded and progression in patients with early (<10 years) AS and longstanding disease were compared.
Results: Radiographs from 63 AS patients (77% HLA-B27 positive) were analysed. Mean (SD) duration of symptoms was 13.6 (±2.6) years and did not differ between groups. Definite radiographic progression was detected in 23 (36%) patients. Mean radiographic follow-up (2.0±3.0 vs. 1,7±1.2 years, respectively) and BASDAI, BASFI, ESR, CRP levels and HLA-B27 status were similar in both groups. Mean mSASSS scores were higher in the longstanding AS group but mean change in mSASSS did not differ significantly (Table I) Progression was more frequent in patients with longstanding disease (Early AS=8/31, 25.8% vs Longstanding AS=15/32, 46.8%; p=0.042).

Table I. mSASSS scores (mean (SD)) at baseline and after 2 years

	Early AS (n=65)	Late AS (n=14)
Baseline	4.52 (7.23)	26.16 (7.0)
Follow-up	8.33 (11.49)	30.23 (23.28)
Change in mSASSS	3.81	4.07

Conclusion: Mean rate of radiographic progression did not differ between AS patients with early and late disease. High mSASSS scores and tendency towards a more frequent radiographic progression in the late stages may implicate the progressive nature and continious formation of new syndesmophytes.

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ENTHESIS ULTRASOUND RESPONSIVENESS IN EARLY SPONDYLOARTHROPATHIES

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Introduction: Enthesis ultrasound (US) has shown to be valid and reliable, but the ability of US to change over a time frame have to be demonstrated and this was the objective of this study.
Materials and Methods: Prospective, blind, longitudinal 6 month study in early SpA. Patients fulfilled the diagnostic classification ESSG criteria. Clinical data was collected. The US MASEI index[1] was used. Smallest detectable change (SDC) and standard response mean (SRM) was calculated. An inter-reader and an inter-explorer was done for reliability.
Results: We analyzed 45 consecutive patients, 34 received only non steroidal anti-inflammatory drugs (NSAIDs). The table shows the six months US score and sub-scores patient's evolution. The SDC was 4.19 for global score, 3.83 for activity sub-index and 1.72 for structural damage sub-index. Using the SDC, 17 (38%) improve the score and 9 (20%) worsened. The SRM was 0.27 for global score, 0.43 for activity sub-index and 0.30 for structural damage sub-index. Using the SMR, 25 (55%) improve and 16 (36%) worsened. Patients that improve had higher MASEI global and activity score ($p<0.01$), erosion ($p<0.05$), Doppler signal and ESR ($p<0.05$) basal values.
The US inter-explorer intraclass correlation coefficients (ICC) was 0.86 and the inter-reader ICC was 0.83.

Table. Longitudinal evolution of ultrasound score.

	Basal	6 Months	p
MASEI score Total	25.96	22.89	0.049*
MASEI score NSAIDs group	25.56	21.91	0.032*
MASEI activity sub-index	13.13	8.62	0.002*
MASEI activity sub-index NSAIDs group	12.38	7.42	0.003*
MASEI structural damage sub-index	12.84	14.24	0.029*
MASEI structural damage sub-index NSAIDs group	13.18	14.50	0.036*

Conclusions: In early SpA ultrasound can be a useful and valid tool to monitoring enthesis responsiveness in a six months period.

Reference:
1 Validity of Enthesis Ultrasound Assessment in Spondylarthropathy. *Ann Rheum Dis* published online 7 Apr 2008; doi:10.1136/ard.2007.084251

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HYPOPHOSPHATAEMIA: AN UNDER-RECOGNIZED CAUSE OF SPONDYLOARTHROPATHY

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Introduction: A 52 year old patient with probable Dent disease had pronounced hypophosphataemia and florid hip joint capsule ossification. For twenty years he was thought to have ankylosing spondylitis (AS) on clinical grounds with the additional finding of minor magnetic resonance imaging (MRI) changes in the sacroiliac joint (SIJ). We therefore studied individuals with other causes of persistent hypophosphataemia for clinical features mimicking AS. X-linked hypophosphataemia (XLH) caused by mutations in the PEX1 gene causes vitamin D resistant rickets. Less commonly appreciated is the widespread enthesopathy which occurs in this disorder which can mimic AS.
Methods: We have identified 4 individuals with XLH attending the Oxford skeletal dysplasia clinic in whom axial skeletal symptoms were prominent. Clinical and radiographic assessments of axial skeletal abnormalities were performed. MRI of the thoraco-lumbar spine and SIJ was undertaken.
Results: One HLA-B27 positive male patient with recurrent iritis aged 52 had severe limitation of spinal movement with ossification of the capsule of both hips grossly restricting movement. The B27 and iritis were felt to be coincidental findings. The second male patient (aged 26) had severe spinal disease and restricted hip movements due to enthesopathy. The other two patients were female; one aged 28 had radicular signs at D10 due to spinal stenosis from ossification of the ligamentun flavum; the other also aged 28 had severe limitation of spinal movement due to enthesopathy. Restricted stature and pronounced bony deformities were apparent in only two of these individuals but all had a positive family history of XLH.
Conclusions: Enthesopathy complicating XLH is common and may affect individuals of either sex. Minor MRI changes in the SIJ may be seen. The clinical features may closely resemble spondyloarthropathy due to other causes but short stature, bony deformities and a positive family history help to discriminate these conditions.

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UNILATERAL SACROILIITIS DETECTED BY QUANTITATIVE BONE SCINTIGRAPHY – DIAGNOSTIC VALUE COMPARED TO BILATERAL SACROILIITIS

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Background: In daily clinical practise unilateral sacroiliitis in quantitative bone scintigraphy is often given a higher diagnostic value for making a diagnosis of axial spondyloarthritis (SpA) compared to bilateral sacroiliits in scintigraphy. However, very limited data is available about the diagnostic value of scintigraphy showing unilateral sacroiliitis.
Methods: We performed a retrospective analysis of patients who have been seen in our rheumatological back pain clinic between August 2004 and May 2007. We screened all patients' charts and identified those patients who had undergone quantitative bone scintigraphy examination for the evaluation of sacroiliitis. A diagnosis of axial SpA or non SpA back pain was made according to the expert's opinion. Sensitivity, specificity and likelihood ratio for scintigraphic sacroiliitis as a diagnostic tool for axial SpA were calculated.
Results: Out of 980 patients who have been referred to our clinic for the evaluation of back pain, in 157 cases (16.0%) a scintigraphy examination of the sacroiliac joints had been performed. Among 73 patients with axial SpA (46 with ankylosing spondylitis and 27 with non-radiographic axial SpA) scintigraphy showed evidence of bilateral sacroiliitis in 35.6% (26/73) while isolated unilateral sacroiliitis was found in 17.8% (13/73). Among 76 patients who had been diagnosed with non-rheumatic back pain (controls) bilateral sacroiliitis as shown by scintigraphy was found in 40.8% (31/76) while isolated unilateral sacroiliitis was found in 9.2% (7/76) resulting in a specificity of 59.2% and 90.8%, respectively. Thus, the likelihood ratio of a positive scintigraphy showing bilateral sacroiliitis was 0.87 while the likelihood ratio showing unilateral sacroiliitis was 1.93.
Conclusion: This analysis confirms a recent analysis (1) that scintigraphy is of very limited value for the diagnosis of axial SpA. Unilateral sacroiliitis is only slightly superior compared to scintigraphy showing a bilateral sacroiliitis and is also associated with a low sensitivity.

Reference:
1 SONG, *et al*. The diagnostic value of scintigraphy in assessing sacroiliitis in Ankylosing Spondylitis - a systematic literature research. *Ann Rheum Dis*. 2008 Jan 29 (Epub ahead of print)

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CHARACTERISTICS OF ANKYLOSING SPONDYLITIS PATIENTS IN THE UNITED KINGDOM

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Introduction: In total 1,983 patients with ankylosing spondylitis (AS) from the UK were recruited for genetic studies. We have recorded the clinical associations in this large patient sample which will be used for future phenotype genotype correlations.
Methods: AS patients of western European origin, fulfilling the New York criteria for AS, were recruited. Clinical details were abstracted from a structured validated questionnaire which included age of symptom onset, presence or absence of uveitis, psoriasis (Ps), inflammatory bowel disease (IBD) - Crohn's disease (CD) or ulcerative colitis (UC). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) were calculated. Associations between continuous variables were assessed with the Student's *t*-test, and between dichotomous variables using the chi-square test. BASDAI and BASFI were uncorrected for disease duration.
Results: 88% of patients are HLA-B27 positive. 41% of patients have uveitis and a younger age of disease onset ([mean±standard deviation] 23.4±9.1 vs. 25.1±10.0, $p=6.0\times10^{-5}$). Average BASDAI is higher in patients with Ps (4.4±2.3 vs. 4.0±2.1, $p=1.0\times10^{-2}$) and IBD (4.6±2.3 vs. 4.0±2.1, $p=1.0\times10^{-5}$) but lower in males (3.9±2.2 vs. 4.3±2, $p=1.0\times10^{-4}$). BASFI is higher in patients with Ps (4.4±2.7 vs. 3.9±2.6, $p=1.0\times10^{-2}$), uveitis (4.1±2.7 vs. 3.9±2.6, $p=2.8\times10^{-2}$) and IBD (4.7±2.6 vs. 3.8±2.6, $p<1\times10^{-5}$). Patients with Ps are more likely to have IBD than those without (24% vs. 16%, $p=8.7\times10^{-4}$) and more likely to have UC (15% vs 10%, $p=1.2\times10^{-2}$). Male patients have more UC (12% vs. 8%, $p=2.4\times10^{-2}$).

Conclusions: It is interesting that patients with AS and Ps are more likely to have IBD as these diseases share significant associations with the IL23R gene. Patients with co-existing Ps and/or IBD are likely to have more severe AS (increased BASDAI and BASFI). AS patients with uveitis have earlier disease onset.

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THE NATURAL COURSE OF RADIOGRAPHIC PROGRESSION IN ANKYLOSING SPONDYLITIS – EVIDENCE FOR NON-LINEAR PROGRESSION IN A LARGE PROPORTION OF PATIENTS

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Background: New bone formation of the spine is pathognomonic in AS. This is best assessed by conventional x-rays.
Objective: To describe the natural course of radiographic progression and to differentiate rates of progression in AS patients.
Methods: 146 AS patients who had never received biologics were retrospectively evaluated. Inclusion criterium was the availability of at least 2 complete sets of cervical and lumbar radiographs within 6 years. Using the mSASSS, two readers quantified the structural changes in concealed time order and assessed different rates of radiographic progression velocity. The association between between baseline characteristics and the degree of progression was also examined.
Results: The mean age of the 146 patients was 54.2±12.3 years and the mean time since onset of AS-related symptoms was 23.6±11.2 years, 81% of the patients were male and 78% were HLA-B27 positive. The mean BASDAI was 4.4±1.9 (range 0.5-7.3) and 58.3% of patients had BASDAI values >4. The mean follow-up time (FU) was 3.8±1.7 years (1-6y). The mean mSASSS change per year was 1.3±2.5 units. However, radiographic progression was not linear since 43% of patients showed a 4-fold higher progression than the mean, and 22.5% had no progression. 'Fast progression' was calculated as a change >5 mSASSS units or >2 new syndesmophytes, 'moderate progression' as change of 2.0-5.0 mSASSS units or <2 new syndesmophytes, and 'slow progression' as change of <2 mSASSS units or no more than 1 new syndesmophyte within 2 years. Only the amount of baseline syndesmophytes was significantly predictive of a later classification.
Conclusions: Radiographic progression in AS is not linear over time in a large group of patients. Different rates and velocities of radiographic progression can be retrospectively identified on an individual level by assessment of new syndesmophytes or change in mSASSS scores every 2 years. Prediction of progression is possible by detection of syndesmophytes at presentation.

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EPIDEMIOLOGY OF HIP INVOLVEMENT IN ANKYLOSING SPONDYLITIS

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Background: Although clinicians recognise hip involvement as an important feature of ankylosing spondylitis, data on the epidemiology, nature of the disease and therapeutic strategies are scarce.
Aims: To describe the epidemiology of hip involvement in ankylosing spondylitis in 2 European countries: Belgium and Spain.
Methods: Two large databases, containing data from 847 Belgian (ASPECT database) and 1421 Spanish (REGISPONSER database) cross-sectionally evaluated AS patients, fulfilling the modified New York criteria for definite AS were merged. In the ASPECT database, hip involvement was defined as current or past hip arthritis. In the REGISPONSER database, hip involvement was defined as pain or limitation of the hips during clinical examination.
Results: One out of four AS patients presented previous or current hip involvement (27% in ASPECT, 24% in REGISPONSER). Patients with hip involvement had significantly worse BASDAI (ASPECT: 5.6 vs. 5.2, p=0.009; REGISPONSER: 4.6 vs 3.9, p<0.001) and worse BASFI (ASPECT: 5.8 vs. 4.8, p<0.001, REGISPONSER: 3.4 vs. 5.2). Patients with hip involvement had also a significant earlier disease onset compared to patients without hip involvement. Other differences are listed in table 1. Also reflecting the hip, 36%, 45% and 19% of patients in ASPECT had normal/mildly, moderately or severely impaired intermalleolar distance and 78%, 12% and 10%had normal/suspicious, mild, moderate/severe damage on conventional radiography of the hip in REGISPONSER.
Conclusion: Hip involvement is a common feature of ankylosing spondylitis involving about one fourth of AS patients. Patients with ankylosing spondylitis have higher disease activity, measured by BASDAI, and an impaired functioning reflected by higher BASFI.

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IS THERE A RELATIONSHIP BETWEEN FUNCTIONALITY AND PRODUCTIVITY IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS? RESULTS FROM THE GO-RAISE STUDY

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Introduction: Patients with ankylosing spondylitis (AS) report significant functional impairment, which could affect their productivity. We wanted to establish the relationship between functionality and productivity in patients with active AS.
Methods: Patients with AS (modified NY criteria: BASDAI and back pain scores each ≥4) were enrolled into a multicenter, randomized, placebo (PBO)-controlled study (GO-RAISE). 356 patients were randomized (1.8:1.8:1 ratio) to receive subcutaneous golimumab (GLM) 50mg or 100mg or PBO q4wks. Endpoints included the change from baseline to wk24 in BASFI and self-reported productivity measured on a 0-10 cm VAS scale. At wk16, PBO or GLM 50mg patients with <20% improvement from baseline in total back pain and morning stiffness entered early escape in a double-blind fashion. All other patients remained on their previous medication until wk24. GLM 50mg or PBO patients who entered early escape had their last observation prior to change in treatment carried forward for the wk24 analyses.
Observed values at wk24 were used for GLM 100mg patients. An ANOVA on van der Waerden normal scores was performed for between-group differences. Spearman's Rank correlation was used to measure the associations between changes in BASFI and productivity at wk24. Regression analysis was used to determine the predicted value of productivity for improvements in BASFI.
Results: GLM 50mg and 100mg groups showed significant (p<0.001) improvements in both BASFI and self-reported productivity at wk24 vs. PBO. There was a positive correlation between change from baseline in BASFI and self-reported productivity at wk24 for all patients (r=0.67, p<0.0001), the GLM 50mg (r=0.68, p<0.0001) and GLM 100mg group (r=0.60, p<0.0001). A significant positive correlation between change from baseline in BASFI and productivity was also evident for PBO (r=0.57, p=0.0001). The regression model showed that a change of one BASFI amounts to a change in the productivity scale of 0.86 (r^2=0.47, p<0.0001) adjusted for treatment.
Conclusions: The GO-RAISE results show a definite relationship between improved functionality and self-reported productivity in GLM-treated AS patients.

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GOLIMUMAB SIGNIFICANTLY IMPROVES PRODUCTIVITY IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: RESULTS FROM THE PHASE 3 GO-RAISE STUDY

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Introduction: We evaluated the impact of golimumab (GLM) on productivity in ankylosing spondylitis (AS) patients.
Methods: GLM was studied in a multicenter, randomized, placebo (PBO)-controlled study (GO-RAISE). 356 patients were randomized (1.8:1.8:1 ratio) to receive subcutaneous GLM 50 mg or 100 mg or PBO q4wks. Patients with AS according to the modified NY criteria (BASDAI and back pain score each ≥4) were eligible. Productivity was measured on a VAS scale (0-10 cm). Change in productivity from baseline to wk16 and wk24 was compared between groups. At wk16, patients in the PBO or GLM 50 mg group who had <20% improvement in total back pain and morning stiffness measures entered early escape in a double-blind fashion. All other patients remained on their previous medication until wk24.
For GLM 50 mg or PBO patients who entered early escape, their last observation prior to change in treatment was carried forward for the wk24 analyses. Observed values at wk24 were used for GLM 100 mg patients. An ANOVA on van der Waerden normal scores was performed for between-group differences.

Results: Patients in the GLM 50 mg, 100 mg, and PBO groups had similar mean ± SD baseline scores of 6.6±2.5, 6.8±2.3 and 6.3±2.5, respectively. Mean improvement in self-reported productivity was significantly greater in the GLM 50 mg group vs. PBO at wk16 (-2.8±3.0 vs. -0.4±2.7; p<0.001) and wk24 (-2.7±3.1 vs. -0.5±3.0; p<0.001), and was also significantly greater in the GLM 100 mg group vs. PBO at wk16 (-2.9±2.9 vs. -0.4±2.7; p<0.001) and wk24 (-2.9±3.0 vs. -0.5±3.0; p< 0.001). The change from baseline in productivity was similar in the GLM 50 mg and GLM 100 mg groups at wk16 and wk24.
Conclusions: AS patients treated with GLM 50 mg and 100 mg had significant improvement in self-reported productivity, with improvement at wk16 maintained through wk24.

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THE PREVALENCE OF ANKYLOSING SPONDYLITIS IN EUROPE

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Objective: To determine the prevalence of ankylosing spondylitis across Europe.
Methods: We carried out a literature review of studies published in the last decade, irrespective language that was listed on PubMed, Cochrane Database, EMBASE and MEDLINE. The key terms included: (first: ankylosing spondylitis, spondylarthropathies, morbus bechterew, spondylitis ankylopoetica), AND (second: prevalence, epidemiology, incidence). Studies with data the prevalence of ankylosing spondylitis in European subjects were included. Review articles and studies from a non European background have been used for further substantiating the literature search, but were excluded from the analysis. Two independent researchers reviewed the titles and abstracts and any differences were agreed by consensus.
Results: Of 13 studies, seven fulfilled the inclusion criteria. Two studies from Norway, and one study each from Bulgaria, Germany, Hungary, one from The Netherlands, and one from the United Kingdom reported prevalence rates for ankylosing spondylitis. These studies reported prevalence rates of 0.05%, 0.08%, 0.11%, 0.15%, 0.19%, 0.23%, 0.45%, and of 0.86%. The overall prevalence for European patients with ankylosing spondylitis were 0.24%.
Conclusion: AS is an inflammatory disease of the spine, with a typical onset in late teenage years. The prevalence of AS in unknown, with current estimates ranging from 0.05% to 0.23% based on data from Hungary and the UK from 1949 and 1977. The findings of this analysis provide a more robust and up to date estimate of the true prevalence of AS. However, overall epidemiological data on AS is scarce. These results may have an impact on the resource planning in different national health services.

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PATIENTS WITH ANKYLOSING SPONDYLITIS ELIGIBILITY FOR ANTI-TNF ALPHA TREATMENT IN THE UNITED KINGDOM

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Background: The anti Tumor Necrosis Factor (TNF) α treatments adalimumab and etanercept have recently been recommended by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom (UK) for the treatment of ankylosing spondylitis (AS). The prevalence of AS has previously been reported to be 0.15%. Recent findings report a mean prevalence of 0.26%.
Objective: To determine the number of AS patients eligible for anti TNF-α treatment in the UK.
Methods: Two independent researchers carried out a literature review of studies and abstracts published in the last decade to identify the overall prevalence of AS. The UK population >18 years of age was identified from the office of national statistics and the proportion of patients eligible for anti TNF-α treatment was estimated according to UK guidelines. We used a linear function to calculate the number of patients eligible for anti TNF-α treatment.
Results: The systematic review of the literature identified a mean prevalence of 0.24%. The adult population >18 years of age for the UK is 47,467,400 people. This results in 113,922 AS patients. The British Society for Rheumatology (BSR) estimates that 38% of these patients are eligible for anti TNF-α treatment. This would result in a potential cohort of 43,290 AS patients eligible for treatment with adalimumab or etanercept. Current calculations used for resource planning in the UK National Health Service (NHS) based on a prevalence of 0.15% estimate 27,056 eligible patients. Resources allocated on the basis of the latter calculation would leave 16,234 AS patients' eligible for anti TNF-α treatment without the necessary funding.
Conclusion: Current estimates appear to underestimate the true number of patients eligible for TNF-α treatment in the UK. This may result in insufficient budget allocation for AS drug therapy, exposing patients to potential suboptimal treatment.

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WORK STATUS, PHYSICAL FUNCTION AND QUALITY OF LIFE IN WORKING-AGE PATIENTS WITH ANKYLOSING SPONDYLITIS

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Introduction: Physical disability and impairment of Quality of Life (QoL) can be major problems in ankylosing spondylitis (AS) patients and result in work disability. Our aim was to determine the relationship between work and QoL in AS patients aged 18-65 years.
Material and Methods: The study was conducted on AS patients defined according to the modified New York criteria. Demographic data were recorded and patients classified by: 1) disease activity – Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), 2) functional repercussion – Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI), 3) QoL – HAQ and SF-36, and 4) radiological severity – mSASSS. Comparisons between working and retired groups of patients were performed.
Results: Among the 224 patients studied, 136 were working (60.7%) and 54 (24.1%) retired. Working patients were younger and had shorter disease duration. The activity, functional/radiological impact of the disease, and QoL parameters were clearly better in the working group (as presented in Table I). Work, after adjusting for sociodemographic, therapeutic and disease characteristics, continued to be positively associated with parameters of wellbeing. Retirement is associated with: increasing age/disease duration; greater physical functional disability as assessed by BASFI (r=0.19; p=0.027), and BASMI (r=0.51; p=0.03); more severe radiological impact as assessed by mSASSS (Pearson=0.86; p=0.018); and greater deterioration of QoL as assessed by HAQ-AS (Pearson=0.51; p=0.037).

Table I.

	Working (n=136)	Retired (n=54)	*p*
Age	40.4 (SD=10.6)	53.7 (SD=7.9)	0.002
Sex	63% male	70% male	ns
Disease Duration	14,6 (SD=10.1)	26.1 (SD=11.5)	0.03
BASDAI	3,9 (SD=2.3)	4.5 (SD=2.3)	0.001
BASFI	3.3 (SD=2.5)	5.2 (SD=2.6)	0.001
BASMI	3 (SD=2.2)	5.6 (SD=2.3)	0.001
HAQ-AS	0,7 (SD=0.5)	1.2 (SD=0.7)	0.001
SF-36	56.9 (SD=18)	48.3 (SD=17.7)	0.005
mSASSS	14.8 (SD=17.2)	32.9 (SD=25.9)	0.001

Conclusion: There are remarkable differences in functional and QoL parameters between the two groups. Disability, disease 'severity', and disease duration, impact on capacity to remain employed in AS.

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FACTORS ASSOCIATED WITH RETURN TO WORK IN PEOPLE WITH ANKYLOSING SPONDYLITIS (AS) RECEIVING BIOLOGIC THERAPY

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Introduction: We have sought associations between demographic and disease-related variables and improvement in work capacity in patients with AS receiving TNF blockade treatment.
Materials and Methods: All patients with AS receiving anti-TNF therapy attending 2 UK hospitals were asked about their work history both "now" (on anti-TNF treatment) and pre-treatment. Data on BASDAI, BASFI and ASQoL scores before and during treatment ("now") were recorded. Statistical significance was assessed using the Wilcoxon sum of ranks test.
Results: Complete data sets were obtained from72 (73.6% male) patients who had received TNF blockade treatment for 3-60 (mean 21.01) months. 28 (38.9%)

patients were receiving Infliximab, 23 (31.9%) Etanercept and 21 (29.16%) Adalimumab. Pre-treatment, 22 were unable to work and 10 were working part-time because of AS. After a mean 21.01 months 5 of the 22 had returned to full- or part-time work and 3 of the 10 part-time workers had progressed to full-time work. Thus, 8 had increased their work commitment whilst 24 had not. Data are shown in Table I. In those who remained in full-time work, the mean days of sick leave improved from 15.6 to 1.76 days (p=<0.0001)

Table I.

	Total pre-treatment (72)	Back to work/ increased (8)	No increase in work (24)
ASQoL	11.11	3.71*	10.84*
BASDAI	6.45	0.97*	2.25*
BASFI	5.89	2.7*	5.01*
Mean age at onset	24.21 (7-60) yrs	18.42 (14-22) yrs	30.82 (8-60) yrs
Mean age at treatment	44.41 (18-64) yrs	40 (27-55) yrs	49.53 (33-63) yrs
Duration of disease	22.47 (4-54) yrs	22.85 (9-43) yrs	21.94 (4-54) yrs
Male/Female	53 /19	7 /1	12 /5

p=<0.05

Conclusions: Increased work capacity is associated with improvement in ASQoL, BASDAI and BASFI. There was a non-significant trend towards improvement with age at onset and age at treatment but not disease duration.

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A TREATMENT OPTION FOR PATIENTS WITH SEVERE ACTIVE ANKYLOSING SPONDYLISTIS: THE COSTS AND BENEFITS ASSOCIATED WITH ETANERCEPT

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Background: Etanercept (ETN) has recently been recommended as a treatment option for adults with severe active ankylosing spondylitis in the UK.
Objective: To examine the costs and benefits associated with long-term treatment of ETN in patients with severe ankylosing spondylitis (AS) in the UK.
Methods: A mathematical model was used to project the long term costs and benefits associated with ETN plus non-steroidal anti-inflammatory drugs (NSAIDs) compared with NSAIDS alone. Individual patient level data from Phase III ETN trials was used to inform the magnitude of initial response. The proportion of responders was estimated using British Society for Rheumatism guidelines. Disease costs were based on a retrospective costing exercise involving patients attending an AS clinic in the UK. A relationship between disease progression (BASDAI and BASFI) and EQ-5D measurements were used to estimate quality adjusted life years (QALYs). Long term disease progression was projected over 25 years using published evidence. Uncertainty was examined using probabilistic sensitivity analyses.
Results: With the majority of results falling below £25k per QALY, this study demonstrates ETN treatment in AS patients in the UK could be considered cost effective. Over the 25 year horizon, patients treated with ETN plus NSAIDs gained 1.58 additional QALYs compared with those receiving NSAID treatment. With an additional cost of £36k the cost per QALY was estimated to be £23k per QALY.
Conclusion: This study provides evidence on the potential cost-effectiveness of ETN plus NSAIDs in adults with severe AS who fail to respond to NSAIDs alone in the UK.

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SICK LEAVE, PRESENTEEISM AND LOSS OF UNPAID PRODUCTION IN PATIENTS WITH ANKYLOSING SPONDYLITIS: IMPACT AND ESTIMATION OF THE SOCIETAL COST

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Introduction: This study describes (1) the influence of AS on sick leave, presenteeism and ability to perform unpaid work and (2) indirect costs for society.

Methods: 135 patients with AS participated a longitudinal observational study (OASIS) and completed the Health & Labour Questionnaire (H&LQ). This validated questionnaire has a recall of two weeks and quantifies disease related sick leave, type and amount of hindrance while being at work and hindrance for unpaid work.
Results: 70% was male, age 49 years, disease duration 15 years. 37/135 (27%) had no work because of official work disability and 71/135 (53%) had paid work of which 15 (21%) also partial work disability. Sick leave occurred more frequent in those with already a partial work disability, (table), also after correcting for disease duration and BASFI. The costs of sick leave and presenteeism over the whole population were €2,657/pt/yr.

Table

	Working, no work disability	Working and partial work disability
Sick leave; n(%)*	6/53 (11.3)	2/14 (14.3)
Days sick; leave/pt/yr; mean (SD)	18.6 (58.7)	18.6 (51.4)
% of hours sick-leave	7.2	7.1
Presenteeism; n(%)*	24/55 (44)	13/15 (87)
Hours presenteeism ; mean/pt/wk (SD)	2.6 (4.6)	7.6 (7.4)
At-work efficiency (VAS 0-10); mean (SD)	7.9 (2.5)	7.1 (2.4)
Extra worked hours to complete unfinished work; mean/pt/wk (SD)	0.8 (2.0)	2.8 (3.8)

* past 2 weeks

Between 10% and 62% of all patients reported hindrance or had not performed planned housekeeping (56%), shopping (45%), jobs around the house (62%), voluntary work (14%) or childcare (18%). Women experienced hindrance more frequently and women (57%) also need more help from formal and informal caregivers than men (38%). The costs associated with informal and formal caregiving mounted to €1930/pt/yr.
Conclusion: Patients with AS that have substantial disease related sick leave, experience inefficiency at work and perform additional work hours to catch up unfinished work. Moreover, patients have hindrances in unpaid tasks and often these have to be taken over by others. The costs associated with paid or unpaid productivity loss are substantial.

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RELATIONSHIP BETWEEN FUNCTIONAL DISABILITY AND BONE LOSS IN SPONDYLOARTHROPATHY PATIENTS

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Introduction: Relationship between functional disability and bone mineral density (BMD) in spondyloarthropathy (SpA) patients were studied.
Materials and Methods: 116 SpA patients (54 ankylosing spondylitis (AS), 31 psoriatic arthritis (PsA), 5 enteropathic arthritis (EA) and 26 reactive arthritis (ReA); 91 rheumatoid arthritis (RA) and 96 healthy controls (HC) were investigated. Groups did not differ in body mass index, comorbidities, congenital predisposition for osteoporosis. SpA group (81M, 35F, mean age 42.81 yrs., SD =12.72) differed from RA (28 M, 63F, mean age 50.14, SD = 11.38) and HC group (32 M, 64F, mean age 48.91 yrs. SD =12.89) by gender and age.
Excluded were persons having metabolic bone diseases or receiving medication effecting bone metabolism (except corticosteroids). BMD was determined at the lumbar spine (LS), and upper part of left and right femur by DEXA. Functional disability of SpA patients were assessed using BASFI, HAQ and spinal mobility (tragus-to-wall distance, lateral flexion, modified Schober's distance, and intermalleolar distance) measurements.
Results: BMD scores of SpA and RA patients did not differ and were significantly lower than HC (p=0.000). No differences were found comparing BMD of AS, PsA, EA, and ReA patients (p=0.000). HAQ correlated with BMD scores of LS (r = -0,185, p=0.08), whereas BMD scores of left and right femur correlated with BASFI (r(left)=-0.256, p=0.006; r(right)= -0.290. p=0.002), HAQ (r(left)=-0.323, p=0.000; r(right)= -0.290, p=000), modified Schober's distance (r(left)=-0.195. p=0.036; r(right)= -0.193, p=0.038), lateral flexion (r(left)= -0.207, p=0.026; r(right)= -0.222, p=0.017), intermalleolar distance (r(left)=-0.292, p=001; r(right)= -0.336, p=0.000), tragus-to-wall distance (r(left)= -0.241, p=0.009; r(right)= -0.242, p=0.009).
Conclusions: Bone loss similar to that of RA patients was found not only in AS but also in PsA, EA, and ReA. Our findings reveal a direct correlation between functional status and BMD of SpA patients, most clearly found at femur sites.

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LOW BONE MINERAL DENSITY IS RELATED TO MALE GENDER AND FUNCTION IN EARLY SPONDYLARTHROPATHIES

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Introduction: Osteoporosis is a well known complication of longstanding Ankylosing Spondylitis (AS). However, data about bone mineral density (BMD) both early in AS and other spondylarthropathies are very scarce. The objective was to determine the value of BMD in early SpA patients and which factors are of influence at a low BMD.
Methods: 131 spondylarthropathy patients with a DEXA of the lumbar spine and hips within 3 years after diagnosis were studied. The outcome measure BMD obtained with DEXA-measurement was defined as three ordinal levels: 1) normal, 2) osteopenia (-2,5< T-score <-1,0) and 3) osteoporosis (T-score ≤2,5). Ordinal logistic regression was used to study univariate and multivariable (backward regression, p-value<0.10) relationships of the variables: gender, age, disease-duration, HLA-B27, CRP, ESR, BASDAI, BASFI, BASMI.
Results: In our cohort 29%/2% of the patients had osteopenia/osteoporosis present in the femur and 30%/8% in the spine. Overall 53% of the early SpA patients had a normal BMD, 38% had osteopenia and 8% had osteoporosis in the femur and/or spine. Univariately; male gender (OR: 4.9; 95%CI 2.1 – 10.9), CRP (OR: 1.0; 95%CI 0.7 – 1.4), BASFI (OR: 1.2; 95%CI 1.0 – 1.4) and BASMI (OR: 1.6; 95%CI 1.3 – 2.0) were significantly associated with a low BMD. Factors retained in the multivariable model; male gender (OR: 3.9; 95%CI 1.7 – 9.3), CRP (OR: 1.0; 95% CI 0.8 – 1.3), BASFI (OR: 1.3; 95%CI 0.9 – 1.3) and BASMI (OR: 1,0; 95%CI 1.0 – 1.6).

Baseline	Characteristics
Male[a]	87 (66)
AS[a]	93 (71)
HLA-B27 pos[a]	97 (75)
Age[b]	37.0 (1.3)
ESR[b]	9.1 (2.6)
CRP[c]	5.0 (2.0-12.0)
BASDAI[d]	4.2 (2.3)
Disease-duration[d]	9 (8.9)

[a]number (percentage), [b]back transformed mean (SD), [c]median (IQR), [d]mean (SD)

Conclusion: Within 3 years after diagnosis 47% of the early SpA patients showed osteopenia or osteoporosis which was significantly associated with male gender, and decreased functional capacity (BASFI and BASMI).

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PANCA, ASCA AND ANTI-OMPC ANTIBODIES ARE PRESENT IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Introduction: About 5-10% of the AS patients suffer from Inflammatory Bowel Disease (IBD) either Crohn's disease (CD) or ulcerative colitis (UC). In asymptomatic AS patients gut inflammation is observed in 25-49%. The presence of antiglycan antibodies to the cell wall mannan of Saccharomyces cerevisiae (ASCA) or antibodies to porin protein C of Escherichia coli (anti-OmpC) are specifically found in CD. These markers rarely occur in healthy controls. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are expressed by the majority of UC patients.
Objectives: To compare prevalence of ASCA (IgA and IgG), pANCA (IgG) and anti-OmpC (IgA) in three groups: patients with IBD, AS and patients with both.
Materials and Methods: Fifty-two AS patients without gastrointestinal complaints were compared with 26 patients with IBD and AS, as well as 50 UC and 51 CD patients matched for age- and sex. IBD was ascertained by clinical, endoscopic and microscopic findings. The UC serological profile was defined as pANCA+ in 1:80, ASCA (IgA or IgG)<25U/ml, anti-OmpC<25U/ml. The serological profile of CD was defined as pANCA- or + in 1:20, ASCA (IgA or IgG)>25U/ml or anti-OmpC>25U/ml.
Results: In 48% of the AS patients without gastrointestinal disease, these serological markers were observed more often than reported in healthy controls (pANCA n=11(21%); ASCA IgA+ n=9 (19%); ASCA IgG+n=4 (8%); Anti-OmpC+ n=10 (19%)). Remarkably, also anti-OmpC, a marker of perforating CD, was positive in 19% of the AS patients. pANCA was more frequently present in AS+UC than in AS alone (OR 8.8, 95%CI (2.0-38.6)), thus being an indicator for IBD-associated spondylarthropathy.
Conclusions: In 48% of the AS patients, without gastrointestinal complaints, serological markers characteristic for IBD are observed. pANCA is more often present in AS+UC than in AS (p=0.004). These results suggest a pathogenic link between AS and IBD, whereas pANCA is an indicator for IBD-associated spondylathropathy in UC-patients.

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ADALIMUMAB (HUMIRA®) EFFECTIVELY PREVENTS UVEITIS FLARES IN PATIENTS WITH ANKYLOSING SPONDYLITIS (AS)

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Objective: To investigate effects of adalimumab on uveitis episodes in AS.
Methods: AS patients with BASDAI≥4 despite ≥1 NSAID received open-label adalimumab 40 mg every other week for 12 weeks (RHAPSODY). History of uveitis (≥1 prior uveitis flare) was documented and characterized as acute (AU) or chronic (persistent uveitis with symptom-free interval <3 months to next relapse). Uveitis episodes within past year prior to baseline were reported as "0 flares," "1–2 flares," or "≥3 flares." Rates of previous flares per 100-patient years (100-PYs) during the past year were calculated using mean of 1–2 flares (1.5) and minimum of ≥3 (3.0) flares. Rate of uveitis flares reported as AEs was calculated as events per 100-PYs. Uveitis flares/100-PYs before vs. during adalimumab therapy were compared.
Results: Of 1,250 patients, 25 (2%) reported 27 AU flares. Of 274 who had a history of uveitis, 23 (8%) reported 25 AU flares. Of 106 patients with symptomatic AU in the past year, 19 (18%) reported 21 AU flares. Of 28 with active AU at baseline, 9 (32%) reported 10 AU flares. New-onset uveitis occurred in 2 males. Of 274 with prior uveitis, 43 had chronic uveitis; 10 flares occurred during adalimumab therapy in this group.

Uveitis flare rates per 100-PYs before and during adalimumab therapy

	Rate of AU flares before adalimumab	Rate of AU flares during adalimumab	Reduction	*p*-value
All patients (n=1,250)	15.0	7.4	–51%	<0.001
History of uveitis* (n=274)	68.4	28.9	–58%	<0.001
Uveitis* in past 12 months (n=106)	176.9	56.0	–68%	<0.001
Symptomatic uveitis* at BL (n=28)	192.9	96.2	–50%	0.001
History of chronic uveitis (n=43)	129.1	71.4	–45%	0.002

*Acute or chronic.

Conclusions: Adalimumab effectively reduced the rate of anterior uveitis flares in AS, including patients with a recent history of AU flares and patients with chronic anterior uveitis.

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CLINICAL FEATURES OF ANKYLOSING SPONDYLITIS IN KOREANS

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Introduction: There have been studies on clinical features of Ankylosing Spondylitis (AS) depending on the race and areas. However, the precise study toward clinical spectrum in a large group of AS has not performed. Therefore, the aim of this study was to determine the clinical profile of AS.
Materials and Methods: A total of 732 men and 98 women with AS were recruited. Clinical data included age, sex, duration of disease, age at onset of AS symptoms, family history of AS, history of uveitis/iritis, peripheral arthritis, enthesitis and HLA-B27 carriage status.
Results: *Demographic features* The mean onset age (SD) was 20.9 (8.1) years. The male to female ratio was about 8:1. Two hundred thirty-six patients (28.7%) were found to be the juvenile onset AS (JoAS). Seven hundred twenty-seven (94.8%) have HLA-B27. Other extra-articular organ involvements such as lung, heart, kidney, and colon are uncommonly seen.
Comparison of clinical features between male and female patients Women had a later age at disease onset. The frequency of uveitis was statistically different (28.2% of men vs. 40.8% of women).

Comparison between JoAS and AoAS JoAS group had more enthesitis than AoAS group. The peripheral arthritis and hip joint involvement were more frequent in JoAS group.
Comparison between HLA-B27 positive and negative patients HLA-B27 positive cases had a significantly younger age of symptom onset (by 5.3 years, p=0.002), more uveitis (p=0.001), and greater hip involvement (p<0.001) than HLA-B27 negative patients.
Conclusion: The clinical features of our patients appeared largely similar to those in other studies, except a few noticeable differences: 1) AS is eight times more common in men than in women, 2) AS patients in Korea had a higher prevalence of peripheral arthritis, 3) female patients had more uveitis than male, 4) JoAS was common in our group.

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ACUTE ANTERIOR UVEITIS IN REITER'S DISEASE (REACTIVE ARTHRITIS)

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Aim of Study: To investigate ocular manifestations - acute anterior uveitis (AAU) in Reiter's disease according to disease form.
Methods: A total of 918 (819 males, 99 females) consecutive pts with Reiter's disease - Rd were treated during the period from 1966 until 2005. The clinical and laboratory data as well as ocular manifestations were analyzed. The diagnosis of AAU was made by an ophthalmologist.
Results: The classic forms of the disease were present in 479 (52%) pts, and two signs in 439 (48%). The age at onset was between 20-39 yrs in 659 (72%) pts. Acute anterior uveitis (AAU) was found in 113 (12.3%) out of 918 pts with Rd. In more than 50% pts it was of a relapsing form, four of them had between 15 and 20 recurrences. The occurrence of AAU depended on the duration of the follow-up: it was present in 31 (5%) pts out of 623 with acute/subacute form of Rd, in 46 (22%) out of 209 with recurrent form and in 31 (42%) out of 86 pts with chronic form of the disease. The appearance of AAU was independent of the severity and the course of articular manifestations. In 18 (16%) out of 113 pts AAU was present before arthritis (in 5 pts from 11 to 22 yrs), in 28 (25%) simultaneously with arthritis and in 66 (58%) pts after arthritis (in five pts after 9 -25 yrs as the only sign of disease). HLA-B 27 antigen was found in 74 (94 %) out of 79 pts with AAU, in 497 (89%) of all pts with Rd and in 11.8% out of 136 control group.
Conclusion: Acute anterioir uveitis (AAU) was present in 12.3% out of 918 pts with Reiter's disease. According to our results, we suggest that AAU appearing in the Reiter's disease and in spondyloarthropathies is an independent event with similar genetic background with spondyloarthropathies and with HLA-B27 antigen as a common genetic marker, but with its own / specific / genetic co/factors.

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THE PATTERN OF ANKYLOSING SPONDYLITIS (AS) IN IBERO-AMERICA (IBA): THE RESPONDIA GROUP REPORT II

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Background: RESPONDIA is an IBA group of rheumatologists interested in SpA whose work started in 2006.
Objective: To describe the demographic and clinical characteristics of patients with AS collected by 85 rheumatologists across Argentina, Brazil, Chile, Costa Rica, México, Perú, Portugal, Uruguay, and Venezuela.
Patients and Methods: This is a cross sectional study including 1099 consecutive AS patients collected between Jan 2006 and Dec 2007. Assessments included demographic and clinical features. Data was stored in the Spanish SpA Registry website.
Results: 75% were males; mean (SD) age at onset was 31 (14) years; 72% had HLA-B27 and 18% family history of SpA. Symptoms at onset: inflammatory back pain (IBP) 840 (76%), peripheral arthritis 483 (44%), neck pain 438 (40%), enthesitis 319 (29%), coxitis 293 (27%), tarsitis 55 (14%) and dactylitis 80 (7%). Mean (SD) time to diagnosis was 8.8 (8.3) years. Baseline data are shown in the Table.
Conclusions: While IBP is the commonest manifestation around 50% of the patients present with or developed peripheral arthritis and/or enthesitis. BASRI score and metrology suggest AS has induced significant structural damage; BASDAI and lab tests indicate the disease is still active, but >10% receive TNF blockers. The role of educational level and diagnosis delay appear important.

Baseline data (n, % or mean SD)

IBP	1057	(96)	NSAID daily	494	(46)
Peripheral arthritis	622	(57)	NSAID on demand	408	(38)
Enthesitis	587	(54)	Sulfasalazine	335	(31)
Buttock pain	614	(56)	Methotrexate	332	(31)
BASDAI	4.5	(3.4)	Glucocorticoids	200	(19)
BASFI	4.8	(2.9)	Infliximab, n (%)	55	(5)
BASRI	8.4	(4.0)	Etanercept	31	(3)
ESR, mm/h	24.7	(20.1)	Adalimumab	8	(1)
CRP, mg/dL	10.2	(21.9)	Married	191	(18)
Modified Schober, cm	2.7	(2.0)	University degree	641	(59)
Chest expansion, cm	2.8	(1.6)	Deficient house living, n (%)	57	(11)
Occiput-to-wall, mean (SD) cm	6.3	(7.7)			

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AGREEMENT BETWEEN EVIDENCE AND BELGIAN RHEUMATOLOGISTS' EXPERIENCE ON THE USE OF DMARDS FOR ARTHRITIS AND/OR ENTHESITIS IN ANKYLOSING SPONDYLITIS

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Objective: To develop an evidence-based and experience-based recommendation to the question: "Is there a place for DMARDs in the treatment of AS patients with peripheral arthritis or enthesitis not responding to NSAIDs?"
Methods: A systematic literature search was conducted during August–October 2007. The following pharmaceuticals were selected for the analysis: sulfasalazine, methotrexate, leflunomide, thalidomide, azathioprine, chloroquine or antimalarials, anakinra, pamidronate, and biphosphonates. Whenever possible, the effect size was calculated. The results of the search were presented to 59 Belgian rheumatologists, analyzed, and discussed. Based on the evidence in the literature, which was categorized according to the EULAR evidence hierarchy (1,2), these rheumatologists developed a recommendation. The strength of the recommendation (1, 2) was assessed by voting on level of agreement.
Results: Through a combination of MeSH terms and keywords, the total number of relevant articles found in PubMed was 360. Eight other articles were identified from reference lists. The search yielded a relatively small number of publications on RCT results (n=11) for the above pharmaceuticals in the treatment of AS. After presentation of the evidence and discussion, the Belgian rheumatologists made the following recommendation: "In case of AS with peripheral enthesitis/arthritis (except hip arthritis) refractory to NSAIDs, corticosteroid injections should first be tried. If they are ineffective, sulfasalazine should be considered for at least 3 months." 73% of the attendees agreed with this recommendation. The category of evidence for advice on corticosteroid use was deemed "IV," and the category for sulfasalazine was "Ib." The strength of the recommendation was deemed "D."
Conclusion: A recommendation on the use of DMARDs in the treatment of arthritis and enthesitis of AS not responsive to NSAIDs was developed using a combination of research-based evidence and expert consensus. There was only a limited amount of evidence available.

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CLINICAL REMISSION IN PATIENTS WITH PSORIATIC ARTHRITIS (PsA) TREATED WITH ADALIMUMAB (HUMIRA®). RESULTS OF THE STEREO TRIAL

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Objectives: To determine percentages of PsA patients who achieve absence of arthritis, psoriasis, or both during 12 weeks of adalimumab therapy.
Methods: In an open-label study (STEREO), patients with PsA (≥3 TJC, ≥3 SJC) despite ≥1 DMARDs received adalimumab 40 mg every other week for 12 weeks, and optionally for another 20 weeks. Evaluations at Weeks 2, 6, and 12 (optional at Week 20) included SJC76 and PGA of psoriasis. Only patients with both arthritis (SJC>0) and symptomatic psoriasis (PGA not "clear") at baseline were included. Remission was both SJC=0 or PGA="clear" together, or either. Remission of psoriatic nail disorder (NAPSI=0) was analyzed for patients who also exhibited nail disorder at baseline.
Results: Of 442 patients, 414 (94%) completed Week 12, and 161 (36%) completed Week 20. 366/442 (83%) had SJC>0 and PGA= not "clear" at baseline. For the 366, baseline PGA was "almost clear" in 76 (21%); "mild" in 84 (23%); "mild to moderate" in 59 (16%); "moderate" in 82 (22%); "severe to moderate" in 46 (13%); and "severe" in 19 (5%). 64% (231/366) exhibited PsA-related nail changes.

Remission during Adalimumab Therapy: Patients with active arthritis and active Ps

	Baseline N=366	Wk 2 N=360	Wk 6 N=355	Wk 12 N=341	Wk 20 N=134
Remission: arthritis SJC=0, n (%)	0	43 (12)	86 (24)	134 (39)	58 (44)
Remission: Ps of the skin PGA= "clear", n (%)	0	16 (4)	46 (13)	48 (24)	49 (37)
Remission: Arthritis + Ps of the skin SJC=0 and PGA= "clear," n (%)	0	1 (0.3)	14 (4)	34 (10)	27 (20)
Remission: psoriatic nail disorder* NAPSI=0, n (%)	0	ND	ND	45 (20)	35 (37)

Observed values.
*only for patients with baseline NAPSI>0 (n=231); ND=not done.

Conclusions: Adalimumab provided clinical remission of arthritis, psoriasis, and psoriatic nail disorder in a clinically relevant percentage of PsA patients.

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ANTI-TUMOUR NECROSIS FACTOR IN ANKYLOSING SPONDYLITIS: TREATMENT LESS EFFECTIVE THAN IN PUBLISHED TRIALS

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Background: Infliximab, etanercept and adalimumab have all been shown in randomised, controlled trials to be effective and safe in the treatment of AS. The prediction of likelihood of response to treatment is an area in which the evidence is weaker. There is clearly a need for further investigation here, along with clinical audit to evaluate efficacy of anti-TNF agents in a non-trial, patient population.
Methods: A retrospective audit was performed to evaluate the outcomes for all patients treated with Anti-TNFs at one specialist rheumatology centre in Scotland. Data was extrapolated from clinical notes in which outcome scores were routinely recorded at follow-up appointments. BASDAI improvement at 3 and 6 months was considered the primary outcome. BASFI, Pain Score, Patient Global Assessment, Physician Global Assessment, ESR and CRP and the proportion of subjects achieving ASAS 20, 40, 50 and 70 responses was also examined.
Results: 32 patients were included. There were 22 males and 10 females. The mean age of females was 47.3 years and the mean age of males was 45.0. The mean duration of disease was 17.4 years. The mean BASDAI change at 3 and 6 months were 2.21cm (32.8%) and 2.34cm (37.2%), respectively; and the proportion of subjects reaching BASDAI 50 was 39.1% and 31.2% at 3 and 6 months. All outcomes indicated improvement over the first six months of treatment, in some cases by up to 50%, and 41.7% of treatments resulted in an ASAS 20 response. Scatter-graphs for each predictor versus outcome showed no obvious relationships and the 2-sample *t*-tests for difference in BASDAI change between CRP positive and CRP negative, and short disease duration and long disease duration were not significant.
Conclusions: The results of this audit show that anti-TNF therapies are moderately effective in a hospital outpatient setting. More than a third of patients responded well. However, compared with published trial results, the responses to anti-TNF therapy were less impressive.
No convincing evidence of a predictor-response relationship was found.

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EFFICACY OF ADALIMUMAB IN THE TREATMENT OF PATIENTS WITH AXIAL SPONDYLOARTHRITIS (SpA) AND NO RADIOGRAPHIC SACROIILITIS: CONTINUOUS ADALIMUMAB (HUMIRA®) THERAPY IS NECESSARY TO PREVENT RELAPSES AFTER TREATMENT WITHDRAWAL

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Objectives: To assess duration of ASAS40 and ASAS partial remission in early axial SpA patients after therapy withdrawal at Week 52; to assess response rates of patients who were treated again with adalimumab after relapse.
Methods: Of 46 patients enrolled, 23 (52% male; mean age, 32 years [range 24–45]; mean disease duration before treatment, 4 years [range 1–10]; 74% HLA-B27+) sustained a major response after 1 year of adalimumab 40-mg eow therapy (mean BASDAI, 1.24±0.9).
Adalimumab was discontinued in these 23 patients and followed up for 1 year without adalimumab treatment. In case of flare (ie, no longer reaching an ASAS40), adalimumab 40-mg eow therapy was started again. 12-week results of this second treatment period for this group of good responders are reported here.
Results: Over the 1-year period without treatment, 19 of 23 (83%) of initial ASAS40 responders had a renewed increase in disease activity (BASDAI 4.8±1.68); 4 of 23 (17%) had maintained their responses. Mean duration of ASAS40 until flare was 14.8 weeks (range 3–27). Nine of the initial 46 (19.6%) reached ASAS partial remission after 52 weeks of adalimumab; 7 of these 9 patients (78%) relapsed during the 1-year observation period without treatment. After restart of adalimumab, 9 of 18 (50%) reached ASAS40 and 4 of 18 (22.2%) attained ASAS partial remission after 12 weeks. In one patient, adalimumab was not re-started because of planned pregnancy.
Conclusions: In 23 patients with early axial SpA who had achieved a good response after 52 weeks of adalimumab, the majority (83%) had a relapse when adalimumab was discontinued. 17% remained in a low state of disease activity over 1 year after withdrawal. When adalimumab was reinstituted, not all relapsed patients responded to re-treatment after 12 weeks. Continuous therapy with adalimumab appears to be necessary to prevent relapses.

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ADALIMUMAB (HUMIRA®) IS EFFECTIVE IN TREATING PATIENTS WITH ADVANCED STAGE OF ANKYLOSING SPONDYLITIS (AS)

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Objective: To evaluate the effectiveness of adalimimab in patients with advanced AS.
Methods: AS patients with BASDAI≥4 despite ≥1 NSAID received adalimumab 40 mg every other week plus standard antirheumatic therapy in a 12-week, open-label study. Investigators documented baseline presence of advanced ankylosis, defined as at least Stage IV (>2 spinal segments=13 to 19 vertebrae). For patients with advanced ankylosis, the investigator provided information about presence of syndesmophytes or fusion for each of 23 intervertebral units (C2/3 to L5/S1). Only patients with radiographs available for all 3 spinal segments were included. Effectiveness parameters were BASDAI50, BASFI, BASDAI, BASMI, duration of morning stiffness (BASDAI variable), PaGA of disease activity, and patient's assessments of total back pain (TBP) and nocturnal pain (Noct P).
Results: Of 1,250 patients, advanced AS was present in 330 (27%) and absent in 897. In 72 of 116 with information about all three spinal segments, advanced AS

was documented: Presence of syndesmophytes or fusion of 13–19 (Stage IV) and 20–23 vertebrae (Stage V) was reported for 31 and 41 patients. Median percentage of complete fusion across all 23 intervertebral units was 36% (Stage-IV patients) and 78% (Stage-V patients).

Adalimumab in Patients with/without Advanced Stage AS

	Definitely Advanced AS (n=72)	Not Advanced AS (n=897)
ASAS20 (%)	63	71
ASAS40 (%)	51	54
BASDAI 50 (%)	63	57
BASDAI [0–10]*	–3.4 (2.6)	–3.3 (2.3)
BASFI [0–10]*	–2.1 (2.5)	–2.3 (2.3)
BASMI [0–10]*	–1.1 (1.5)	–0.9 (1.5)
Morning stiffness [0–10]*	–3.4 (3.0)	–3.7 (2.7)
PatGlobal [0–100]*	–38 (29)	–35 (30)
TBP [0–100]*	–32 (29)	–33 (28)
NoctP [0–100]*	–34 (32)	–35 (30)

Observed values.
*Mean change from baseline (SD).

Conclusions: After 12 weeks of adalimumab, patients with advanced ankylosis achieved improvements in AS similar to those achieved by patients without advanced ankylosis.

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PREDICTORS OF GOOD CLINICAL RESPONSE (BASDAI 50 OR ASAS PARTIAL REMISSION) IN 1,250 PATIENTS TREATED WITH ADALIMUMAB (HUMIRA®) FOR ACTIVE ANKYLOSING SPONDYLITIS (AS)

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Objective: To identify predictors of good clinical response (GCR) in AS.
Methods: AS patients with BASDAI ≥4 received ADA 40 mg every other week plus standard antirheumatic therapies in a 12-week, open-label study (RHAPSODY). GCR was 50% improvement in BASDAI, or achievement of ASAS partial remission (PR). Possible Week-12 predictors were selected a priori. Continuous variables included age, duration of AS, BASFI, BASDAI, CRP, ESR, BASMI, morning stiffness (BASDAI variable, 0–10), both PhGA and PAGA of disease activity, and total back pain. Categorical variables included male sex; HLA-B27+; ≥1 swollen joint; ≥1 inflamed enthesis; IBD symptoms; psoriasis symptoms; history of uveitis; prior anti-TNF therapy; systemic use of ≥1 NSAIDs, of ≥1 DMARDs, and ≥1 glucocorticoids. Logistic regression with backward elimination was used to identify predictors.
Results: 1,159 of 1,250 patients (92.7%) completed Week 12. At Week 12, ASAS20, ASAS40, BASDAI 50, and ASAS PR response rates were 70%, 54%, 57%, and 28% (observed). Logistic regression revealed 5 identical predictors for BASDAI 50 and PR and 1 additional predictor for each parameter (Table).

Odds Ratios (OR) for BASDAI 50 and Partial Remission (PR) at Week 12

Predictors	BASDAI 50 OR	BASDAI 50 95% CI	BASDAI 50 p-value	PR OR	PR 95% CI	PR p-value
Age [decades]	0.76	0.68–0.85	<0.001	0.67	0.58–0.78	<0.001
HLA-B27+*	1.71	1.22–2.41	=0.002	2.09	1.34–3.26	=0.001
CRP [mg/dl]	1.23	1.15–1.32	<0.001	1.20	1.13–1.29	<0.001
Prior anti-TNF therapy*	0.36	0.27–0.48	<0.001	0.31	0.21–0.46	<0.001
BASFI	0.89	0.83–0.96	=0.002	0.77	0.72–0.83	<0.001
Total back pain	0.99	0.99–1.00	=0.023	—	—	—
BASMI	—	—	—	0.92	0.85–0.99	=0.029

*Yes *vs*. no.

Conclusions: RHAPSODY identified several predictors of good clinical response in patients with active AS after 12 weeks of adalimumab therapy: younger age, greater CRP concentration, lower BASFI, HLA-B27+, and no history of anti-TNF therapy.

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EXERCISE IN ANKYLOSING SPONDYLITIS: DISCREPANCY BETWEEN RECOMMENDATIONS AND REALITY

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Introduction: The ASAS/EULAR recommendations for management of ankylosing spondylitis (AS) identifies exercise as the cornerstone of comprehensive management of AS.
The purpose of this study was to examine patients' perceptions of exercise and to determine the type and extent of exercise/physical activity used by the AS population.
Methods: The Exercise Benefits and Barriers Scale (EBBS) and an exercise inventory questionnaire were administered to AS patients attending the spondylitis clinic of a large teaching hospital. Benefits and barriers subscales of the EBBS were analyzed to identify the degree of perceived benefits of, and barriers to, exercise. Higher benefits scores (range 29-116) indicate a more positive perception of exercise. Higher barriers scores (range 14-56) indicate a greater perception of barriers to exercise.
Results: Sixty-one patients (46 males) with AS completed the questionnaires. Mean age was 38.0 years, and mean disease duration was 14.7 years. The mean benefits EBBS score was 87.1±12.5. Most frequently reported benefits of exercise were "exercising increases my level of physical fitness" (96.4%) and "exercise improves functioning of my cardiovascular system" (96.4%). The mean barriers EBBS score was 29.2±5.3, and the most frequently reported barrier to exercise was "exercise tires me" (71.4%). Walking (twice/week or greater), and home stretching (twice/week or greater) were the most commonly reported types of exercise; however, these were reported in only 46.7% and 41.0% respectively. Overall, 14.8% of patients reported exercising once per month or less.
Conclusions: Scores on the EBBS benefits subscale revealed that patients perceive the benefits of exercise, with average EBBS benefits scores comparable to historical controls with OA and RA. Despite positive perceptions of the benefits of exercise, the majority of AS patients did not report participating in forms of exercise on a frequent basis. Strategies to improve adherence to recommendations for exercise in AS will have to address disincentives through comprehensive and sustainable education programs.

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NEUROLOGICAL ADVERSE EVENTS ON ANTI-TNF THERAPY

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Background: We present a series of seven patients who developed neurological manifestations while on anti-TNF treatment.
Methods: All patients attended a rheumatology clinic in a teaching hospital, with 150 patients currently on anti-TNF therapy. In the past three years seven patients developed various neurological adverse effects. Data was collected by chart review.
Results: Five patients had AS while 2 had RA. The median (range) age was 49 (31-67) yrs. The median (range) disease duration was 14 (4-41) years. Two patients had family history of autoimmunity. Five patients were on infliximab (3-5 mg/Kg Q8Wk) and 1 each was on adalimumab (40 mg weekly) and etanercept (50 mg weekly). Three patients were on methotrexate ± HCQ before the event. The median (range) duration of anti-TNF therapy at the time of onset of neurological events was 24 (4-60) months. All patients had good control of their rheumatic disease at the time of the neurological event. The adverse events were (i) peripheral numbness and pareasthesiae (3 patients) (ii) diplopia with trochlear nerve palsy (iii) memory loss (iv) intention tremor (v) recurrent falls (one patient each). NCV revealed axonal ulnar neuropathy in one patient and was normal in one patient. Brain MRI was performed in 3 patients and was normal in all. ANA developed in 3/5 AS patients and one RA patient. Anti-TNF was stopped in 6 patients and all patients recovered neurologically over a median (range) duration of 6 (4-8) months. The serial autoantibody (ANA ± dsDNA) titer decreased after stopping anti-TNF medication in all patients. One patient was restarted on infliximab with resultant worsening of symptoms. The respective biological agent was changed to an alternative anti-TNF agent in 2 patients with no recurrence of the neurological symptoms.
Conclusions: Anti-TNF therapy can be associated with significant, but reversible neurological adverse events. In our experience a switch to an alternative anti-TNF agent was safe in such patients.

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A 3-MONTH, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF INFLIXIMAB IN JUVENILE-ONSET SPONDYLOARTHRITIS (SpA) AND A 52-WEEK OPEN EXTENSION

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Objectives: To demonstrate superior clinical efficacy with infliximab compared with placebo, in active Jo-SpA over 12 weeks and sustained efficacy, safety and tolerability in 52-week open phase.
Methods: Patients with JO-SpA (ESSG criteria; onset <16 years; screening <18 years) with >2 active joints; >3 tender entheses; pain >40 mm; and no response to NSAID/sulfasalazine.
Primary efficacy measure: number of active joints; secondary and exploratory outcome measures also included. Groups: Infliximab (I-Inflix) 5mg/kg or placebo (P-Inflix) at weeks 0, 2, and 6. Open phase: Infliximab given every 6 weeks.
Results: 26 patients (25 males, median age at onset 15.2 years [9-18]; u-SpA in 21/AS in 5) were included in the double-blind phase; 12 on infliximab, 14 on placebo. All patients entered the open phase; 2 (one from each group were prematurely discontinued). Groups were similar at baseline; differences between them favored infliximab in most variables at week 12. Such improvement was sustained during the open phase (selected variables in table). No serious adverse events were recorded.
Conclusions: Infliximab is superior to placebo in controlling disease activity in Jo-SpA. In the long-term it induces sustained control of disease activity. Infliximab is safe and well tolerated.

	P-Inflix		I-Inflix			P-Inflix		I-Inflix	
selected variables	w-0	w-12	w-0	w-12	p	w-0	w-52	w-0	w-52
active joints	6.1	4.1	4.6	0.7	0.007	6.4	0.1	4.7	0
tender enthuses	8.4	6.8	8.7	0.8	0.001	8.8	0.2	11.9	0
NRS pain	7.5	5.8	7.2	2.4	0.001	7.7	1.7	7.2	1.7
CHAQ	1.2	1.0	1.0	0.4	0.023	1.3	1.2	1.1	1.1
CRP, mg/dL	24.4	19.7	24.8	3.2	0.008	26.8	3.0	24.8	1.3

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A RANDOMIZED CONTROLLED TRIAL OF INFLIXIMAB SHOWS CLINICAL AND MRI EFFICACY IN HLA B27 POSITIVE VERY EARLY ANKYLOSING SPONDYLITIS

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Introduction: TNF alpha blocking agents have revolutionized the treatment of established ankylosing spondylitis however, the benefits of treatment of AS in the preradiographic phase have not been established. The aim of this study was to assess the clinical and MRI efficacy of infliximab in very early AS.
Materials and Methods: HLA B27 positive patients with inflammatory back pain by Calin criteria (<3 years duration) and SIJ bone marrow oedema were randomized 1:1 to infliximab 5 mg/kg or placebo infusions at 0, 2, 6 and 12 weeks. MRI scans of the spine and sacroiliac joints were performed at baseline and at 16 weeks. Lesions in the sacroiliac joints (subdivided into 8 regions) were scored using a semi-quantitative scale by two assessors, blinded to treatment and order. The primary endpoint was change in MRI score from baseline to week 16.
Results: Forty patients were randomised. The mean age was 28.8 years (SD 7.5), 75% of patients were male, mean symptom duration was 15.3 months (SD 8.8). There were no statistically significant differences between the 2 groups at baseline. Primary and secondary endpoints are described in the table. Compared to the placebo group, significant improvements in MRI and clinical endpoints were observed in the infliximab group.

	Baseline (n=40)	Change with infliximab (n=20)	Change with placebo (n=20)	p-value
Total MRI score of sacroiliac joints, mean (95% CI)	5.1	-2.0 (-6.25–0)	0 (–2-1.5)	0.033†
Sacro-iliac MRI lesions resolving, N (%)	-	47 (62.7)	20 (29.4)	0.001†
New SI lesions on MRI, N (%)	-	1 (1.2)	11 (12)	0.004†
BASDAI, mean (SD)	5.81 (1.46)	-3.41 (2.53)	-0.75 (2.42)	0.002†
ASAS partial remission, N (%)	-	10 (55.6)	2 (10)	0.009†
ASAS20, N (%)	-	14 (77.8)	5 (31.3)	0.006†
ASAS50, N (%)	-	11 (61.1)	3 (18.8)	0.012†
ASAS70, N (%)		10 (55.6)	2 (12.5)	0.009†

Conclusion: Infliximab is an effective therapy for very early inflammatory back pain, providing a rapid reduction in disease activity clinically and on MRI. This is the first therapy to show suppression of the inflammatory lesions on MRI in very early ankylosing spondylitis.

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DRUG FREE CLINICAL REMISSION AFTER INFLIXIMAB THERAPY IN A PATIENT NEWLY DIAGNOSED WITH ANKYLOSING SPONDYLITIS

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Introduction: Infliximab significantly improves clinical signs and symptoms of patients with active AS. Attempts to discontinue anti-TNF therapy for long time in AS have been mostly unsuccessful.
Objective: We present a case of a recently diagnosed AS patient who, after therapy with infliximab for 3 years, has remained in drug-free remission.
Methods: Clinical and imaging data were collected at the initiation of therapy (BL), thereafter continuously for 3 years (FU1), and then 4 years after discontinuation (FU2).
Results: This 30-year-old HLA-B27-positive patient started infliximab within one year after the onset of clinical symptoms and 5 months after the diagnosis made based on of the 1984 New York criteria. The CRP was 5.3 mg/l at BL and 1.4 mg/l and 1.2 mg/l at FU 1 and FU2, respectively. The corresponding BASDAI values were 7.0, 0.2 and 0.4. Already after 2 weeks the patient was a BASDAI 50% and an ASAS 5/6 responder, showing later persistent partial clinical remission. Antibodies to infliximab were not detected after treatment discontinuation.
Conventional radiographs at BL showed only one syndesmophyte at the level of C2 and no change occurred after 7 years. MR images at FU2 showed minor inflammatory activity in 4 thoracic vertebral edges. No NSAIDs nor extra analgesic medication was required after infliximab discontinuation.
Conclusions: This is the first example of an AS patient in drug-free clinical remission after anti-TNF therapy with infliximab. Discontinuation of anti-therapy is currently the only way to identify such patients. Patients with early and strong clinical responses are likely to be the best candidates for such an intervention. It is unclear how long the anti-TNF therapy should have at least lasted before trying that. Although this seems to be an overall rare event this case may encourage rheumatologists to proceed accordingly. Further studies are needed to clarify whether patients with early disease and short disease duration are the best candidates for this attempt.

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LONG TERM EFFICACY AND SAFETY OF PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH ETANERCEPT FOR 5 YEARS – ANALYSIS OF DIFFERENT TYPES OF RESPONSE

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Background: Etanercept has shown significant clinical efficacy in patients with active AS with no concomitant treatment.
Objectives: To assess the long-term clinical efficacy and differences to response to etanercept treatment in AS after 5 years.
Methods: After an initial treatment of 12 weeks and readministration following a short discontinuation, 26 patients started continuous open-label etanercept treatment (BL) up to 5 years until now. Primary clinical outcome was the proportion of patients in clinical remission according to the ASAS criteria after 5 years. Furthermore, possible differences in response to therapy over time were analysed and reported.
Results: Of the 26 patients at BL, 18 (69%) completed week 260 of the study. In the completer analysis, 6/18 patients (33%) were in partial remission. A BASDAI 50% response was achieved by 58%, an ASAS 40% response by 62% and a '5-out-of-6' response by 65% of the patients. All clinical parameters showed significant improvement over the entire study period. Detailed analysis confirmed differentiation to response type A (remission at most time points), response type B (state of low disease activity (BASDAI<3) at most time points), and response type C (remainder), as recently proposed: 5/6 patients (83%) in clinical remission already at week 12 showed clinical remission in more than 90% of all visits. Similarly, 8/11 patients (72.7%) with a BASDAI<3 showed this result also in more than 90% of all following visits. In comparison, in 4/18 patients (22%), did not reach ASAS 20%

response during the entire study period. There were no serious adverse events leading to treatment discontinuation.
Conclusion: The majority of AS patients remained on anti-TNF-α treatment with etanercept, being in a state of clinical remission or showing low levels of disease activity over time. The degree of response to anti-TNF therapy varied among patients, confirming the differentiation between different types of response to anti-TNF therapy, as recently proposed.

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PERSISTENT CLINICAL EFFICACY AND SAFETY OF INFLIXIMAB IN PATIENTS WITH ANKYLOSING SPONDYLITIS OVER 7 YEARS – EVIDENCE FOR DIFFERENT RESPONSE TO ANTITNFA THERAPY

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Background: There is limited knowledge on the long-term efficacy and safety of anti-TNF-α treatment in AS.
Objective: To study the long-term clinical response and differentiate types of response to anti-TNF treatment in patients with AS after 7 years.
Methods: Sixty-nine patients with active AS at baseline (BL) were continuously treated with infliximab (5mg/kg i.v./6w) with the exception of a short discontinuation period after 3 years (FU1). Primary outcome of this extension was remission according to the ASAS criteria after 7 years (FU2). Secondary outcome was the identification of differences in the response to therapy.
Results: Of the 42 patients who continued after discontinuation, 37 (88%) finished year 7. Partial remission was achieved in 12/37 patients (32.4%) at FU1 and FU2, showing no signs of loss of response. All other parameters (BASDAI, BASFI, BASMI) similarly showed persistence of efficacy of infliximab over 7 years. BASDAI values <4 were seen in 78% of patients at FU1 and FU2. ASAS 20% and 40% responses were seen in 31 (82%) and 23 (62%) patients at FU2, respectively. Three groups of patients were identified according to the level and degree of response: A) patients who were in remission at most time points, B) patients in a state of low disease activity (BASDAI <3) at most time points, and C) the remainder. Some differences between these groups in age, disease duration and function at baseline could be identified. No major side effects occurred during years 4 to 7 of infliximab therapy.
Conclusions: The majority of the patients with AS remained on infliximab therapy which proved to be safe and efficacious over 7 years. Most patients remained in remission or had low levels of disease activity over time. Continuous therapy is necessary to achieve a lasting effect in almost all patients. Different types of response to anti-TNF treatment could be confirmed.

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DISEASE ACTIVITY AND QUALITY OF LIFE IN CROHN'S-ASSOCIATED SPONDYLOARTHROPATHY AFTER SWITCHING FROM INFLIXIMAB TO ADALIMUMAB

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Introduction: No published studies have addressed the effect of switch from infliximab to adalimumab in Crohn's associated spondyloarthropaty. Purpose of the present study was to evaluate the clinical response to adalimumab in patients with Crohn's-associated spondyloarthritis discontinued from infliximab treatment due to intolerance or loss of efficacy.
Materials and Methods: 17 patients were studied (9 Males and 10 Females, mean age 47.0±12.5 years). All patients had been discontinued from infliximab due to side effects (n=6) or articular recrudescence (n=11), and started on adalimumab 40 mg eow after 6 to 8 weeks. Follow-up visits were performed at 1, 3, 6, 9, and 12 months of treatment. Articular disease was assessed by the BASFI and the BASDAI scores, Crohn's activity by the CDAI score, and quality of life by the SF-36 questionnaire. Mean differences were evaluated by Wilcoxon test.
Results: In two patients adalimumab was discontinued due to Crohn's or articular flare-ups. The table shows the changes in disease scores during adalimumab treatment. At no time point differences vs. basal values were significant (p>0.05).

Disease Scores during treatment with Adalimumab

	Weeks of Treatment with Adalimumab					
	5	4	12	24	36	52
BASDAI	4.7 ± 2.5	3.3 ± 1.9	3.3 ± 1.6	4.2 ± 1.8	4.1 ± 1.6	4.6 ± 1.4
BASFI	3.2 ± 2.5	2.5 ± 2.2	2.5 ± 1.9	3.0 ± 1.7	2.7 ± 1.6	2.0 ± 1.1
CDAI	76.8 ± 35.2	72.6 ± 22.7	58.8 ± 15.3	46.6 ± 28.4	54.2 ± 27.5	56.5 ± 37.6
SF-36 Physical	34.3 ± 10.2	36.8 ± 9.2	37.5 ± 7.9	35.8 ± 10.4	34.8 ± 9.4	35.1 ± 11.2
SF-36 Mental	46.1 ± 12.7	46.6 ± 13.4	45.0 ± 11.9	47.0 ± 10.7	42.0 ± 11.6	41.4 ± 14.0

Conclusions: The results of our study suggest that switching to adalimumab in patients with intolerance or poor response to infliximab may successfully control both articular and intestinal disease activity in patients with Crohn's-associated spondyloarthropathy.

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DECREASED CLINICAL RESPONSE TO ADALIMUMAB IN ANKYLOSING SPONDYLITIS IS ASSOCIATED WITH ANTIBODY FORMATION

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Introduction: Despite the good response to adalimumab in the majority of the Ankylosing Spondylitis (AS) patients this treatment does not seem to be effective in approximately 40% of the cases. An explanation could be that disease activity in these patients is caused by a different mechanism than TNF-alpha or because of insufficiently high adalimumab levels. The latter might be caused by antibody formation against adalimumab (anti-adalimumab).
Previously we found that formation of anti-infliximab was associated with a poor response to infliximab. In AS patients treated with etanercept however, antibodies against etanercept could not be detected within 6 months of therapy.
Objective: To examine whether the production of anti-adalimumab is associated with a poor response of AS to treatment with adalimumab.
Methods: Consecutive AS patients treated with 40 mg of adalimumab every other week according to the international ASAS consensus statement were enrolled. Sera were collected at baseline, after 3 and 6 months of treatment. Clinical response was defined as an improvement of 50% or as an absolute improvement of 2 points of the BASDAI (0-10). As previously described, anti-adalimumab was measured at Sanquin, the Netherlands, with an antigen binding test, with a cut-off value for positive of 12 AE / ml.
Results: A total of 42 patients was enrolled. After three months of treatment 21 patients (50%) were ASAS responders. Within 6 months 11 patients (26%) showed anti-adalimumab, of whom 9 were ASAS non-responders (p=0.023). One of these patients clinically developed an allergic reaction with hyperaemia and dyspnoea.
Conclusions: In AS there is a significant association between anti-adalimumab formation and low efficacy of adalimumab.

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IMPROVING FUNCTIONALITY IMPROVES SLEEP IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: RESULTS FROM THE GO-RAISE STUDY

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Introduction: Patients with ankylosing spondylitis (AS) report significant functional impairment, which could affect their sleep. We wanted to establish the relationship between functionality and sleep in patients with active AS.
Methods: Data from a multicenter, randomized, placebo (PBO)-controlled study (GO-RAISE) were used to establish the relationship between functionality and sleep as measured by the Bath Ankylosing Spondylitis Functional Index (BASFI)

and the Jenkins Sleep Evaluation Questionnaire (JSEQ). Patients with definite AS (modified NY criteria: BASDAI and back pain score each ≥4) were eligible. 356 patients were randomized (1.8:1.8:1 ratio) to receive subcutaneous golimumab (GLM) 50 mg or 100 mg or PBO q4 wks. Clinical endpoints included the change from baseline in BASFI and the JSEQ at wk14. An ANOVA on van der Waerden normal scores was performed for between group comparisons.
Spearman's Rank correlation was used to measure the associations between change in BASFI and change in JSEQ at wk14, and regression analysis was performed to determine the predictive value of BASFI for improvements in JSEQ.
Results: GLM 50 mg and 100 mg treatment resulted in significant ($p<0.001$) improvements in both BASFI and JSEQ at wk14 vs. PBO. There was a positive correlation between changes from baseline in BASFI and JSEQ at wk14 ($r=0.37$; $p<0.001$) for all patients. In the GLM 50 mg and 100 mg groups, there was a significant positive correlation between changes from baseline in BASFI and JSEQ at wk14 ($r=0.30$, $p=0.0005$; $r=0.44$, $p<0.0001$, respectively).
This correlation was not evident in the PBO group at wk14 ($r=0.11$, $p=0.34$). The regression model showed that a change of one unit in BASFI at wk14 amounts to a change in the JSEQ of 0.69 ($r^2=0.14$, $p<0.0001$) adjusted for treatment.
Conclusions: The GO-RAISE results show a definite relationship between improvement in functionality and corresponding improvement in sleep in patients with active AS. GLM 50 mg and 100 mg treatment significantly improved functionality leading to improved sleep in AS patients.

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GOLIMUMAB SIGNIFICANTLY IMPROVES SLEEP IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: RESULTS FROM THE PHASE 3 GO-RAISE STUDY

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Introduction: We evaluated the impact of golimumab (GLM) on reducing sleep disturbance in patients with ankylosing spondylitis (AS).
Methods: GLM was studied in a multi-center, randomized, placebo (PBO)-controlled study (GO-RAISE). 356 patients were randomized (1.8:1.8:1 ratio) to SC GLM 50mg or 100mg or PBO q4wks. Patients with definite AS according to the modified NY criteria (BASDAI and back pain score each ≥4) were eligible. Sleep disturbance was assessed using the change from baseline in the Jenkins Sleep Evaluation Questionnaire (JSEQ) at wk14 and wk24. Primary efficacy analyses were performed at wk14. At wk16, patients in PBO or 50mg group with <20% improvement from baseline in total back pain and morning stiffness entered early escape in a double-blind fashion. All other patients remained on their previous medication until wk24. GLM 50mg or PBO patients who entered early escape had their last observation prior to change in treatment carried forward for the wk24 analyses. Observed values at wk24 were used for GLM 100mg patients. Spearman's Rank correlation measured the associations between changes in the JSEQ and night back pain scores at wk24. An ANOVA on van der Waerden normal scores was performed for between-group comparisons.
Results: The GLM 50mg, 100mg, and PBO groups had mean ± SD JSEQ baseline scores of 10.3±4.4, 11.1±4.8 and 9.9 ±4.7, respectively, indicating similar levels of disturbed sleep.
GLM 50mg and 100mg patients showed significantly greater improvement (decline in score) in JSEQ vs. PBO at wk14 (-3.1±4.4 and -3.2±5.1 vs. -0.5±3.8, respectively; $p<0.001$, for both groups vs. PBO) and wk24 (-3.3±4.2 and -3.8±4.9 vs. 0.6±4.0, respectively; $p<0.001$, for both groups vs. PBO). In the combined GLM group, there was a significant correlation between changes from baseline in JSEQ and night back pain at wk24 ($r=0.42$, $p<0.0001$).
Conclusions: GLM 50mg and 100mg significantly reduced sleep disturbance as measured by the JSEQ in AS patients, with improvements at wk14 maintained through wk24.

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GOLIMUMAB, A NEW, HUMAN, TNF-ALPHA ANTIBODY ADMINISTERED SUBCUTANEOUSLY EVERY 4 WEEKS, IN ANKYLOSING SPONDYLITIS: 24-WEEK EFFICACY AND SAFETY RESULTS OF THE RANDOMIZED, PLACEBO-CONTROLLED GO-RAISE STUDY

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Introduction: This multicenter, randomized, placebo (PBO)-controlled study was conducted to evaluate the efficacy of golimumab (GLM) on signs and symptoms of active ankylosing spondylitis (AS).
Methods: Patients (n = 356) were randomized to subcutaneous GLM 50 mg or 100 mg or PBO q4 wks. Patients with AS according to the modified New York criteria (Bath AS Disease Activity Index score of ≥4 and a back pain score of ≥4) were eligible. The primary efficacy endpoint was the proportion of patients with an ASAS20 response at wk 14. At wk 16, patients in PBO or 50 mg group who had <20% improvement from baseline in total back pain and morning stiffness measures entered early escape in a double-blind fashion. All other patients remained on their previous medication until wk 24.
Results: The primary endpoint at wk 14 was met. ASAS 20 responses for both GLM groups were significantly higher than that for PBO (GLM 50 mg, 59% and GLM 100 mg, 60% vs. PBO, 22%; $p<0.001$ for each comparison). Clinical benefit was maintained through wk 24, with ASAS 20 responses for both GLM groups significantly higher vs. PBO (56% and 66%, respectively, vs. 23% for PBO; $p<0.001$ for each comparison). All secondary endpoints were achieved except for the change from baseline in BASMI score at wk 14. Antibodies to GLM were detected in 11 patients (4.1%) through wk 24. Adverse events through 24 wks were reported in 79.9% of GLM-treated patients and 76.6% of PBO-treated patients, with an increased incidence of infections, primarily upper respiratory, in GLM-treated patients.
Through wk 24, 5 patients (6.5%) receiving PBO, 5 patients (3.6%) receiving 50 mg GLM, and 9 patients (6.4%) receiving 100 mg GLM reported a serious adverse event.
Conclusions: GLM improved signs and symptoms and physical function in AS patients through 24 wks. GLM was generally well-tolerated.

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GOLIMUMAB, A NEW, HUMAN, TNF-ALPHA ANTIBODY ADMINISTERED AS A SUBCUTANEOUS INJECTION IN PSORIATIC ARTHRITIS: 24-WEEK RESULTS OF THE RANDOMIZED, PLACEBO-CONTROLLED GO-REVEAL STUDY

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Introduction: We assessed the efficacy and safety of golimumab (GLM) for treatment of active psoriatic arthritis (PsA).
Methods: Adult PsA patients with ≥3 swollen/tender joints were randomized to SC placebo (PBO) or GLM (50mg or 100mg) at wks 0,4,8,12,16, and 20. Patients with inadequate arthritis response after receiving PBO or GLM 50mg at wk16 were switched in a blinded manner to GLM 50mg (PBO group) or GLM 100mg (GLM 50mg). PBO and GLM 50mg patients had their last observation prior to change in treatment carried forward for the wk24 efficacy analyses. Observed values at wk24 were used for GLM 100mg patients. Concomitant methotrexate (MTX) was allowed but not required. The primary endpoint (ACR20 at wk14) was analyzed by the Cochran-Mantel-Haenszel test with stratification by MTX use.
Results: 405 PsA patients were randomized (median age: 47.0 years). Baseline characteristics (range) were: mean swollen/tender joint counts (12-14/22-24),

mean Health Assessment Questionnaire scores (1.0-1.1), and mean PASI scores (8.4 -11.1). The PBO and GLM groups were balanced for baseline characteristics. The GLM 50mg and 100mg groups showed significant improvement from baseline in ACR20 response vs. PBO at wk14 (51% and 45%, vs. 9%, respectively) and wk24 (52% and 61%, vs. 12%, respectively; p<0.001 for each comparison, GLM 50mg vs. PBO and GLM 100mg vs. PBO). The proportion of patients with PASI75 responses was significantly greater for both GLM doses vs. PBO at wk14 (40% and 58%, vs. 3%, respectively) and wk24 (56% and 66%, vs. 1%, respectively; p<0.001 for each comparison). 2.4% of GLM patients experienced a serious adverse event (SAE) through wk24 vs. 6.2% of PBO patients. Injection site reactions were rare and occurred in 4.8% of GLM and 2.7% of PBO patients. One SAE of malignancy (prostate cancer) and 2 cases of basal cell carcinoma were reported in GLM patients, with no reports of tuberculosis or opportunistic infections.
Conclusions: GLM 50mg and 100mg q4wks significantly improved active PsA through wk24, and was generally well-tolerated.

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ELEVATED LIVER ENZYMES ASSOCIATED WITH ETANERCEPT IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Introduction: TNF-alpha blocking agents are very effective in patients with ankylosing spondylitis (AS). Well-known adverse events are injection site reactions and infections. A few cases of liver disease, secondary to autoimmune and granulomatous hepatitis, have been published. As we, unexpectedly, observed several patients with liver enzyme elevations in our clinical practice we subsequently studied the frequency of this potential side effect in our AS patients treated with etanercept.
Methods: Consecutive AS patients treated with etanercept for at least 3 months were included. Liver disease was defined as elevated liver enzymes more then 1.5x the upper normal limit (UNL) at least at two time points and were categorised as probably, possibly, probably not or not related to etanercept treatment. Patients with and without raised liver enzymes were compared for prognostic factors.
Results: A total of 105 patients were included (mean age 43 years, 74% male). 15 patients (14 men) had elevated liver enzymes more than once. In 9 cases the liver disease was probably (5) or possibly (4) related to etanercept treatment. The liver enzyme elevations were serious in 6 cases (>3x UNL) and resulted in cessation of etanercept in at least 2 cases. The 9 patients with liver disease were compared with the patients without elevated enzymes. No differences were found in age or use of alcohol, however, in patients with liver disease a higher body mass index and a higher atherogenic index (i.e. total cholesterol/HDL-cholesterol ratio) were observed. Hepatic steatosis, diagnosed with ultrasonography, was observed in 5 of 6 patients with elevated liver enzymes.
Conclusions: Elevated serum aminotransferases, probably or possibly related to etanercept treatment were observed in 9% of the AS patients. An increased risk for elevation of liver enzymes was found in patients with a high body mass index and high atherogenic index.

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AGREEMENT BETWEEN EVIDENCE AND BELGIAN RHEUMATOLOGISTS' EXPERIENCE ON THE ROLE OF CRP IN DIAGNOSIS OF ANKYLOSING SPONDYLITIS

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Objective: To develop an evidence-based and experience-based recommendation to the question, "Is (persistent) CRP related to outcome in AS?"
Methods: A systematic literature search was conducted during August-October 2007 for publications on CRP in AS. Whenever possible, the estimated relative risk and odds ratios or factors associated with outcome/progression of disease found in the publications were calculated. The results of the search were presented to 59 Belgian rheumatologists, analyzed, and discussed. Based on the evidence in the literature, which was categorized according to the EULAR evidence hierarchy (1,2), these rheumatologists developed a recommendation on the use of CRP in daily practice. The strength of the recommendation (1,2) was assessed by voting on level of agreement.
Results: Through a combination of MeSH terms and keywords, the total number of broadly relevant articles found in PubMed was 861. Two other articles were identified from reference lists in those publications. Overall, the search yielded a relatively small number of useful studies for analysis of the role of CRP in outcome of disease. No studies were found on long-term outcome parameters, and none of 15 key, selected manuscripts contained data on persistent CRP elevation. The Belgian rheumatologists made the following recommendation: "CRP must be evaluated in all AS patients, including those with stable clinical status or those without overt articular disease activity (persistent increased CRP must be further investigated)." 88% of the attendees agreed with this recommendation. The category of evidence was deemed "IV," and the strength of the recommendation was deemed "D."
Conclusion: A recommendation on the role of CRP in relationship to outcome of AS was developed using a combination of research-based evidence and expert consensus. Because of lack of evidence concerning the topic, the recommendation was based on expert opinion (Level IV).

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ESR AND CRP ARE ASSOCIATED WITH DISEASE ACTIVITY IN ANKYLOSING SPONDYLITIS

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Background: Disease activity in Ankylosing Spondylitis (AS) is generally measured with a self-administered instrument, i.e. the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
Objectives: To investigate the relationship between frequently used inflammatory markers (ESR and CRP) and the BASDAI in AS patients treated with anti-TNF, and the association with Ankylosing Spondylitis (ASAS) non-response.
Methods: Patients were included consecutively before start of treatment with etanercept or infliximab. Questionnaires, ESR and CRP were obtained at baseline, after 1 and after 3 months of treatment. ASAS response was calculated after 3 months of treatment.
Standardized beta's were calculated for comparison of associations between ESR, CRP and clinical response. Longitudinal data analysis was performed as well.
Results: The etanercept cohort comprised of 117 patients and the infliximab cohort of 38 patients. After three months of treatment, 80 (70%) and 27 (71%) were ASAS responders in the etanercept and infliximab cohort respectively. Median ESR levels (range) were 21 (1-104), 6 (1-58), 5 (1-60) at baseline, 1 month and 3 months respectively. Median CRP levels (range) were 15 (0-143), 3 (1-97), 4 (0-47) at baseline, 1 months and 3 months respectively. During treatment both inflammatory parameters decreased significantly. Longitudinal linear regression analysis showed significant association between BASDAI and ESR or CRP which remained after correction for confounders (gender, age, HLA B27 and the presence of peripheral arthritis) (p<0.0001). The standardized beta's were 7.12 for ESR and 4.0 for CRP.
A normal baseline levels of CRP (<10 mg/L) was significantly associated with ASAS non-response (p=0.004).
Conclusion: Treatment of AS with etanercept or infliximab significantly reduces ESR and CRP. These inflammatory markers were both significantly associated with the BASDAI, but the association with ESR was stronger. Normal baseline CRP might help to identify AS patients less likely to respond to treatment with anti-TNF.

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CROSS-VALIDATION OF 4 DISEASE ACTIVITY SCORES FOR ANKYLOSING SPONDYLITIS (ASDAS) IN THE NORDMARD DATABASE

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Introduction: To further evaluate 4 ASDAS scores and the BASDAI for the aspects of truth and discrimination.
Materials and Methods: Analyses were done in the NORDMARD database in patients with AS started with sulfasalazine, methotrexate and/or TNF-blockers. The 4 ASDAS scores include the following items: ASDAS1:back pain (BP), morning stiffness (MS), patient global (PG), ESR, CRP; ASDAS2: BP, MS, PG, VAS periph symptoms, ESR; ASDAS3: BP, MS, PG, VAS periph symptoms, CRP; ASDAS4: BP, MS, Fatigue, ESR, CRP. (VAS on a 10cm scale; CRP in mg/l). Data at baseline and after 3 and 6 months of treatment were available.
Scores were related to patient and physician global, patient acceptable symptom

state (PASS), and considerable improvement in health by the patient. Sensitivity to change (SRM) and discrimination between groups of different status and/or change scores were analysed.
Results: 650 treatment starts at baseline were available; Between 90 and 450 patients for 3 and 6 month scores depending on the anchor variable. Correlations between the ASDAS scores and physician global assessment of disease activity were moderate and with patient global assessment of disease activity good. The SMD in patients judging themselves being in PASS vs not being in PASS and the discrimination between high and low disease activity according to the physician was high for all ASDAS scores. Also presence or absence of considerable improvement by the patient showed good discrimination; SRMs were good for all ASDAS scores. Discrimination between response to TNF-blockers versus DMARDs was good. In all comparisons the ASDAS scores performed very similar and at least as good as the BASDAI. This was confirmed for patients with normal and elevated CRP.
Conclusion: The performance of 4 ASDAS scores with respect to truth and discrimination was similar and at least as good as the BASDAI. The ASDAS is the first index in AS that correlates well with both patient and physician global assessment of disease activity and promises to be a highly discriminatory tool in clinical trials.

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AN EVALUATION OF THE GLASGOW ENTHESIS INDEX (GEI) IN ANKYLOSING SPONDYLITIS (AS) AND A COMPARISON WITH THE MODIFIED MASES INDEX (MMI)

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Background: Enthesitis is a common feature of the Seronegative Spondarthritides but is difficult to evaluate clinically. We have previously published a Musculo-skeletal ultrasound (MSUS) assessment of the lower limb component of the GEI and shown a good correlation between clinical and MSUS findings although the MSUS proved to be more sensitive. There are a number of enthesis indices and in this study we have validated the GEI and compared it with the MMI.
Methods: 21 unselected patients with AS (modified New York criteria) were assessed by 2 independent observers and the GEI and MMI were recorded. Standard indices of disease activity such as BASDAI, ESR and CRP were measured and the time taken to perform the GEI and MMI on each patient was noted. Inter-observer variation between the observers for the GEI was recorded and the intra-class correlation calculated. Non-parametric statistics were used to calculate correlation of continuous variables.
Results: 21 AS patients were examined by 2 observers for the GEI and 15 were assessed by one observer for the time taken to measure the GEI and MMI. A good level of agreement for the GEI was achieved by the 2 observers (intra-class correlation 0.85, 95% CI. 0.68-0.94).
There was no correlation between AS disease activity measures and the GEI. The mean time to undertake the GEI was 2.4 mins (SD 0.83) and for the MMI was 2.5 mins. (SD 0.92). The Pearson correlation between the GEI and MMI scores was 0.840 indicating an acceptable level of agreement.
Conclusions: The GEI is a quick and easy clinical measure of enthesitis with a good inter-observer agreement. It compares well with the MMI but does assess slightly different sites of entheseal insertion. Longitudinal studies to compare several Enthesitis indices are required to determine the best method of measuring this clinical feature and to quantitate the influence of Enthesitis on functional outcome in AS.

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THE DEVELOPMENT OF A SIMPLE ACCULTURATION INDEX AND ITS USE IN SPONDYLOARTHRITIDES

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Acculturation is the process by which members of one culture acquire the norms and values of another culture.
Methods: An acculturation index developed based on perceived ethnicity, country of birth, ancestry origin, and language spoken in household. Grade 0 represents not needing acculturation, while grade 3t o those not acculturated. Grades 1 suggests fully acculturated foreign inhabitants who can be considered close to no need acculturation and grade 2 suggests partly acculturated foreign inhabitants by birth but speaking both native language and the host county's language. SpA clinical, epidemiological, social and dietary data were analyzed with regards to acculturation.
Results: Acculturation index was produced from 363 patients. The total BASDAI and BASFI scores of the group (mean + SD) were 6.1+ 2.0 and 5.1 + 2.7 respectively. The wellbeing (past week) was 5.8 + 2.7, well-being (past 6 mo) was 6.3 + 2.4. No statistical significance difference between the acculturation index groups and BASDAI, BASFI [Pearson's (0.033, p=0.5, and -0.090, p=0.098 respectively)], while significance found with smoking (-0.427**; p=0.000); alcohol (-0.551**, 0.000); disease duration -0.150**, p=0.008); BASDAI2 (0.125; p=0.021); BASDAI6 (-.0118 p=0.029); BASFI4 (-0.112*. p=0.03); steroid use (-0.116* p=0.04); being partly vegetarian (0.220** p 0.000), fish intake (-.0.198** p=0.001), egg intake (-0.262**, p=0.000) fish oil intake (-0.143**, 0.009) and reason of unemployment (-0.163*, p=0.010). Acculturation and clinicians opinion, showed negative association with the Undifferentiated cohort (-0.183*, p=0.012); positive association with symmetrical disease (0.405**, p=0.000); asymmetrical disease (0.300**, p=0.004) symmetrical hand disease (0.295**, p=0.004); wrists disease (right 0.412**, p=0.000; left 0.307**, p=0.006); symmetrical feet disease (0.437**, p= 0.000); ankle disease (p=0.000), shoulders disease (p=0.002); knees (p= 0.000) and right but not left hip (0.337**, p = 0.003).
Conclusions: Disease differences between ethnic groups can be studied through separation of the groups into acculturation categories.

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DEVELOPMENT AND TESTING OF A OMERACT PSORIATIC ARTHRITIS MRI SCORING SYSTEM (PSAMRIS)

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Background: The MRI features of peripheral joint pathology in psoriatic arthritis (PsA) have been described, but no well-accepted semi-quantitative scoring system for outcome assessment exists. The aim of this study was, within the OMERACT MRI in Inflammatory Arthritis Special Interest Group, to develop a consensus-based semi-quantitative tool for MRI-scoring of peripheral PsA.
Methods: At a 2-day consensus meeting in Spain in June 2007, MRI definitions of key PsA pathologies were developed, and decisions were made concerning features to include in the score sheet, based on data from a previous preliminary exercise. All features were scored separately at each of MCP 2-5, PIP 2-5, DIP 2-5 (range of possible scores in parentheses): Synovitis (0-3), flexor tenosynovitis (0-3), periarticular inflammation (0-1, volar and dorsal aspects separately), bone oedema (0-3, proximal and distal bone separately), bone erosion (0-10, proximal and distal bone separately); bone proliferation (0-1). Subsequently, MRI sets of 2nd-5th fingers of 10 PsA patients (3D T1-weighted gradient-echo (voxel size 0.5x 0.5x1.0 mm) before and after i.v. contrast, with subsequent axial, coronal and sagittal reconstructions, and sagittal and axial STIR sequences) were read blindly by 8 readers, without formal prior reader calibration.
Results: The intraclass correlation coefficients (ICCs, average measure) of sum scores were: Synovitis: 0.88, tenosynovitis 0.84, periarticular inflammation 0.25, bone oedema 0.86, bone erosions 0.91 and bone proliferation 0.91. The MRI definitions and the score sheet will be presented at the conference.
Conclusions: MRI definitions of relevant PsA pathologies and a preliminary score sheet were developed by consensus. Without prior reader calibration, the inter-reader reliability was good to very good for synovitis, tenosynovitis, bone oedema, bone erosions, and bone proliferation, but poor for periarticular inflammation. Further development, testing and reader calibration is needed before the OMERACT PsAMRIS can be recommended for use in clinical trials.

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EARLY AND SIGNIFICANT INCREASES IN HEALTH RELATED QUALITY OF LIFE IN SPONDYLOARTHRITIS PATIENTS TREATED WITH TNFα INHIBITORS

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Introduction: Health-related quality of life (HRQoL) is an important outcome in clinical trials. We evaluated changes in the generic quality of life questionnaire Short-Form Health Survey (SF-36) in SpA patients during anti-TNF-α treatment.

Materials and Methods: 54 patients fulfilling the ESSG criteria for SpA, with sacroiliitis on MRI or x-rays, and BASDAI>30 mm despite NSAIDs were included. At week 22 treatment response/non-response was evaluated according to the BASDAI50%-criteria.
Results: 37 patients were responders. At baseline, responders scored lower in social functioning (p=0.03). All 10 SF-36 scores rapidly (at week 2) and markedly improved (p<0.001) in responders and stayed increased at week 22 (p<0.001). In non-responders, bodily pain, vitality and mental health (p=0.01-p=0.03) improved at week 2, but at week 22 all scores were unchanged.
Conclusion: In SpA patients receiving anti-TNF-α therapy, HRQoL rapidly and markedly improved in clinical responders but not in clinical non-responders. (Median (range),*p<0.001; †p<0.05)

	Responders at week 22			Non-responders at week 22		
SF-36 scales	Inclusion	Week 2	Week 22	Inclusion	Week 2	Week 22
Physical function	60(5-95)	80(20-95)*	85(25-100)*	56(15-95)	70(20-90)	65(10-90)
Physical role function	25(0-100)	50(0-100)*	75(0-100)*	0(0-100)	25(0-100)	25(0-75)
Bodily pain	31(0-62)	52(0-84)*	72(22-100)*	41(10-74)	52(21-100)†	41(12-74)
General health	38(10-87)	52(22-97)*	52(25-100)*	50(20-72)	52(15-82)	51(10-87)
Vitality	25(0-75)	50(15-85)*	65(25-100)*	30(5-70)	60(5-100)†	28(15-85)
Social functioning	50(0-100)	88(25-100)*	88(25-100)*	75(38-100)	75(12.5-100)	75(38-100)
Role emotional	50(0-100)	100(0-100)*	100(0-100)*	67(0-100)	67(0-100)	50(0-100)
Mental health	68(20-96)	80(32-100)*	84(28-100)*	70(32-88)	72(44-100)†	64(52-96)

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RADIOGRAPHIC SEVERITY CORRELATES POORLY WITH QUALITY OF LIFE IN ANKYLOSING SPONDYLITIS

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Introduction: There is growing attention being paid to quality of life (QoL) assessment in the management of ankylosing spondylitis (AS). The ASQoL questionnaire is increasingly being used in clinical trials and routine practice. However, how this instrument correlates with established indices has received very little attention. We address this issue in the current study.
Methods: AS patients in a large teaching hospital are evaluated according to a standard protocol, which includes a number of self-reported instruments such as ASQoL, BASDAI, BASFI. Mean (±SD) were calculated. The ASQoL and BASFI were compared with BASDAI, BASMI and mSASSS using Pearson correlation coefficients.
Results: Data was available for 220 AS patients. 80.9% male, 81.5% HLA-B27 positive, 26.4% were receiving an anti-TNF agent at time of assessment, and 26% had juvenile onset AS. Mean (±SD) BASDAI was 4.7 (±2.5), mean BASMI was 3.2 (±2.6), and mean mSASSS was 19.5 (±24.2). Mean ASQoL was 8.2 (±5.8), and mean BASFI was 3.9 (±2.8). The strongest correlation with BASFI was seen with ASQoL (r=0.754, p<0.001) and BASDAI (r=0.689, p<0.001). BASFI correlated modestly with BASMI (r=0.561, p<0.001) but poorly with mSASSS (r=0.227, p=0.001). ASQoL had a better correlation with BASDAI than BASFI (r=0.710, p<0.001). ASQoL had a poor correlation with BASMI (r=0.327, p<0.001) and did not significantly correlate with mSASSS. For every single individual question in the BASFI there was a greater correlation with the ASQoL than BASDAI, BASMI or mSASSS. Question 9 of the BASFI (doing physically demanding activities) and question 10 (doing a full days activities) were highly correlated with the ASQoL score (r values were 0.805 and 0.810 respectively, p<0.001).
Conclusion: Our study indicates that the ASQoL questionnaire correlates very well with the established measurements of both disease activity and function. But ASQoL bore little relationship to radiographic severity of disease in AS.

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DISEASE ACTIVITY AND QUALITY OF LIFE IN ANKYLOSING SPONDYLITIS AFTER TREATMENT WITH INFLIXIMAB

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Objectives: To determine from single center data changes in disease activity and quality of life in patients with ankylosing spondylitis (AS), treated with infliximab as their first biological antirheumatic drug during 56 weeks.
Methods: 19 consecutive patients with active AS [Bath AS Disease Activity Index (BASDAI) > 4] and fulfilling the modified New York criteria were treated with infliximab 5 mg/kg at 0, 2, 6 weeks, thereafter at 6 week intervals for totally 56 weeks. Response to treatment was defined as 50% or 2 cm improvement in BASDAI according to ASAS International Working Group remission/partial remission criteria. Disease activity was also measured by erythrocyte sedimentation rate, C-reactive protein and magnetic resonance imaging (MRI) of the sacroiliac joints at inclusion, 16, and 56 weeks. Quality of life was assessed according to SF-36.
Results: 19 patients completed treatment for 16 weeks, 18 for 56 weeks. Sixteen (85%) achieved BASDAI response at 16 weeks with sustained benefit at 56 weeks in 14 patients; one additional patient was late responder. At baseline, patients with active AS demonstrated a significant decrease in both physical and mental health summary scales compared with a sex and age matched healthy population. However, patients with active AS improved significant from baseline to week 16 in the physical health summary scale, which was maintained at week 56. MRI showed active disease at baseline in 15 patients. At 16 weeks four patients remained active, at 56 weeks two patients. Joint function, spinal pain, peripheral arthritis and acute phase reactants improved similarly.
Conclusion: Infliximab treatment in patients with active AS resulted in significant and rapid improvement, sustained during the course of the study. No severe adverse events were reported. MRI is important for diagnosis and management of AS and SF-36 is useful for health survey in AS.

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ASSOCIATION OF PATIENT CHARACTERISTICS WITH ATTAINING PATIENT ACCEPTABLE SYMPTOM STATE (PASS) IN ANKYLOSING SPONDYLITIS (AS)

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Introduction: Patient Acceptable Symptomatic State (PASS) is the acceptable level of symptoms at which patients with rheumatic diseases consider themselves well. PASS is a single-question tool validated in AS.
Objective: To understand potential variability of PASS, we sought to determine whether AS patient characteristics are associated with attaining PASS.
Methods: Week-12 data were analyzed from ATLAS, a Phase III study of the efficacy and safety of adalimumab vs. placebo in AS. Several PRO tools were assessed during ATLAS.
Logistic regression analyses were conducted to determine the associations of particular patient characteristics with PASS [patients consider their current disease states to be satisfactory, yes/no] and other clinically related PROs (ASAS20, ASAS40, ASAS5/6, Partial Remission, BASDAI 50) as dependent variables.
Results: 315 patients were enrolled in ATLAS. Results of the regression model for PASS are provided (table). Age, male sex, duration of AS since diagnosis, and treatment group all had independent, statistically significant associations with attainment of PASS at Week 12.
Results of regression analysis for the other PROs (response criteria and partial remission) demonstrated that adalimumab therapy was significantly associated with improved scores for all other PROs. In addition, greater age revealed independent, significant associations with lower scores for ASAS20 (p=0.011), ASAS5/6 (p=0.207), and BASDAI 50 (p=0.0056). Age demonstrated no association with ASAS40 (p=0.145). Disease duration since diagnosis and sex were not associated with the other PROs.

PASS Logistic Regression Model	Odds Ratio	*p*-value	95% CI
Age (years)	0.965	0.005	0.941–0.989
Male sex	1.950	0.029	1.072–3.546
Duration since AS diagnosis (years)	1.037	0.016	1.007–1.068
Treatment group (adalimumab vs. placebo)	2.335	0.002	1.354–4.029

Conclusion: This analysis demonstrates that age and adalimumab therapy are independently associated with all PROs measured, including PASS. AS duration and sex also demonstrate independent associations with attainment of PASS, but not the other PROs.

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DISEASE SEVERITY IN ANKYLOSING SPONDYLITIS: THE INFLUENCE OF ASSOCIATED INFLAMMATORY BOWEL DISEASE AND PSORIASIS

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Introduction: Ankylosing Spondylitis (AS) is a common form of inflammatory arthritis, affecting ~5/1000 Caucasians. Although predominantly affecting the axial skeleton, the clinical link between AS, psoriasis (Ps) and inflammatory bowel disease (IBD) is well known. The aim of this study was to determine whether these patients have similar disease activity and severity.
Methods: 40 pre-TNF patients were identified from the AS Specialist Clinic, Brisbane. Disease severity was assessed by questionnaire (BASDAI, BASFI), metrology (BASMI), and blood tests (ESR and CRP). Questionnaire data was then compared with the Oxford cohort of 2570 AS cases. All patients in both cohorts met the modified New York diagnostic criteria. BASFI and BASMI were corrected for disease duration from symptom onset.
Results: Considering the Brisbane cohort, AS patients with Ps had higher ESR (44 vs. 39), CRP (57 vs. 32), BASDAI (7.3 vs. 5.9), BASFI (6.7 vs. 5.7) and BASMI (4.7 vs. 4.2) than AS patients without Ps, although only the BASDAI finding was statistically significant (P=0.03).
No difference was noted in age of symptom onset or frequency of uveitis. AS patients with IBD also had higher CRP (44 vs. 33), BASDAI (6.6 vs. 6.0) and BASFI (6.2 v.s 5.7) than those without IBD but similar ESR (40 both groups) and BASMI (5.3 both groups). In the Oxford cohort, BASDAI and BASFI were also increased in both Ps (BASDAI 4.5 vs. 4.2, P=0.01; BASFI 4.5 vs. 4.0, P=0.002) and IBD (BASDAI 4.7 vs. 4.1, P=4x10-5; BASFI 4.7 vs. 4.0, P=2x10-7), confirming the Brisbane findings. Patients with both Ps and IBD had even higher BASDAI and BASFI than those with either Ps or IBD alone (mean BASDAI 5.0, BASFI 5.3).
Conclusion: These findings suggest that AS patients with coexistent Ps, and potentially IBD, are a worse prognostic group than those with primary AS.

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DOES INITIAL JOINT INVOLVEMENT PATTERN INFLUENCE RADIOGRAPHIC DAMAGE IN PATIENTS WITH USPA/AS?

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Introduction: Axial manifestations of spondyloarthritis (SpA) can be minimal or are not always present at disease onset. We investigated whether there are differences in clinical and radiographic features among undifferentiated SpA or ankylosing spondylitis (AS) patients in terms of initial joint involvement pattern.
Methods: We studied the consecutive 102 patients with undifferentiated SpA (USpA) or AS who visited the Rheumatology clinic from Jan 2008 to March 2008.
Results: Joint involvement patterns at disease onset were axial (51%), peripheral (19%), enthesopathic (5%) or mixed (26%). Men were predominant, especially in peripheral arthritis group (M:F 18:1), compared to the others (4:1). Age at onset was younger in enthesopthy (median age 15 years) and in peripheral arthritis group (18 years) than axial disease group (27 years; p<0.05). Disease duration of axial onset group (11 years) was not different from that of peripheral onset group (9 years). Uveitis was more common in peripheral group (37%) than axial group (14%; p=0.043). Enthesopathy occurred in 14% of axial patients and 37% of peripheral arthritis patients. Spinal symptoms developed during the disease course in 68% of patients with peripheral arthritis onset. 69% of axial disease patients had peripheral joint disease after the onset. Frequency of radiographic sacroiliitis more than grade III/IV was similar among groups (46-53%), except for enthesopathy onset (0%). Spinal syndesmophytes were found more frequently in axial onset patients (33%), compared to patients with initial peripheral arthritis (16%), but it was not statistically significant.
Conclusions: No matter what patients with USpP/AS have as an initial symptom, more than half of them, except for enthsopathy onset group, had both axial and peripheral disease after the onset of disease. There seemed to be no difference in radiographic damage between patients with axial disease and those with peripheral arthritis at disease onset.

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REPRODUCIBILITY OF PERFORMANCE MEASURES OF PHYSICAL FUNCTION IN ANKYLOSING SPONDYLITIS

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Introduction: The objective of this study was to establish the test-retest reproducibility of performance measures of physical function in patients with Ankylosing Spondylitis (AS).
Materials and Methods: Data were obtained from 65 AS patients. Patients were tested on two occasions by one assessor with a one-week interval. Physical function was assessed via eight performance measures representing activities of daily living which AS patients frequently report to be problematic. For each activity a performance score was determined. For all activities, pain and exertion were also measured using a 10-cm horizontal Visual Analogue Scale (VAS) and Borg's modified scale, respectively. Test-retest reproducibility was assessed for all measurements using intraclass correlation coefficients (ICC) and by calculating the standard error of measurement (SEM).
Results: Adequate intra-rater reliability was found. For performance scores, ICCs ranged from 0.73-0.96. Measurements of exertion and pain also showed adequate intra-rater reliability, with the exception of one performance measure, namely the test for the ability to look over one's shoulder. For this test the ICCs were 0.66 and 0.69 for exertion and pain, respectively. The remaining ICCs for exertion ranged from 0.71-0.88 and for pain from 0.74-0.83. The SEM for performance scores ranged from 4-9% of the observed score. The SEM for exertion ranged from 8-11% and for pain from 10-15%, respectively.
Conclusions: Performance measures of physical function have adequate to excellent test-retest reproducibility. The performance measures are accurate for group assessment. Repeated measurements are advised for an adequate assessment of individual patients, due to the presence of measurement error.

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RELATIONSHIPS BETWEEN THE BASFI QUESTIONNAIRE AND PERFORMANCE MEASURES OF PHYSICAL FUNCTIONING IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Introduction: The objective of this study was to assess the relationships between the BASFI questionnaire and eight performance measures of daily activities extracted from the BASFI in patients with AS.
Materials and Methods: Data were obtained from 75 patients with AS. They all completed a BASFI questionnaire and eight performance measures within a one-month period. Eight performance measures reflecting daily physical function were extracted from the BASFI. (1. Putting on socks. 2. Bending forward. 3. Reaching up. 4. Reclining and declining from a chair. 5. Getting up from the. 6. Climbing stairs. 7. Looking over the shoulder. 8. Doing physically demanding activities). 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 compound movement of the rotation of the neck and the field of vision. Relationships between the BASFI items and corresponding performance tests were established by calculating Spearman Correlation Coefficients.
Results: Correlations between tests 1-6 and the corresponding BASFI items ranged from 0.36 to 0.49 (p=0.01). Test 7 showed a significant correlation of -0.55 (p=0.01). For test 8 no significant correlation was found with the corresponding BASFI item.
Conclusions: The BASFI seems to poorly reflect actual physical performance. This could indicate that performance tests provide unique information on physical functioning, in addition to the BASFI questionnaire. Further validation of the performance measurements has to be done in future.

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CORRELATIONS BETWEEN METROLOGY AND RADIOGRAPHIC SCORES IN AS

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Introduction: Patients with AS are routinely assessed in the clinical setting using the BASMI. The mSASSS is widely used to quantify radiographic change. The aim of this study was to determine the correlation between the two known methods of assessment whilst considering the extra components of radiographic cervical facet joint and hip disease.
Methods: 100 patients were randomly identified from the AS Specialist Clinic, Brisbane, all of whom met the modified New York diagnostic criteria. Each patient's mSASSS, and scores assessing the extent of cervical facet joint and hip damage, were determined by 2 scorers. BASMI measurements were performed by trained metrologists.
Results: The mSASSS and BASMI were closely correlated with each other (R=0.827). Both mSASSS and BASMI were correlated with disease duration (R=0.488, mSASSS; R=0.383, BASMI). The relationship of both scores with disease duration was linear, and there was no tendency for either score to plateau over time. By 18 years disease duration all patients had spinal radiographic change, suggesting that this outcome is inevitable in AS. mSASSS does not assess hip disease; removing the intermalleolar distance from the BASMI score did not improve the correlation of BASMI and mSASSS (R=0.816). The cervical component of the mSASSS was more closely correlated to cervical rotation than the tragus to wall measurement (R=0.811 vs. R=0.726). The cervical facet score was less strongly correlated with either cervical rotation or tragus to wall measurement (R=0.787 and 0.639 respectively) than cervical mSASSS. Cervical spine disease was more severe than lumbar spine disease in this cohort (mean cervical mSASSS 12.8, LS 6.2; $p<10\text{-}4$). Intermalleolar distance correlated with radiographic hip disease and disease duration. No patient with an intermalleolar distance of >116cm had radiographic hip disease.
Conclusion: Both mSASSS and BASMI document accurately the relentless progressive spinal fusion associated with AS. Metrology closely reflects radiographic change.

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