Ankylosing spondylitis

Jürgen Braun, Joachim Sieper

Ankylosing spondylitis is a common inflammatory rheumatic disease that affects the axial skeleton, causing characteristic inflammatory back pain, which can lead to structural and functional impairments and a decrease in quality of life. New imaging techniques and therapies have substantially changed the management of this disease in the past decade. Whether inhibition of radiographic progression and structural damage can be reached with available drugs is as yet unclear. Furthermore, treatment with non-steroidal anti-inflammatory agents and physiotherapy remains an important approach to long-term management of patients with ankylosing spondylitis. The new treatment options with tumour necrosis factor blockers seems a breakthrough for patients refractory to conventional treatment.

Lancet 2007; 369: 1379–90

Ruhr-Universität Bochum, Rheumazentrum Ruhrgebiet, 44652 Herne, Germany (Prof J Braun MD); **Medical Department I, Rheumatology, Charité, Campus Benjamin Franklin, Berlin, Germany** (Prof J Sieper MD)

Correspondence to: Prof Jürgen Braun **j.braun@rheumazentrum-ruhrgebiet.de**

Ankylosing spondylitis is the major subtype and a main outcome of an inter-related group of rheumatic diseases now named spondyloarthritides. Clinical features of this group include inflammatory back pain, asymmetrical peripheral oligoarthritis (predominantly of the lower limbs), enthesitis, and specific organ involvement such as anterior uveitis, psoriasis, and chronic inflammatory bowel disease. Aortic root involvement and conduction abnormalities are rare complications of ankylosing spondylitis. Five subgroups are differentiated clinically: ankylosing spondylitis, psoriatic spondyloarthritis, reactive spondyloarthritis, spondyloarthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthritis. The subgroups are genetically linked—the strongest known contributing factor is the MHC class I molecule HLA B27, although others still remain to be identified.

Epidemiology

Ankylosing spondylitis is a disease that affects young people, who generally present at around 26 years of age. Men are more often affected than are women, with a ratio of roughly 2 to 1.[1] About 80% of patients develop the first symptoms at an age younger than 30 years, and less than 5% of patients present at older than 45 years.[1] There is a rough correlation between the prevalence of HLA B27 and the incidence and prevalence of this disease in a specific population.[2] HLA B27 is most prevalent in northern countries and some tribes (with up to 50% of cases), and is highest in Eskimo populations and Haida Indians. Overall, the prevalence of ankylosing spondylitis is between 0·1% and 1·4%, with most of these data coming from Europe. In mid-Europe a prevalence of 0·3–0·5% for ankylosing spondylitis[3,4] and 1–2% for the whole group of spondyloarthritides seems probable, which is similar to that for rheumatoid arthritis.[5] The incidence of ankylosing spondylitis is between 0·5 and 14 per 100 000 people per year in studies from different countries.[6,7] Several factors contribute to these differences. First is the selection of the target populations; second, the selection of screening criteria such as back pain and the choice of diagnostic criteria to confirm the diagnosis; and third, the prevalence of HLA B27 and the distribution of its subtypes, which differs in populations with ethnic background.

Functional restrictions in patients with ankylosing spondylitis and a disease duration of 20 years are greater in those with a history of physically demanding jobs, more comorbid conditions, and in smokers, than in those with higher levels of education and a family history of this disease.[8] Young age at onset of symptoms is associated with worse functional outcomes.[9] In juvenile patients with spondyloarthritides, clinical symptoms can be different and include severe tarsitis.[10] Male patients have more structural changes, including bamboo spine, than do female patients.

Clinical features

Irrespective of the spondyloarthritis subtype, the main clinical features of this group are inflammatory back pain (panel 1) caused by sacroiliitis and inflammation at other locations in the axial skeleton, peripheral arthritis, enthesitis,[11] and anterior uveitis,[12] whereas manifestations in other organs, such as the heart, are rare.[13] Characteristic symptoms of ankylosing spondylitis are spinal stiffness and loss of spinal mobility, which are explained by spinal inflammation, structural damage, or both.[14] Spinal inflammation can arise as spondylitis, spondylodiscitis, or spondylarthritis. Structural changes are mainly caused by osteoproliferation rather than osteodestruction. Syndesmophytes and ankylosis are the most characteristic features of this disease, which are visible on conventional radiographs after some months to many years. Low bone density, osteoporosis,[15] and an increased rate of fractures,[16] which may add to the hyperkyphosis predominantly seen in male patients,[17] add to the burden of disease.

The peripheral arthritis is usually monoarticular or oligoarticular, and affects mainly but not exclusively the lower limbs.[18] The hip and shoulder joints become affect-

Search strategy and selection criteria

The Cochrane Library and Medline were searched from 2000–2006. The search terms "ankylosing spondylitis" and "spondyloarthritis" were used in combination with the terms "epidemiology", "pathogenesis", "genetics", "diagnosis", "management", and "therapy". Publications from the past 6 years were preferentially selected but important ones from the past millennium were also included according to our judgment.

Panel 1: **Modified New York criteria 1984 for ankylosing spondylitis**

Clinical criteria

- Low back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest
- Restriction of motion of the lumbar spine in both the sagittal and frontal planes
- Restriction of chest expansion relative to normal values correlated for age and sex

Radiological criterion

- Sacroiliitis grade ≥2 bilaterally, or grade 3–4 unilaterally

Definite ankylosing spondylitis is present if the radiological criterion is associated with at least one clinical criterion.[70]

ed in about 20% of patients with this disease. Hip involvement is regarded as a bad prognostic sign,[19] but there is no agreement on the definition of severe disease. Inflammation of entheseal sites takes place not only at classic sites such as the Achilles tendon and the plantar fascia but at many locations, including the spine. Eye inflammation in spondyloarthritides is largely restricted to the uvea and takes place usually unilaterally, but can switch from one side to the other.[12] For reactive spondyloarthritis, the eye can be affected by conjunctivitis.

Skin involvement (psoriasis) and colitis associated with inflammatory bowel disease can be regarded as basic subtype-defining entities with their own genetic background, different from HLA B27, rather than as disease manifestations. However, the spondyloarthritides have also been regarded as one disease with a common genetic background[20] and two major phenotypes.[21]

There are no good studies of prognosis in ankylosing spondylitis. Two retrospective studies[22,23] have suggested that much radiographic progression happens early in the first 10 years of disease, and more recent studies have shown that structural damage at presentation is the best predictor of further damage.[24] Amor and colleagues[19] proposed a list of prognostic items for the whole group of spondyloarthritis including hip involvement and early onset, which has been confirmed.[4]

Pathogenesis

The cause of ankylosing spondylitis and other spondyloarthritides is unknown. The two central features that deserve explanation are inflammation and new bone formation, especially in the spine. Although inflammation is assumed to trigger new bone formation, there is no close correlation between inflammation and osteoproliferation. There is a strong genetic effect in spondyloarthritides, especially in ankylosing spondylitis. About a third of this effect is explained by HLA B27; the remainder, as yet largely undefined, is associated with genes in and outside the MHC.[25] 90–95% of patients with ankylosing spondylitis are positive for HLA B27,[26] and the risk of this disease developing is as high as about 5% in HLA B27-positive individuals, and substantially higher in HLA B27-positive relatives of patients.[27] However, most HLA B27-positive individuals remain healthy.

The possible interaction between bacteria and HLA B27 has a crucial role in models of the pathogenesis of spondyloarthritides. The fact that reactive arthritis is triggered by genitourinary infections with *Chlamydia trachomatis* or by enteritis caused by gram-negative enterobacteria, such as *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter* spp[28] provides a solid background for this approach, but the evidence for triggering infections in other spondyloarthritides is marginal. The presence of microbial antigens in the synovium of patients with reactive arthritis[29] has suggested that persistence of microbial antigens could be essential for continuing joint inflammation. About 10–20% of HLA B27-positive patients with reactive arthritis develop the full clinical picture of ankylosing spondylitis after 10–20 years.[30] A possibly central role of bacteria in the pathogenesis of spondyloarthritides is further supported by the relation between Crohn's disease, HLA B27 positivity, and ankylosing spondylitis: 54% of HLA B27-positive patients with Crohn's disease develop ankylosing spondylitis, but only 2·6% of HLA B27-negative patients develop this disease.[31] Leakage of the gut mucosa, a result of inflammation caused by colitis such as found in Crohn's disease, leads to an interaction of the immune system with gut bacteria. In about 50% of patients with ankylosing spondylitis but no known Crohn's disease, macroscopic or microscopic mucosal chronic lesions resembling Crohn's disease have been detected in the gut mucosa.[32]

Finally, some evidence of the importance of the B27-bacteria interaction comes from work in animals. HLA B27 transgenic rats develop spondyloarthritis-like features, but many transgene copies are needed to transfer disease. Environmental factors also have a role since HLA B27 transgenic rats bred in a germ-free environment do not develop disease,[33] and gut flora contribute to the colitis.[34] However, persistence of microbial antigens in human spondyloarthritis in typically associated locations seems unlikely, and no candidate bacteria were detected by PCR in biopsies from sacroiliac joints.[35]

Cartilagenous structures—collagen type II and proteoglycan—have been studied as probable targets of an autoimmune response in ankylosing spondylitis.[11,36–39] Although the collagen-II-induced arthritis model resembles rheumatoid arthritis, animals immunised with proteoglycan show features typical of ankylosing spondylitis.[40] In patients with this disease, mononuclear cells invade cartilaginous structures of sacroiliac joints and intervertebral discs leading to destruction and ankylosis.[41] T-cell responses to aggrecan have been seen not only in spondyloarthritides but also in other arthritides.[42] Both CD4+[43] and CD8+ T-cell responses[44] to aggrecan and collagen-derived peptides have been reported in peripheral blood and synovial fluid specimens of patients with ankylosing spondylitis.[45] Immunohistological studies on sacroiliac joint biopsies have shown cellular infiltrates, including T cells and macrophages (figure 1).[36,46] Immunohistological examination of femoral heads of patients with this disease

undergoing total hip replacement[47] showed infiltrates of CD4+ and CD8+ T cells at the cartilage-bone interface, which are possibly dependent on the presence of cartilage. Immunohistological examination of zygapophysal joints from patients with this disease undergoing spinal surgery because of severe kyphosis[48] showed persistence of inflammation even in longstanding disease (figure 1).

Both innate and adaptive immune responses could have a role in spondyloarthritides. The finding that tumour necrosis factor (TNF)-α is overexpressed in sacroiliac joints (figure 1)[46] provided a strong rationale for the use of TNF-inhibitors, which are very effective in spondyloarthritides.

The remodelling of bone that explains squaring of vertebral bodies in ankylosing spondylitis is histologically based on acute and chronic spondylitis with destruction and simultaneous rebuilding of the cortex and spongiosa of the vertebral bodies. The development of square vertebral bodies is based on a combination of a destructive osteitis and repair.[49] The process of joint ankylosis partly recapitulates embryonic endochondral bone formation in a spontaneous model of arthritis in DBA-1 mice. Bone growth factors such as bone morphogenetic protein signalling are key molecular pathways associated with pathological changes.[50] Systemic gene transfer of noggin, an antagonist of bone morphogenetic protein, is effective both as a preventive and therapeutic strategy in this mouse model, since noggin interferes with enthesial progenitor cell proliferation. Immunohistochemical staining for phosphorylated smad1/5 in entheseal biopsies of patients with spondyloarthritides shows active bone morphogenetic protein signalling in similar target cells,[51] which suggests a role for these proteins in the pathogenesis of ankylosing spondylitis. In psoriatic arthritis[52] and ankylosing spondylitis,[47] an increased osteoclast activity has been reported. Osteoclasts are key in inflammation-associated bone loss in rheumatic diseases.[53]

Patients with ankylosing spondylitis are frequently given non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase (COX)-2-selective inhibitors. COX-2 is an inducible enzyme that converts arachidonic acid to prostaglandin E2, a modulator of bone metabolism.[54] The inhibition of radiographic progression by continuous intake of NSAIDs[55] could be explained by the inhibition of prostaglandins by these drugs. However, this finding needs to be confirmed. Several in-vitro studies and work in animals showed impaired bone healing in the presence of NSAIDs.[56] The steps associated with bone healing include an inflammatory response, bone resorption, and new bone formation. Prostaglandins have been shown to elicit and participate in inflammatory responses, increase osteoclast activity and subsequent bone resorption, and raise osteoblast activity and new bone formation. Through inhibition of COX and subsequently prostaglandins, NSAIDs could inhibit new bone formation. This inhibition is clinically used to prevent ossification after surgery, and there may be differences related to the degree of COX-1 and COX-2 inhibition.[57]

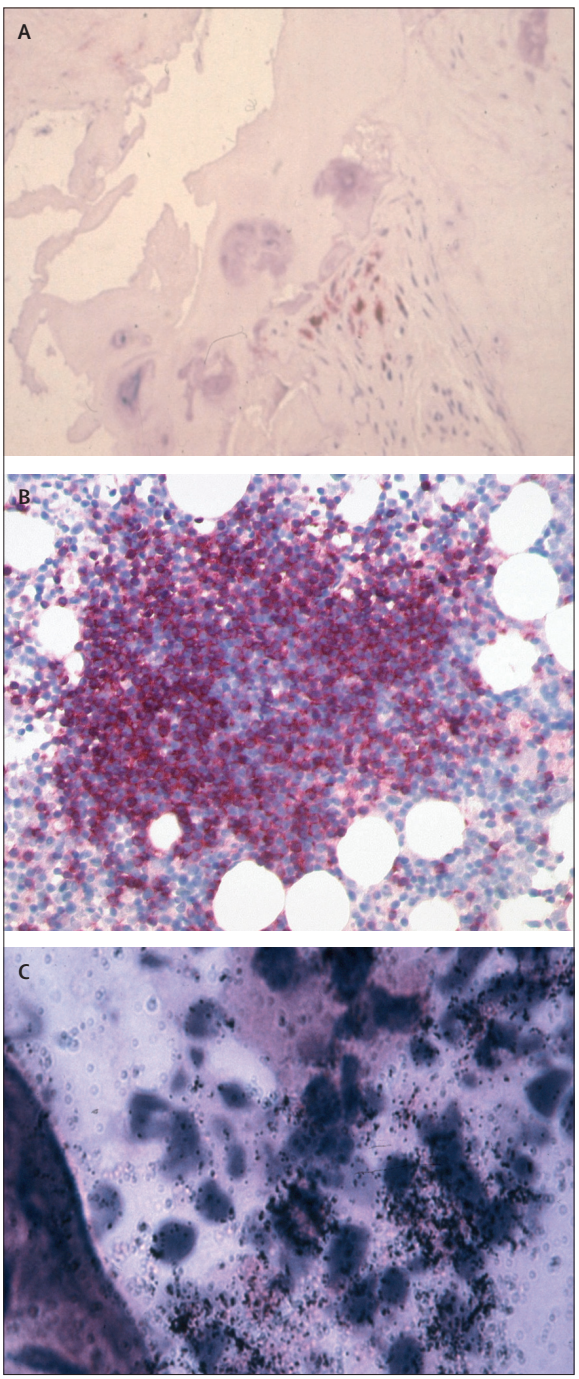

Figure 1: **Immunohistology in ankylosing spondylitis**
(A) T-cell infiltrate in a biopsy specimen obtained from the sacroiliac joint of a patient with ankylosing spondylitis. Reproduced from Bollow et al[36] with permission from BMJ Publishing Group. (B) Immunohistology of bone marrow close to a zygapophyseal joint of a patient with ankylosing spondylitis who underwent spinal surgery for correction of rigid hyperkyphosis. The presence of CD3+ T cell aggregates indicates ongoing inflammation in longstanding disease. Reproduced from Appel et al[48] with permission from Wiley-Liss, a subsidiary of John Wiley & Sons. (C) TNFa mRNA (in-situ hybridisation) in a biopsy specimen obtained from the sacroiliac joint of a patient with ankylosing spondylitis. Reproduced from Braun et al[37] with permission from Wiley-Liss, a subsidiary of John Wiley & Sons.

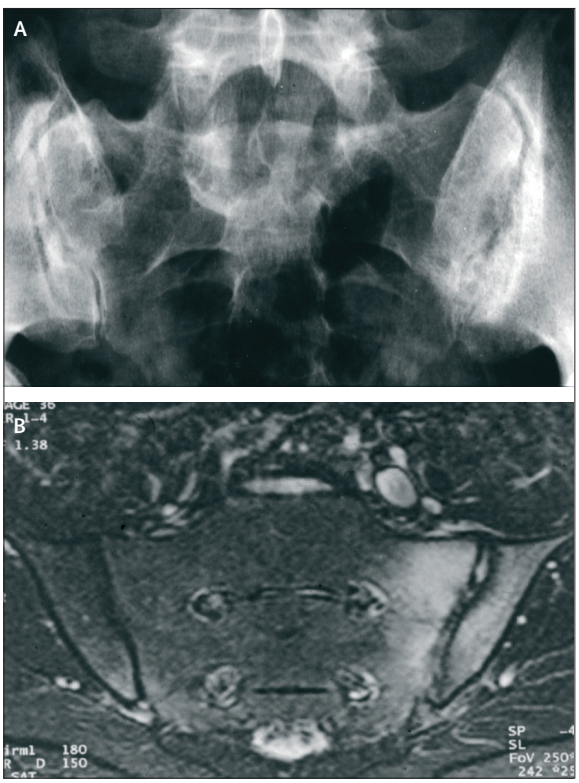

Figure 2: **Pelvic radiograph and MRI of the sacroiliac joint in two different patients with spondyloarthritis**
Radiograph showing chronic changes in the sacroiliac joints in a patient with ankylosing spondylitis (A) and MRI (STIR technique) showing active changes (sacroiliitis) in a patient with undifferentiated spondyloarthritis (B).

Possible combination of clinical, laboratory, or imaging SpA features	Post-test probability
IBP plus family history	51%
IBP plus heel pain	35%
IBP plus uveitis	54%
IBP plus synovitis	39%
IBP plus dactylitis	42%
IBP plus family history plus heel pain	78%
IBP plus uveitis plus NSAID*	85%
IBP plus heel pain plus synovitis plus alternating buttock pain	89%
IBP plus family history plus heel pain plus NSAID*	95%
IBP plus heel pain plus HLA-B27	83%
IBP plus NSAIDs* plus HLA-B27	88%
IBP plus heel pain without HLA-B27	6%
IBP plus NSAIDs* without HLA-B27	8%
IBP plus dactylitis plus ESR/CRP	62%
IBP plus HLA-B27 plus ESR/CRP	78%
IBP plus HLA-B27 without ESR/CRP	47%
IBP plus HLA-B27 plus MRI	93%
IBP plus HLA-B27 without MRI	14%
IBP plus heel pain plus HLA-B27 without MRI	35%

The pretest probability of low back pain is assumed to be 5%. IBP=inflammatory back pain. SpA=axial spondylarthritis. CRP=C-reactive protein. *A good response to NSAIDs is needed. Adapted from Radwaleit et al[16] with permission of BMJ Publishing Group.

Table: **Probability of axial spondylitis with or without various combinaions of features in patients with low back pain**

Genetics

Although HLA B27 itself is the most important gene predisposing to ankylosing spondylitis, there is clear evidence of association of other genes with susceptibility to this disease. Studies (in twins)[25] suggest a contribution of HLA B27 of only about 20–30% of the total genetic risk in this disease, whereas the whole MHC contributes about 40–50%. The concordance rate is 63% for B27-positive monozygotic twin pairs, and 23% for dizygotic twin pairs. Furthermore, HLA B27-positive individuals with a first-degree relative having ankylosing spondylitis have a six to 16 times greater risk of developing the disease themselves than do B27-positive individuals with no family history.[25,58] All these data suggest that non-B27 familial factors have a strong effect on the risk of developing this disease.

Besides HLA B27, other MHC genes such as HLA B60 and HLA DR1 seem to be associated with ankylosing spondylitis but they are of minor importance. The TNFα gene is another candidate gene located within the MHC, but a major role of TNF polymorphisms in patients with this disease is unlikely.[59] Genome-wide linkage screens have suggested several additional genetic markers distributed on different chromosomes,[60,61] none of which is conclusive. There is some evidence for the presence of a non-MHC susceptibility locus for spondyloarthritides mapping to 9q31-34.[62] No linkage of the X chromosome (suspected to be a candidate gene because of the sex bias of ankylosing spondylitis), has been reported.[63] Suggestive gene markers include genes associated with diseases that predispose to spondyloarthritides such as psoriasis and inflammatory bowel disease, or markers that could encompass genes relevant for immune responses, such as antigen processing and presentation or cytokine responses. For example, occurrence of acute anterior uveitis might be associated with a gene region located on chromosome 9.[64] The interleukin-1 gene cluster located on chromosome 2 is involved in ankylosing spondylitis,[65] but which exact genes are causatively involved is as yet unclear. NOD 2 (nucleotide-binding oligomerisation domain protein 2, CARD15) genotypes located on chromosome 16 are associated with Crohn's disease but not with primary ankylosing spondylitis.[66] Other candidate gene analyses in this disease, such as on TGFβ (transforming growth factor β) and interleukin-6 polymorphisms, were negative. Thus, there is a definite contribution of genes other than HLA B27. Most genetic studies are on susceptibility but there are also some on severity that also suggest a strong genetic rather than an environmental effect.[67]

Diagnosis and classification

Radiography

Sacroiliitis is a hallmark of ankylosing spondylitis, especially in earlier disease stages. It has become a major means for the development of classification criteria because of its very high prevalence in patients with ankylosing spondylitis. The first criteria set for classification, developed in 1961 in

Rome, Italy,[68] did not need radiographs of the sacroiliac joints to make a diagnosis, but in the 1966 New York (USA) criteria radiographic evidence of sacroiliac joint changes were included.[69] The proposed grading system scored a healthy radiograph of the sacroiliac joints as 0, suspicious changes as 1, minor changes as 2, moderate changes as 3 (figure 2), and ankylosis as 4. The last modification of the New York criteria[70] introduced the clinical parameter of inflammatory back pain, and changed the criterion restriction of chest expansion by age and sex adjustment of the normal values (panel 1). These 1984 criteria are used not only for classification, but also for diagnosis of patients with ankylosing spondylitis.

Since radiographs of the sacroiliac joints could appear normal in the early phase of disease, structural changes might become apparent only after some years, which is relevant for a rather large proportion of patients with this disease.[71,72] With the introduction of MRI the fact that radiography of the sacroiliac joints detects the structural results of inflammation (cartilage and bone damage) rather than inflammation itself has become obvious. Accordingly, the MRI technique allows for the detection of inflammation in the sacroiliac joints in patients early in the course of their disease when no chronic changes are detectable.[37] This latency in the radiographic detection of chronic changes in the sacroiliac joints contributes to the diagnostic delay in ankylosing spondylitis.[1,73]

Clinical criteria

To allow for an earlier diagnosis of spondyloarthritides for patients with predominant axial or peripheral manifestations of disease, two sets of criteria were developed about 15 years ago which are more clinically based—the European Spondyloarthropathy Study Group[18] and the Amor criteria.[74] Radiographic evidence of sacroiliitis was included in both criteria sets as an optional item but not as a prerequsite for diagnosis. Both sets work well as classification criteria—validation studies in various populations showed a sensitivity and specificity of about 85%.[75] However, even though these criteria sets have also been used to make a diagnosis in clinical practice because of few alternatives, all sets for ankylosing spondylitis and spondyloarthritis were developed for classification but not for diagnostic purposes. The process of classification implies a diagnostic selection beforehand, and, by contrast with diagnostic criteria, knowledge of the pretest probability of having the disease is not necessary.[72] The use of classification criteria for diagnosis could result in an overestimation or underestimation of the frequency of the disease.

A systematic approach to diagnose patients presenting with early predominantly axial spondyloarthritis has been developed.[72,76] The first step is an estimation of the pretest probability of the disease.[77] In a cohort of patients with chronic low back pain in a primary care physician setting, spondyloarthritis was diagnosed in 5% of cases, which is the assumed pretest probability of this disease.[78] The likelihood of a diagnosis of spondyloarthritis is best if at least three clinical, laboratory, or imaging indices are positive (table).[72,76] The pretest probability could be different in other settings.

***Panel 2:* New criteria for inflammatory back pain in young to middle-aged adults (<50 years) with chronic back pain.**

- Morning stiffness >30 minutes
- Improvement in back pain with exercise but not with rest
- Awakening because of back pain during the second half of the night only
- Alternating buttock pain

The criteria are fulfilled if at least two of four of the parameters are present (sensitivity 70·3%, specificity 81·2%). Adapted from Rudwaleit et al[80] with permission from Wiley-Liss, a subsidiary of John Wiley & Sons.

The clinical symptom of inflammatory back pain is important for the diagnosis of spondyloarthritis and ankylosing spondylitis,[79] including early and late stages, and also classification.[18,70,74] However, because of restricted sensitivity and specificity of inflammatory back pain, a combination with other indices suggestive of spondyloarthritis is needed. A novel set of classification criteria for inflammatory back pain has been developed on the basis of a controlled study showing a specificity of 81% and a sensitivity of 70% if two of four indices are positive.[80] However, the diagnostic yield is better than this result when three of four indices are fulfilled (panel 2).

The development of criteria allowing for an early diagnosis of ankylosing spondylitis is important to alert primary care physicians to consider spondyloarthritis in patients with chronic back pain. To establish when to refer patients to a rheumatologist for diagnosis is of similar relevance. Screening indices for early referral of patients with ankylosing spondylitis by primary care physicians have been proposed.[81] A diagnosis of spondyloarthritis was predicted in every third to fifth patient with chronic (>3 months) low back pain that started at an age younger than 45 years who either has the clinical symptom of inflammatory back pain, carries HLA B27, or has sacroiliitis shown by imaging. How such criteria perform in daily clinical practice remains to be seen.

Laboratory tests

There are two main laboratory indices that are potentially relevant for a diagnosis of spondyloarthritis—HLA B27 and C-reactive protein.[76] However, the role of the erythrocyte sedimentation rate is less clear. HLA B27 is an important factor for diagnosis of early spondyloarthritis. The performance of the HLA-B27 test depends on the population prevalence of HLA B27, which varies for different races. There is no need to measure HLA-B27 subtypes in white patients, but subtyping might be needed for Chinese patients, in whom some subtypes (eg, HLA-B*2706) are not associated with ankylosing spondylitis. The correlation of disease activity with laboratory indices of inflammation is restricted. Only half of patients with this disease have raised C-reactive protein concentrations.[82]

Imaging

Imaging is crucial for the diagnosis and classification of spondyloarthritides, especially ankylosing spondylitis, because conventional radiography is sufficiently sensitive in established disease since more than 95% of patients have structural changes in the sacroiliac joints (figure 2).[83] Furthermore, the detection of typical syndesmophytes (figure 3) could be useful for diagnosis in individual patients. These possible osteoproliferative changes, however, do not tend to take place early in the course of the disease. Therefore, MRI, with its capacity to visualise active inflammation, has been of much additional diagnostic benefit in early disease when a field strength of T2 for fat saturated and short T1 inversion recovery (STIR) or a field strength of T1 after application of contrast agents such as gadolinium-diethylenetriamine penta-acetic acid are used. For screening purposes, contrast agents are not necessary since the STIR technique is sufficient.[84]

MRI has proved especially useful for identification of early sacroiliitis (figure 2)[37] and spondylitis (figure 3),[85] including patients with undifferentiated spondyloarthritis.[86] MRI of the sacroiliac joints can predict the development of structural radiographic changes in these joints with a positive predictive value of 60% 3 years before they occur.[87] MRI measurements of the spine (figure 3)[88] as assessed by a new scoring system are sensitive to change in patients with ankylosing spondylitis and inflammatory back pain on antiTNF therapy.[89,90] The assessment of chronic changes by MRI[91] is still under investigation, but conventional radiography is more sensitive to detect structural changes than is MRI.[92] Therefore, a radiograph of the sacroiliac joints is always needed, especially at early disease stages because 20–30% of patients within the first 2 years of inflammatory back pain will already have developed structural changes. MRI is not only useful for detection of enthesitis and synovitis in the axial skeleton but also in peripheral joints and entheses,[93] which are also well assessed by ultrasonography.[94]

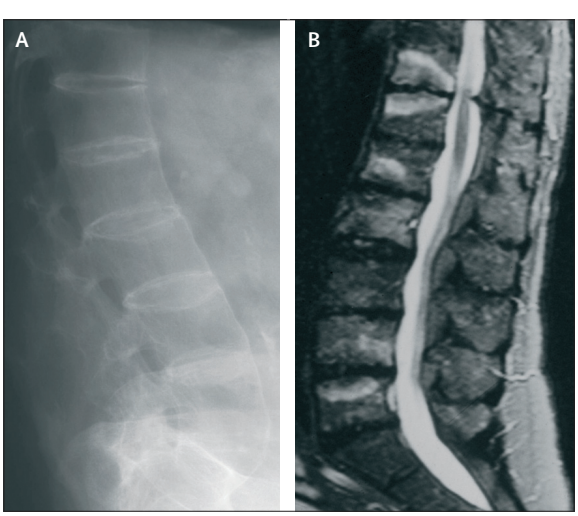

Figure 3: **Chronic and active changes in the lumbar spine of a patient with ankylosing spondylitis**
Syndesmophytes shown on radiograph (A) and spondylitis and spondylodiscitis shown by T2 weighted MRI (B).

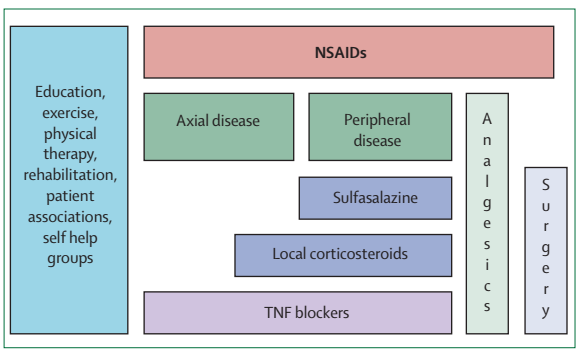

Figure 4: **Flow chart of the ASsessment of Ankylosing Spondylitis (ASAS) and European League Against Rheumatism (EULAR) recommendations for the management of ankylosing spondylitis.**
Adpated from Zochling et al[98] with permission from BMJ Publishing Group. NSAIDs=non-steroidal anti-inflammatory drugs.

The cost-effectiveness of these imaging techniques in early disease has not yet been assessed. Nevertheless, from a clinical point of view there seems little doubt that MRI should be included in future classification and diagnostic criteria for early spondyloarthritides. In the assessment of patients with possible spondyloarthritides and low back pain, differentiation between the search for active and acute changes from chronic changes is important. For active and acute changes, MRI with appropriate sequences such as STIR are useful, and in centres of excellence scintigraphy is also of use, especially when the indication includes screening for other affected sites. For the detection of chronic changes in the sacroiliac joints CT is most useful;[95] however, the technique should not be used routinely because of a high exposure to radiation. Conventional radiography is still the gold standard for the detection of chronic structural changes in the sacroiliac joints and spine. The modified Stoke ankylosing spondylitis spinal score is the most useful scoring method for assessment of spinal damage in clinical studies.[96] In this system, syndesmophytes are most important. Radiographic damage at baseline is the strongest predictor of future structural changes.[97]

Management

Ten main recommendations for the management of ankylosing spondylitis have been proposed by a combined ASsessment in Ankylosing Spondylitis working group (ASAS) and European League Against Rheumatism (EULAR) task force (figure 4).[98] Briefly, the treatment of ankylosing spondylitis should be tailored according to the manifestations of the disease at presentation, severity of symptoms, and several other features that include the wishes and expectations of the patient. The disease monitoring of patients should include history, clinical features, laboratory tests, and imaging. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drugs. The best treatment needs a combination of non-pharmacological

and pharmacological treatment methods, including education and physical therapy. AntiTNF therapy should be given according to ASAS recommendations.[99] Joint replacement has to be considered in patients with radiographic evidence of advanced hip involvement who have refractory pain and disability. Spinal surgery is useful in selected patients with symptoms and disability because of disabilitating posture or instable spine.

Basic principles of treatment

The standard treatment of spinal symptoms for patients with ankylosing spondylitis has consisted of NSAIDs[100]and structured exercise programmes[101] for decades. Whether and to what extent physical therapy and exercise are beneficial in every stage of the disease (eg, in very active disease) is unknown. Disease activity, especially the degree of spinal inflammation, function, and damage, probably affects the outcome of physical therapy and regular exercise. Non-pharmacological therapy consists of spa treatment,[102] education, and self-help groups, as well as physical therapy. A Cochrane review[103] showed that there is little evidence for effectiveness of non-pharmacological intervention, but there is strongly positive expert opinion. Although the general effect size is believed to be rather small, it is clear from clinical experience that individual patients with ankylosing spondylitis may have definite benefit from intensive physiotherapy. Intensive spa therapy has proved more effective than standard prescriptions of exercises in an outpatient setting, especially after several months.[102]

NSAIDs

In general, NSAIDs work rather well in patients with ankylosing spondylitis. A good response to NSAIDs has even been identified as a diagnostic sign for spondyloarthritides,[74] although a state of non-responsiveness to these drugs might identify those with a poor prognosis.[19] Clinical experience suggests that patients with active disease should be continuously given NSAIDs in a dose sufficient to control pain and stiffness. Some researchers[55] have even suggested that continuous dosing with NSAIDs rather than the usual on-demand prescription decelerates radiographic progression over 2 years. However, NSAIDs, including COX-2 inhibitors, are known to have gastrointestinal and possible cardiovascular toxic effects,[104] which could restrict their use. Furthermore, about half of patients with this disease report insufficient control of their symptoms by NSAIDs alone.[98]

Disease-modifying antirheumatic drugs

The use of disease-modifying antirheumatic drugs for the treatment of axial disease in spondyloarthritides has been rather disappointing. Treatments that are effective in suppression of disease activity and slowing of progression in rheumatoid arthritis have notably failed to affect patients with spondyloarthritides, especially those with spinal disease.[90,98] Sulfasalazine improves peripheral arthritis associated with spondyloarthritis, but not spinal pain.[105,106] However, there are differences between the trials related to disease duration and the proportion of patients with peripheral arthritis. Thus, the effectiveness of sulfasalazine in earlier disease stages might differ from that at later stages. Indeed, in a controlled trial[107] of sulfasalazine in undifferentiated spondyloarthritis and early ankylosing spondylitis, some improvement of spinal pain was noted since patients with inflammatory back pain but no peripheral arthritis had substantially more improvement in disease activity than did the placebo group despite use of fewer NSAIDs.[107] However, all patients improved, and definite conclusions are difficult to draw.

Methotrexate is generally used in patients with rheumatoid arthritis to improve symptoms and slow progression of erosive disease. However, such improvement is not seen in ankylosing spondylitis, suggesting

***Panel 3:* Updated assessment in ankylosing spondylitis (ASAS) criteria for antiTNF therapy in ankylosing spondylitis**

Diagnosis

Patients who usually fulfil modified New York criteria (panel 1) for definitive AS

Active disease

Active disease for at least 4 weeks

BASDAI ≥4 (range 0–10) and an expert opinion*

Treatment failure

All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as:

- Treatment for at least 3 months at maximum recommended or tolerated anti-inflammatory dose unless contraindicated
- Treatment for <3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications

Patients with pure axial features do not have to take DMARDs before antiTNF therapy can be started

Patients with symptomatic peripheral arthritis should have undergone at least one local corticosteroid injection if appropriate and should have responded insufficiently

Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine†

Patients with symptomatic enthesitis must have failed appropriate local treatment

All three of the above points have to be fulfilled before treatment with TNF blockers is started.

Contraindication

Women who are pregnant or breastfeeding; effective contraception must be practised

Active infection

Patients at high risk of infection including:

- Chronic leg ulcer
- Previous tuberculosis
- Septic arthritis of a native joint within the past 12 months
- Sepsis of a prosthetic joint within the past 12 months, or indefinitely if the joint remains in situ
- Persistent or recurrent chest infections
- Indwelling urinary catheter

History of lupus or multiple sclerosis

Malignant disease or premalignant states excluding:

- Basal cell carcinoma
- Malignant diseases diagnosed and treated more than 10 years previously (where the probability of total cure is very high)

(Continues on next page)

(Continued from previous page)

Assessment of disease

ASsessment of Ankylosing Spondylitis (ASAS) core set for daily practice

- Physical function (BASFI or Dougados functional index)
- Pain (VAS, last week, pain at night and spine pain in general)
- Spinal mobility (chest expansion and modified Schober and occiput to wall distance and lateral lumbar flexion)
- Patient's general assessment (VAS, last week)
- Stiffness (duration of morning stiffness, spine, last week)
- Peripheral joints and entheses (number of swollen joints [44 joints count], enthesitis score such as developed in Maastricht, Berlin, or San Francisco)
- Acute phase reactants (ESR or CRP)
- Fatigue (VAS)

BASDAI

- VAS overall level of fatigue/tiredness past week
- VAS overall level of AS neck, back, or hip pain past week
- VAS overall level of pain/swelling in joints other than neck, back, or hips past week
- VAS overall discomfort from any areas tender to touch or pressure past week
- VAS overall level of morning stiffness from time of awakening past week
- Duration and intensity (VAS) of morning stiffness from time of awakening (up to 120 mins)

Assessment of response

Responder criteria

- BASDAI: 50% relative change or absolute improvement of 20 mm (0–100) and expert opinion: continuation yes/no

Time of assessment

- Between 6 and 12 weeks

VAS=visual analogue scale; all VAS can be replaced by a numerical rating scale (NRS). BASDAI=Bath ankylosing spondylitis disease activity index. BASFI=Bath ankylosing spondylitis functional index. AS=ankylosing spondylitis. *A physician, usually a rheumatologist, with expertise in inflammatory back pain and the use of biological substances. Expert should be locally defined. An expert opinion consists of both clinical features (history and examination) and either serum acute-phase reactant concentrations or imaging results, such as radiographs showing rapid progression or MRI scans indicating continuing inflammation. †Treatment for at least 4 months at standard target dose or maximum tolerated dose unless contraindicated or not tolerated. Treatment for less than 4 months, in which treatment was withdrawn because of intolerance or toxicity or contraindicated. Adapted from Braun et al[99] with permission from BMJ Publishing Group.

another pathomechanism. A systematic review[108] of the use of methotrexate in ankylosing spondylitis showed that there was no evidence for an effect on inflammatory back pain and inconclusive evidence of effectiveness for peripheral joint disease. The only randomised controlled trial[109] of this drug in patients with ankylosing spondylitis failed to show a significant effect of oral methotrexate (7·5 mg per week) on spondylitis, but there was some improvement of peripheral arthritis. A 16-week open label trial[110] of methotrexate, 20 mg subcutaneously, in 20 patients with ankylosing spondylitis did not show any effect on axial symptoms and only some improvement in peripheral symptoms. In contrast to these findings, many rheumatologists are still using methotrexate for ankylosing spondylitis because there used to be no other options. The differences in response between peripheral and axial symptoms might be explained by predominant synovitis for peripheral manifestations and predominant enthesitis for axial manifestations.

Similarly, leflunomide is effective in treatment of symptoms and slowing radiographic change in rheumatoid arthritis. In ankylosing spondylitis, leflunomide was not effective for axial manifestations,[111,112] but patients with peripheral arthritis had some benefit.[111] However, this drug is effective in patients with psoriatic arthritis.[113] Maksymowych and co-workers[114] suggested that bisphosphonates could be useful for spinal symptoms for patients with ankylosing spondylitis. However, other studies with pamidronate failed to show a similar effect.[115] Thalidomide was also used with some success[116] but is regarded as too toxic for widespread use.

TNF blockers

The introduction of TNF blockers has been the most substantial development in the treatment of ankylosing spondylitis and other spondyloarthritides in the past few years.[98] Three such agents are now approved for ankylosing spondylitis: the monoclonal chimeric antibody infliximab, which is given intravenously in a dose of 3–5 mg per kg every 6–8 weeks (approved regimen is 5 mg/kg every 6–8 weeks), the fully humanised monoclonal adalimumab which is given subcutaneously in a dose of 40 mg every other week, and the 75 kD TNF receptor fusion protein etanercept given subcutaneously in a dose of 50 mg once per week or 25 mg twice per week. The success of antiTNF treatment in spondyloarthritis is probably a class effect. There is some evidence that this treatment works even better in spondyloarthritis than in rheumatoid arthritis.[117]

Large randomised, placebo-controlled trials[118,119] of infliximab, etanercept,[120,121] and adalimumab[122,123] in patients with ankylosing spondylitis have shown impressive short-term improvements in spinal pain, function, and inflammatory markers. As experience with these therapies increases to 2–5-year trials,[124,125] effectiveness could persist with continuing treatment, and more than a third of patients are in remission. These trials show substantial improvement of pain, function, and disease activity in patients with active disease compared with placebo. Indeed, all outcome measures including Bath ankylosing spondylitis disease activity index (BASDAI), functional index (BASFI), and metrology index (BASMI), and the physical component of the SF-36 health survey improved greatly after 24 and 102 weeks. The improvement usually starts within 2 weeks of therapy and C-reactive protein concentrations also tend to decrease rapidly.

Alongside the reported long-term effectiveness and safety of TNF blockers in ankylosing spondylitis, the loss of response after cessation of continuous therapy with infliximab for 3 years is important,[126] but readministration has been successful and has not caused problems. Treatment with infliximab decreases active spinal inflammation as detected by MRI.[89,90] No substantial radiological progression of disease as assessed by the modified Stoke ankylosing spondylitis spine score (SASSS), which scores radiographs in ankylosing spondylitis,[127] was seen in a few patients with this disease who were given infliximab for 2 years.[128]

The effectiveness of etanercept in this disease was also seen,[129] and the higher percentage of assessment of

ankylosing spondylitis responders in the active therapy group was confirmed in randomised controlled trials,[120,121] in which 20–30% of patients continued treatment with disease-modifying antirheumatic drugs and corticosteroids. After several months without etanercept therapy[129,130] all patients had had a relapse of disease activity, but reintroduction of the treatment was effective and safe. The clinical effectiveness of etanercept was also confirmed by MRI.[131] Adalimumab was also proved effective in patients with ankylosing spondylitis in a pilot study,[122] and this result was confirmed in a randomised controlled trial[123] in which the pain of some patients with even advanced spinal ankylosis also improved.

The first pilot studies[129,132] of infliximab and etanercept in undifferentiated spondyloarthritis have also been successful. Similarly to infliximab, etanercept and adalimumab are effective for peripheral joint and skin symptoms in patients with psoriatic arthritis.[133] Etanercept is effective for rheumatic manifestations in inflammatory bowel disease for joint and spine but not gut symptoms.[134] Furthermore, etanercept has no effect on inflammatory bowel disease,[135] unlike infliximab, which is approved for Crohn's disease[136] and ulcerative colitis.[137] Thus, etanercept is not recommended for the small spondyloarthritis subgroup with concomitant inflammatory bowel disease. There could also be a difference in the prevention and treatment of anterior uveitis.[138]

Clinical disease activity and spinal inflammation as detected by MRI are substantially reduced by TNF blockers, as shown after short-term and long-term antiTNF therapy.[122,131,139] Whether antiTNF treatment is able to stop radiographic progression has not yet been proven. In a disease with pronounced long-term functional disability due to the development of syndesmophytes and spinal ankylosis,[14] any treatment that does not only suppress disease activity but also prevents or decelerates structural damage and decline of function will be of great importance for patient care. Recommendations on which patients with ankylosing spondylitis should be given TNF-blockers are especially needed because of possible side-effects and the high costs of these drugs. Thus, patients with the best risk to benefit ratio should be treated preferentially. An international assessment of ankylosing spondylitis consensus statement for the use of antiTNF agents in patients with this disease was reported in 2003[140] and updated in 2006.[99] Panel 3 shows a summary of these recommendations for the initiation of antiTNF α therapy. Prediction of response is difficult. However, it seems clear that patients early in the course of their disease, with raised C-reactive protein concentrations,[141] positive MRI findings, or less structural damage are more likely to respond than are patients with advanced disease, but overall all patient subgroups could benefit from this treatment.

Anakinra is a recombinant human interleukin-1 receptor antagonist, which is directed at a different cytokine in the inflammatory response than TNF blockers. By contrast with TNF, whether interleukin-1 is present in sacroiliac joints is unclear. Two open studies[142,143] of anakinra in ankylosing spondylitis showed partly conflicting results. Other biological compounds have not been tested so far.

Socioeconomics

Cost-effectiveness is an issue when expensive treatments are discussed. Despite the high costs, the clinical benefits[118] and improvements in quality of life in patients with ankylosing spondylitis given infliximab result in lower disease-associated costs than does standard care, which translates to a short-term cost of about US$70 000 (GB£35 000) per quality-adjusted life year (QALY) gained[144]—an amount societies might be willing to pay. However, the calculated costs were higher than this figure in other analyses.[145] When modelling for long-term therapy, with yearly disease progression of 0·07 of the BASFI in the sensitivity analysis, the cost per QALY gained is reduced to less than $20 000 (£10 000).[144] Until long-term data on disease progression with antiTNF therapy in patients with ankylosing spondylitis are available, these conclusions remain hypothetical, but the costs for antiTNF therapy seem to fall well inside what is thought of as cost effective. Furthermore, the daily productivity of patients with active disease, which was substantially associated with functional impairment and disease activity, greatly improved with infliximab, and this was associated with reduced workday loss in employed patients.[146]

Conflict of interest statement

J Braun and J Sieper have received consultancy and speaker's fees, honoraria, and research funding from several companies including Abbott, Amgen, Centocor, MSD, Novartis, Pfizer, Roche, Schering-Plough, and Wyeth but they had no conflict when writing this paper.

References

1 Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003; **23:** 61–66.

2 Khan MA. Epidemiology of HLA-B27 and arthritis. *Clin Rheumatol* 1996; **15** (suppl 1): 10–12.

3 Braun J, Bollow M, Remlinger G, et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998; **41:** 58–67.

4 Braun J, Listing J, Sieper J. Reply. *Arthritis Rheum* 2005; **52:** 4049–50.

5 Saraux A, Guedes C, Allain J, et al. Prevalence of rheumatoid arthritis and spondyloarthropathy in Brittany, France. Societe de Rhumatologie de l'Ouest. *J Rheumatol* 1999; **26:** 2622–27.

6 Akkoc N, Khan MA. Epidemiology of ankylosing spondylitis and related spondyloarthropathies. In: Weisman MH, Reveille JD, van der Heijde D, eds. Ankylosing spondylitis and the spondyloarthropathies. London: Mosby, 2005: 117–131.

7 Bakland G, Nossent HC, Gran JT. Incidence and prevalence of ankylosing spondylitis in Northern Norway. *Arthritis Rheum* 2005; **53:** 850–55.

8 Ward MM, Weisman MH, Davis JC, Jr., Reveille JD. Risk factors for functional limitations in patients with long-standing ankylosing spondylitis. *Arthritis Rheum* 2005; **53:** 710–17.

9 Stone M, Warren RW, Bruckel J, Cooper D, Cortinovis D, Inman RD. Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. *Arthritis Rheum* 2005; **53:** 445–51.

10 Burgos-Vargas R, Vazquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. *Arthritis Rheum* 1995; **38:** 835–44.

11 McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet* 1998; **352:** 1137–40.

12 Martin TM, Smith JR, Rosenbaum JT. Anterior uveitis: current concepts of pathogenesis and interactions with the spondylo-arthropathies. *Curr Opin Rheumatol* 2002; **14:** 337–41.

13 Lautermann D, Braun J. Ankylosing spondylitis—cardiac manifestations. *Clin Exp Rheumatol* 2002; **20** (suppl 28)**:** S11–15.

14 Wanders A, Landewe R, Dougados M, Mielants H, van der Linden S, van der Heijde D. Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: can assessment of spinal mobility be a proxy for radiographic evaluation? *Ann Rheum Dis* 2005; **64:** 988–94.

15 Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol* 2005; **32:** 1290–98.

16 Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Fracture risk in patients with ankylosing spondylitis: a population based study. *J Rheumatol* 1994; **21:** 1877–82.

17 Vosse D, van der Heijde D, Landewe R, et al. Determinants of hyperkyphosis in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 770–74.

18 Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; **34:** 1218–27.

19 Amor B, Santos RS, Nahal R, Listrat V, Dougados M. Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol* 1994; **21:** 1883–87.

20 Said-Nahal R, Miceli-Richard C, D'Agostino MA, et al. Phenotypic diversity is not determined by independent genetic factors in familial spondylarthropathy. *Arthritis Rheum* 2001; **45:** 478–84.

21 Porcher R, Said-Nahal R, D'Agostino MA, Miceli-Richard C, Dougados M, Breban M. Two major spondylarthropathy phenotypes are distinguished by pattern analysis in multiplex families. *Arthritis Rheum* 2005; **53:** 263–71.

22 Carette S, Graham D, Little H, Rubenstein J, Rosen P. The natural disease course of ankylosing spondylitis. *Arthritis Rheum* 1983; **26:** 186–90.

23 Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: a study of 100 patients. *Br J Rheumatol* 1997; **36:** 766–71.

24 van der Heijde D. Radiographic progression in ankylosing spondylitis. *Ann Rheum Dis* 2004; **63** (suppl 1)**:** 98.

25 Brown MA, Kennedy LG, MacGregor AJ, et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. *Arthritis Rheum* 1997; **40:** 1823–28.

26 Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A 27. *Lancet* 1973; **301:** 904–07.

27 van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984; **27:** 241–19.

28 Sieper J, Braun J, Kingsley GH. Report on the fourth international workshop on reactive arthritis. *Arthritis Rheum* 2000; **43:** 720–34.

29 Granfors K, Jalkanen S, von Essen R, et al. Yersinia antigens in synovial-fluid cells from patients with reactive arthritis. *N Engl J Med* 1989; **320:** 216–21.

30 Leirisalo-Repo M, Helenius P, Hannu T, et al. Long-term prognosis of reactive salmonella arthritis. *Ann Rheum Dis* 1997; **56:** 516–20.

31 Purrmann J, Zeidler H, Bertrams J, et al. HLA antigens in ankylosing spondylitis associated with Crohn's disease. Increased frequency of the HLA phenotype B27,B44. *J Rheumatol* 1988; **15:** 1658–61.

32 De Vos M, Cuvelier C, Mielants H, Veys E, Barbier F, Elewaut A. Ileocolonoscopy in seronegative spondylarthropathy. *Gastroenterology* 1989; **96:** 339–44.

33 Taurog JD, Richardson JA, Croft JT, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; **180:** 2359–64.

34 Onderdonk AB, Richardson JA, Hammer RE, Taurog JD. Correlation of cecal microflora of HLA-B27 transgenic rats with inflammatory bowel disease. *Infect Immun* 1998; **66:** 6022–23.

35 Braun J, Tuszewski M, Ehlers S, et al. Nested polymerase chain reaction strategy simultaneously targeting DNA sequences of multiple bacterial species in inflammatory joint diseases. II. Examination of sacroiliac and knee joint biopsies of patients with spondylo-arthropathies and other arthritides. *J Rheumatol* 1997; **24:** 1101–05.

36 Bollow M, Fischer T, Reisshauer H, et al. Quantitative analyses of sacroiliac biopsies in spondyloarthropathies: T cells and macrophages predominate in early and active sacroiliitis-cellularity correlates with the degree of enhancement detected by magnetic resonance imaging. *Ann Rheum Dis* 2000; **59:** 135–40.

37 Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum* 1995; **38:** 499–505.

38 Poole AR. The histopathology of ankylosing spondylitis: are there unifying hypotheses? *Am J Med Sci* 1998; **316:** 228–33.

39 Maksymowych WP. Ankylosing spondylitis—at the interface of bone and cartilage. *J Rheumatol* 2000; **27:** 2295–301.

40 Zhang Y. Animal models of inflammatory spinal and sacroiliac joint diseases. *Rheum Dis Clin North Am* 2003; **29:** 631–45.

41 Bardos T, Szabo Z, Czipri M, et al. A longitudinal study on an autoimmune murine model of ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 981–87.

42 Guerassimov A, Zhang Y, Banerjee S, et al. Cellular immunity to the G1 domain of cartilage proteoglycan aggrecan is enhanced in patients with rheumatoid arthritis but only after removal of keratan sulfate. *Arthritis Rheum* 1998; **41:** 1019–25.

43 Zou J, Zhang Y, Thiel A, et al. Predominant cellular immune response to the cartilage autoantigenic G1 aggrecan in ankylosing spondylitis and rheumatoid arthritis. *Rheumatology (Oxford)* 2003; **42:** 846–55.

44 Zou J, Appel H, Rudwaleit M, Thiel A, Sieper J. Analysis of the CD8+ T cell response to the G1 domain of aggrecan in ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 722–29.

45 Atagunduz P, Appel H, Kuon W, et al. HLA-B27-restricted CD8+ T cell response to cartilage-derived self peptides in ankylosing spondylitis. *Arthritis Rheum* 2005; **52:** 892–901.

46 Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum* 1995; **38:** 499–505.

47 Appel H, Kuhne M, Spiekermann S, et al. Immunohistochemical analysis of hip arthritis in ankylosing spondylitis: evaluation of the bone-cartilage interface and subchondral bone marrow. *Arthritis Rheum* 2006; **54:** 1805–13.

48 Appel H, Kuhne M, Spiekermann S, et al. Immunohistological analysis of zygapophyseal joints in patients with ankylosing spondylitis. *Arthritis Rheum* 2006; **54:** 2845–51.

49 Aufdermaur M. Pathogenesis of square bodies in ankylosing spondylitis. *Ann Rheum Dis* 1989; **48:** 628–31.

50 Reddi AH. Cartilage morphogenetic proteins: role in joint development, homoeostasis, and regeneration. *Ann Rheum Dis* 2003; **62** (suppl 2)**:** 73–78.

51 Lories RJ, Derese I, Luyten FP. Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. *J Clin Invest* 2005; **115:** 1571–79.

52 Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003; **111:** 821–31.

53 Walsh NC, Crotti TN, Goldring SR, Gravallese EM. Rheumatic diseases: the effects of inflammation on bone. *Immunol Rev* 2005; **208:** 228–51.

54 Radi ZA, Khan NK. Effects of cyclooxygenase inhibition on bone, tendon, and ligament healing. *Inflamm Res* 2005; **54:** 358–66.

55 Wanders A, Heijde D, Landewe R, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005; **52:** 1756–65.

56 Einhorn TA. Cox-2: where are we in 2003? - The role of cyclooxygenase-2 in bone repair. *Arthritis Res Ther* 2003; **5:** 5–7.

57 Barthel T, Baumann B, Noth U, Eulert J. Prophylaxis of heterotopic ossification after total hip arthroplasty: a prospective randomized study comparing indomethacin and meloxicam. *Acta Orthop Scand* 2002; **73:** 611–14.

58 van der Linden S, Valkenburg H, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals: a family and population study. *Br J Rheumatol* 1983; **22** (suppl 2)**:** 18–19.

59 Rudwaleit M, Hohler T. Cytokine gene polymorphisms relevant for the spondyloarthropathies. *Curr Opin Rheumatol* 2001; **13:** 250–54.

60 Laval SH, Timms A, Edwards S, et al. Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci. *Am J Hum Genet* 2001; **68:** 918–26.

61 Zhang G, Luo J, Bruckel J, et al. Genetic studies in familial ankylosing spondylitis susceptibility. *Arthritis Rheum* 2004; **50:** 2246–54.

62 Miceli-Richard C, Zouali H, Said-Nahal R, et al. Significant linkage to spondyloarthropathy on 9q31-34. *Hum Mol Genet* 2004; **13:** 1641–48.

63 Hoyle E, Laval SH, Calin A, Wordsworth BP, Brown MA. The X-chromosome and susceptibility to ankylosing spondylitis. *Arthritis Rheum* 2000; **43:** 1353–55.

64 Martin TM, Zhang G, Luo J, et al. A locus on chromosome 9p predisposes to a specific disease manifestation, acute anterior uveitis, in ankylosing spondylitis, a genetically complex, multisystem, inflammatory disease. *Arthritis Rheum* 2005; **52:** 269–74.

65 Maksymowych WP, Reeve JP, Reveille JD, et al. High-throughput single-nucleotide polymorphism analysis of the IL1RN locus in patients with ankylosing spondylitis by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry. *Arthritis Rheum* 2003; **48:** 2011–18.

66 Crane AM, Bradbury L, van Heel DA, et al. Role of NOD2 variants in spondylarthritis. *Arthritis Rheum* 2002; **46:** 1629–33.

67 Hamersma J, Cardon LR, Bradbury L, et al. Is disease severity in ankylosing spondylitis genetically determined? *Arthritis Rheum* 2001; **44:** 1396–400.

68 Kellgren JH. Diagnostic criteria for population studies. *Bull Rheum Dis* 1962; **13:** 291–92.

69 Bennett PH, Burch TA. Population studies of the rheumatic diseases. Amsterdam: Excerpta Medica Foundation, 1968: 456–57.

70 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; **27:** 361–68.

71 Mau W, Zeidler H, Mau R, et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J Rheumatol* 1988; **15:** 1109–14.

72 Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005; **52:** 1000–08.

73 van der Linden S, van der Heijde D. Ankylosing spondylitis. Clinical features. *Rheum Dis Clin North Am* 1998; **24:** 663–76.

74 Amor B, Dougados M, Listrat V, et al. Are classification criteria for spondylarthropathy useful as diagnostic criteria? *Rev Rhum Engl Ed* 1995; **62:** 10–15.

75 Collantes-Estevez E, Cisnal del Mazo A, Munoz-Gomariz E. Assessment of 2 systems of spondyloarthropathy diagnostic and classification criteria (Amor and ESSG) by a Spanish multicenter study. European Spondyloarthropathy Study Group. *J Rheumatol* 1995; **22:** 246–51.

76 Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004; **63:** 535–43.

77 Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet* 2005; **365:** 1500–05.

78 Underwood MR, Dawes P. Inflammatory back pain in primary care. *Br J Rheumatol* 1995; **34:** 1074–77.

79 Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *JAMA* 1977; **237:** 2613–14.

80 Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006; **54:** 569–78.

81 Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. *Ann Rheum Dis* 2005; **64:** 659–63.

82 Spoorenberg A, van der Heijde D, de Klerk E, et al. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. *J Rheumatol* 1999; **26:** 980–84.

83 Krebs W. Das Röntgenbild des Beckens bei der Bechterewschen Krankheit. *Fortschr Röntgenstrahlen* 1934; **50:** 537.

84 Hermann KG, Landewe RB, Braun J, van der Heijde DM. Magnetic resonance imaging of inflammatory lesions in the spine in ankylosing spondylitis clinical trials: is paramagnetic contrast medium necessary? *J Rheumatol* 2005; **32:** 2056–60.

85 Braun J, Bollow M, Sieper J. Radiologic diagnosis and pathology of the spondyloarthropathies. *Rheum Dis Clin North Am* 1998; **24:** 697–735.

86 Brandt J, Bollow M, Haberle J, et al. Studying patients with inflammatory back pain and arthritis of the lower limbs clinically and by magnetic resonance imaging: many, but not all patients with sacroiliitis have spondyloarthropathy. *Rheumatology (Oxford)* 1999; **38:** 831–36.

87 Oostveen J, Prevo R, den Boer J, van de Laar M. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *J Rheumatol* 1999; **26:** 1953–58.

88 Baraliakos X, Hermann KG, Landewe R, et al. Assessment of acute spinal inflammation in patients with ankylosing spondylitis by magnetic resonance imaging: a comparison between contrast enhanced T1 and short tau inversion recovery (STIR) sequences. *Ann Rheum Dis* 2005; **64:** 1141–44.

89 Braun J, Baraliakos X, Golder W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. *Arthritis Rheum* 2003; **48:** 1126–36.

90 Braun J, Landewe R, Hermann KG, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis Rheum* 2006; **54:** 1646–52.

91 Braun J, Baraliakos X, Golder W, et al. Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. *Ann Rheum Dis* 2004; **63:** 1046–55.

92 Heuft-Dorenbosch L, Landewe R, Weijers R, et al. Combining information obtained from magnetic resonance imaging and conventional radiographs to detect sacroiliitis in patients with recent onset inflammatory back pain. *Ann Rheum Dis* 2006; **65:** 804–08.

93 McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Emery P. Characteristic magnetic resonance imaging entheseal changes of knee synovitis in spondylarthropathy. *Arthritis Rheum* 1998; **41:** 694–700.

94 Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; **61:** 905–10.

95 van Tubergen A, Heuft-Dorenbosch L, Schulpen G, et al. Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? *Ann Rheum Dis* 2003; **62:** 519–25.

96 Wanders AJ, Landewe RB, Spoorenberg A, et al. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. *Arthritis Rheum* 2004; **50:** 2622–32.

97 Baraliakos X, Listing J, Rudwaleit M, et al. Progression of radiographic damage in patients with ankylosing spondylitis—Defining the central role of syndesmophytes. *Ann Rheum Dis* 2007; published online Feb 28. DOI:10.1136/ard.2006.066415.

98 Zochling J, van der Heijde D, Burgos-Vargas R, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 442–52.

99 Braun J, Davis J, Dougados M, Sieper J, van der Linden S, van der Heijde D. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 316–20.

100 Dougados M, Dijkmans B, Khan M, Maksymowych W, van der Linden S, Brandt J. Conventional treatments for ankylosing spondylitis. *Ann Rheum Dis* 2002; **61** (suppl 3)**:** 40–50.

101 Kraag G, Stokes B, Groh J, Helewa A, Goldsmith C. The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis—a randomized controlled trial. *J Rheumatol* 1990; **17:** 228–33.

102 van Tubergen A, Landewe R, van der Heijde D, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum* 2001; **45:** 430–38.

103 Dagfinrud H, Kvien TK, Hagen KB. The Cochrane review of physiotherapy interventions for ankylosing spondylitis. *J Rheumatol* 2005; **32:** 1899–906.

104 Ward MM, Kuzis S. Medication toxicity among patients with ankylosing spondylitis. *Arthritis Rheum* 2002; **47:** 234–41.

105 Dougados M, vam der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 1995; **38:** 618–27.

106 Chen J, Liu C. Sulfasalazine for ankylosing spondylitis. *Cochrane Database Syst Rev* 2005; **2:** CD004800.

107 Braun J, Zochling J, Baraliakos X, Alten RH, Burmester GR, Grasedyck K, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomized controlled trial. *Ann Rheum Dis* 2006.

108 Chen J, Liu C. Methotrexate for ankylosing spondylitis. *Cochrane Database Syst Rev* 2004; **3:** CD004524.

109 Gonzalez-Lopez L, Garcia-Gonzalez A, Vazquez-Del-Mercado M, Munoz-Valle JF, Gamez-Nava JI. Efficacy of methotrexate in ankylosing spondylitis: a randomized, double blind, placebo controlled trial. *J Rheumatol* 2004; **31:** 1568–74.

110 Haibel H, Brandt HC, Song IH, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis. 2007; **66:** 419–21.

111 Haibel H, Rudwaleit M, Braun J, Sieper J. Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 124–26.

112 Van Denderen JC, Van der Paardt M, Nurmohamed MT, De Ryck YM, Dijkmans BA, Van der Horst-Bruinsma IE. Double-blind, randomised, placebo-controlled study of leflunomide in the treatment of active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 1761–64.

113 Kaltwasser JP, Nash P, Gladman D, et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; **50:** 1939–50.

114 Maksymowych WP, Jhangri GS, Fitzgerald AA, et al. A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; **46:** 766–73.

115 Haibel H, Brandt J, Rudwaleit M, Soerensen H, Sieper J, Braun J. Treatment of active ankylosing spondylitis with pamidronate. *Rheumatology (Oxford)* 2003; **42:** 1018–20.

116 Huang F, Gu J, Zhao W, Zhu J, Zhang J, Yu DT. One-year open-label trial of thalidomide in ankylosing spondylitis. *Arthritis Rheum* 2002; **47:** 249–54.

117 Heiberg MS, Nordvag BY, Mikkelsen K, et al. The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. *Arthritis Rheum* 2005; **52:** 2506–12.

118 Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; **359:** 1187–93.

119 van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005; **52:** 582–91.

120 Davis JC, Jr., Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; **48:** 3230–36.

121 Calin A, Dijkmans BA, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004; **63:** 1594–600.

122 Haibel H, Rudwaleit M, Brandt HC, et al. Adalimumab reduces spinal symptoms in active ankylosing spondylitis - clinical and magnetic resonance imaging results of a fifty-two week open label trial. *Arthritis Rheum* 2006; **54:** 678–81.

123 van der Heijde D, Kivitz A, Schiff M, et al. Adalimumab therapy results in significant reduction of signs and symptoms in subjects with ankylosing spondylitis: the ATLAS trial. *Arthritis Rheum* 2006; **54:** 2136–46.

124 Baraliakos X, Brandt J, Listing J, et al. Outcome of patients with active anklyosing spondylitis after 2 years of therapy with etanercept —clinical and magnetic resonance imaging data. *Arthritis Res Ther* 2005; **53:** 856–63.

125 Braun J, Baraliakos X, Brandt J, et al. Persistent clinical response to the anti-TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. *Rheumatology (Oxford)* 2005; **44:** 670–76.

126 Baraliakos X, Listing J, Brandt J, Rudwaleit M, Sieper J, Braun J. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res Ther* 2005; **7:** R439–44.

127 Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis* 2005; **64:** 127–29.

128 Baraliakos X, Listing J, Rudwaleit M, Brandt J, Sieper J, Braun J. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. *Ann Rheum Dis* 2005; **64:** 1462–66.

129 Brandt J, Khariouzov A, Listing J, et al. Successful short term treatment of patients with severe undifferentiated spondyloarthritis with the anti-tumor necrosis factor-alpha fusion receptor protein etanercept. *J Rheumatol* 2004; **31:** 531–38.

130 Brandt J, Listing J, Haibel H, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. *Rheumatology (Oxford)* 2005; **44:** 342–48.

131 Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. *Arthritis Rheum* 2005; **52:** 1216–23.

132 Brandt J, Haibel H, Reddig J, Sieper J, Braun J. Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-alpha monoclonal antibody infliximab. *J Rheumatol* 2002; **29:** 118–22.

133 Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; **50:** 2264–72.

134 Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept for treatment of Crohn's related spondyloarthritis but not colitis. *Ann Rheum Dis* 2003; **62:** 74–76.

135 Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2001; **121:** 1088–94.

136 Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359:** 1541–49.

137 Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353:** 2462–76.

138 Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; **52:** 2447–51.

139 Sieper J, Baraliakos X, Listing J, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. *Rheumatology (Oxford)* 2005; **44:** 1525–30.

140 Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003; **62:** 817–24.

141 Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004; **63:** 665–70.

142 Tan AL, Marzo-Ortega H, O'Connor P, Fraser A, Emery P, McGonagle D. Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. *Ann Rheum Dis* 2004; **63:** 1041–45.

143 Haibel H, Rudwaleit M, Listing J, Sieper J. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. *Ann Rheum Dis* 2005; **64:** 296–98.

144 Kobelt G, Andlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). *Rheumatology (Oxford)* 2004; **43:** 1158–66.

145 Boonen A, van der Heijde D, Severens JL, et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 201–08.

146 van der Heijde D, Han C, Devlam K, et al. Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: results from a randomized, placebo-controlled trial. *Arthritis Rheum* 2006; **55:** 569–74.