Ankylosing Spondylitis: Field in Progress

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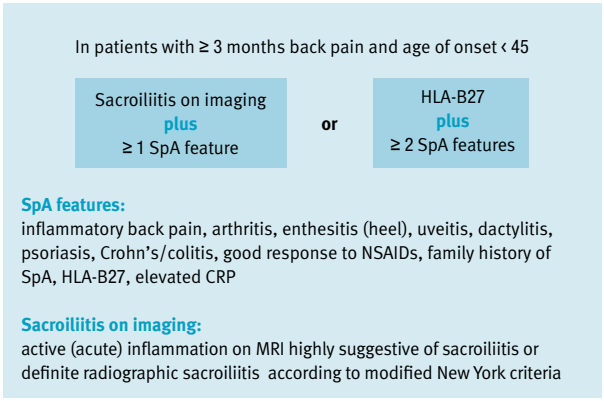
Ankylosing spondylitis, the prototype disease in the spectrum of spondyloarthritides, is a chronic disabling inflammatory disorder strongly associated with HLA-B27. Sacroiliitis, spinal inflammation and enthesitis are the hallmarks of AS, but the disease may involve also peripheral joints, eye, gut and aorta. The study of AS has made significant progress in the last decade. New knowledge in the genetics and pathophysiology of this disorder as well as better understanding of the dynamics of disease development led to the new diagnostic approach and efficient treatment for the majority of AS patients and opened new horizons for both basic and clinical research in this field. In this review we summarize and discuss these new achievements in the study of AS, emphasizing the most problematic issues in both the understanding of the disease mechanisms and the real-life management of AS patients.

THE CONTINUUM OF AS: THE AXIAL SPONDYLOARTHRITIS APPROACH

One of the major clinical problems is, and always has been, the search for proof of sacroiliitis in patients who present with the typical clinical picture of AS and normal X-ray films of sacroiliac joints. These patients might be classified for years as having undifferentiated SpA or diagnosed with an alternative rheumatic disorder or even a non-rheumatic condition, such as mechanical back pain. In view of the new effective therapies that have become available, the long delay in diagnosing patients with AS is unacceptable. The need for a new diagnostic approach thus emerged. The observation that many patients with inflammatory back pain but without sacroiliitis on X-ray films represent the earliest phase of AS and will develop radiographic changes diagnostic for AS within a period of time, usually measured in years, has created a platform for the development of the new disease concept [1]. It has been demonstrated that the presence of HLA-B27 and/or magnetic resonance imaging findings of active SIJ inflammation in these patients could, with a significant degree of accuracy, help to predict which patients will subsequently develop the classical picture of AS [2]. This led to the development of the concept of pre-radiographic AS, which, together with classical AS, formed the basis for the new entity of axial SpA (AxSpA). Other SpA with predominant spinal involvement, such as related to psoriasis or inflammatory bowel disease, and sharing many clinical and imaging features with AS can also be classified in the group of AxSpA by recently suggested criteria [3] [Figure 1]. Thus, the umbrella of AxSpA not only unifies patients with a similar disease pattern, permitting advanced research, but also provides the opportunity for earlier diagnosis and better management of patients with pre-radiographic AS and AS-like psoriatic and inflammatory bowel disease-related arthritis. Studies, however, still have to show whether implementation of this new approach will shorten the diagnostic delay in AS patients.

Figure 1. ASAS classification criteria for axial spondyloarthritis



EPIDEMIOLOGY AND SIGNIFICANCE

PREVALENCE

The prevalence of AS is recognized as 0.5% of the general population. However, the prevalence of AxSpA, which comprises also patients with pre-radiographic AS as well as other

AS = ankylosing spondylitis
SpA = spondyloarthritis

SIJ = sacroiliac joint

SpA with predominantly SIJ/spinal involvement, may be significantly higher, reaching well beyond 1% of the general population.

GENDER DIFFERENCES

The mystifying significant male predominance among patients with AS began to abate several decades ago along with studies demonstrating a 2–3:1 male-to-female ratio rather than the previously thought 5–6:1. Very recent studies on patients with AxSpA, which did not show any gender difference in disease prevalence, raised the possibility that female patients may have some atypical disease manifestations, with inflammatory back pain being less frequent on presentation and enthesopathy and generalized pain syndrome heading the clinical picture, as well as slower development of typical radiographic changes of AS, as compared to males [1,4].

SURVIVAL AND COMORBIDITIES

Survival in patients with AS may be decreased, particularly in those with elevated serum levels of C-reactive protein and with work disability, seen in up to 40% of patients [5]. The most common cause of death in AS patients is cardiovascular disease. Accelerated atherosclerosis has been demonstrated repeatedly in AS patients. Osteoporosis with consequent vertebral fractures has been reported as another frequently under-recognized and potentially treatable comorbidity in AS [6].

New tools for the diagnosis of early stages of ankylosing spondylitis, including the new classification criteria for axial spondyloarthritis and MRI, became available in the last decade

SMOKING

Several large studies from Europe and the United States have recently demonstrated the previously unknown harmful influence of smoking on disease activity and radiographic progression in patients with AS or AxSpA [7]. The mechanisms of this phenomenon are not yet understood.

MECHANISMS OF DISEASE

ANIMAL MODELS

Rats transgenic for the human HLA-B27/β2-microglobulin represent the most known of all animal models of human SpA. This model is characterized by the spontaneous development of colitis, arthritis, psoriasiform skin lesions and orchitis – all typical features of human SpA. While contributing a great deal to current knowledge on the immunology of the disease, animal models have not given answers regarding the precise mechanisms of disease development, including the enigmatic role of HLA-B27. Recent studies on the role of HLA-B27 have questioned the possibility that HLA-B27 may undergo excessive misfolding in the cytoplasmic reticulum resulting in cellular unfolded protein response and cytokine production, or form heavy chain homodimers on the cell surface which can be recognized by killer immunoglobulin receptors. Those and other studies – which have demonstrated that on one hand the disease development in transgenic rats cannot be prevented by elimination of CD8 lymphocytes, and that HLA-B27 positive dendritic cells may function improperly on the other – suggest primary involvement of the innate and rather adaptive immunity in the disease pathogenesis and move away from the classical arthritogenic peptide theory of HLA-B27 engagement in AS where HLA-B27 acts as a canonical major histocompatibility complex class I molecule, presenting peptides to CD8 lymphocytes [8,9].

HUMAN GENETIC STUDIES

The genetics of AS has become an attractive field of research since recognition of the high (> 90%) heritability of the disease. Although about 90% of Caucasians with AS carry the HLA-B27 gene, not more than 5% of HLA-B27-positive individuals develop AS. It has been calculated that the contribution of HLA-B27 to the genetic susceptibility to the disease stands at about 25–40%. The role of HLA-B27 in susceptibility to AS, however, remains an enigma. Recent discoveries in human genetics questioning the conformity of the HLA-B27 transgenic rat model to the human spondyloarthritis suggest that the mechanism of HLA-B27 action in AS patients may still involve peptide handling (the canonical function of HLA-B27 as a MHC class I molecule). This suggestion is supported by the finding of a close association of endoplasmic reticulum amino-peptidase 1 (ERAP1) – a non-MHC gene – with AS, but only in HLA-B27-positive patients, while the known function of ERAP1 is to trim the peptides, partially processed by proteosome, down to nine amino acids in length before presentation by HLA-B27 and other MHC class I molecules. Additional indirect evidence of MHC class I-CD8 lymphocyte interaction in AS comes from the association of the disease with the gene, RUNX3, which influences CD8 lymphocyte count [10]. Other important findings in genetics include strong associations of IL-23R, LTBR (lymphotoxin-beta receptor) and TNFR1 (tumor necrosis factor receptor 1) alleles with AS in both HLA-B27-positive and negative patients, which clearly indicate the involvement of these pathways in the disease pathogenesis. The significance of other genes also associated with AS, such as KIF21B, remains unknown. Thus, recent progress in the genetics of AS enhances our understanding of disease mechanisms and can also be directly applied to the development of new therapies.

MHC = major histocompatibility complex

PATHOLOGY AND CYTOKINES

Relatively few studies using biopsies of affected SIJs or spine of AS patients have been published. A recent study based on the open biopsies of SIJs of patients with AS demonstrated that CD3+ T cells and CD68+ macrophages are the main inflammatory cell types in AS. TNFα, interleukins-1 and 6 were demonstrated in and around inflammatory lesions, while transforming growth factor-beta was detected mainly in cases of advanced AS [11]. The cytokines of Th17 pathway (IL-17, IL-23) were evaluated in another study, which demonstrated high numbers of IL-17+ producing cells, particularly IL-17+ neutrophils, at the primary site of inflammation in the subchondral bone marrow of affected facet joints of AS patients [12].

Biologic treatments have proved to be highly efficacious in patients with ankylosing spondylitis, particularly in those with early disease

DISEASE PROGRESSION

The earliest lesion in AS, as demonstrated by MRI studies, is osteitis [Figure 2]. Erosions, which show up later in the course of disease mostly in SIJs and at vertebral corners, are a classic finding in patients with AS, as well as a major radiographic criterion for AS diagnosis. The progression of AS, however, is measured by new bone formation, which manifests in the appearance of syndesmophytes and, eventually, ankylosis of the SIJs and vertebral column. The presence of inflammation at the sites of subsequent osseous proliferation is considered to be the necessary trigger. However, the rate of new bone formation in AS is not a simple function of the inflammatory activity of the disease; the precise mechanisms of the ongoing ankylosis are unknown. Involvement of molecular signaling pathways of bone formation, such as bone morphogenic proteins and *wnt*, is being intensively studied in this regard [13]. The observation that local growth of spinal syndesmophytes and/or ankylosis of SIJs in these patients is accompanied by systemic bone loss and osteoporosis complicates the conundrum even further. Of importance, the course of new bone formation is individual, with some AS patients having radiographic ankylosis already at the first clinical presentation while others do not develop ankylosis even after longstanding disease [14]. The factors determining this significant variability in both the rate and magnitude of new bone formation in individuals with AS are not known. Since anti-TNFα treatments failed to stop the radiographic progression of AS, the hypothesis of alternating periods of active inflammation and consequent intensive compensatory osseous proliferation emerged, leading to the suspicion that TNF blockade may even reinforce extensive bone formation by suppressing the inflammatory component of AS [15]. Finally, the prostaglandin-based pathway of activation of osteoblasts seems to be important in AS progression, particularly in view of findings that prolonged treatment of AS patients with non-steroidal anti-inflammatory drugs slows new bone formation in these patients [16].

TNFα = tumor necrosis factor-alpha
IL = interleukin

DIAGNOSTIC IMAGING

MAGNETIC RESONANCE IMAGING

MRI is recognized as the most useful imaging modality for sacroiliitis. Being able to detect inflammatory changes in both soft tissues and bone, MRI allows visualization of sacroiliitis in patients in whom conventional radiography (pre-radiographic AS) did not show any changes and provides objective evidence of disease activity [Figures 2 and 3]. MRI findings indicating active sacroiliitis include juxta-articular bone marrow edema and joint space or joint capsule enhancement, best seen on fat-saturated T2-weighted, STIR or post-gadolinium T1-weighted sequences. Chronic changes include bone erosions, sclerosis, ankylosis and periarticular fat deposition seen on T1-weighted sequence. A detailed description of inflammatory and chronic lesions of the

Figure 2. MRI: Bone arrow edema of both iliac bones adjacent to SIJ, more evident on the right, is seen on fat-saturated T2-weighted sequences (arrow). X-ray films of SIJ were normal in this patient with 1 year history of inflammatory back pain

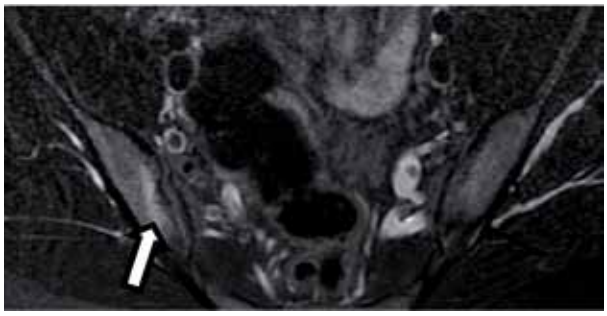
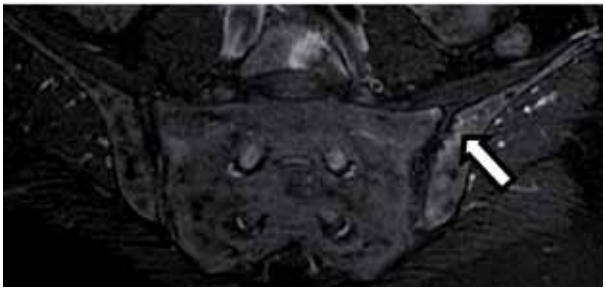


Figure 3. MRI: Erosions of the left iliac bone with widening of SIJ are seen on this fat-saturated T2-weighted sequence. Bone marrow edema, which creates picturesque contrast to the erosions (arrow), is compatible with active ongoing inflammation



SIJs and the spine typical of AS can be found in the Assessment in SpondyloArthritis international Society handbook [www.asas-group.org/education/ASAS-handbook.pdf]. It should be noted, however, that MRI visualization of sacroiliitis alone is far from the gold standard for the diagnosis of AS or AxSpA. First, the sensitivity of MRI in AxSpA was found to be persistently lower than 70% in almost all published studies, which means that about one-third of patients do not have evidence of disease by MRI [3]. Second, the single lesions of bone marrow edema and even erosions were found on MRI of SIJs in about 25% of patients with non-specific low back pain, as well as in a similar percentage of healthy volunteers, reducing the MRI specificity to about 75% [17]. Third, MRI findings of active disease may be relatively dynamic, being a subject of spontaneous change (deterioration as well as improvement) in a matter of weeks, probably reflecting the intermittent character of inflammation in AS [18]. Thus, while recognizing the tremendous contribution of MRI to diagnostic abilities and better understanding of the pathogenesis of AS, one should be cautious when diagnosing or ruling out AS or AxSpA based solely on the MRI data.

Better understanding of the epidemiology and mechanisms of the disease should further improve the management of patients with ankylosing spondylitis and early axial spondyloarthritis

COMPUTED TOMOGRAPHY

CT as a modality for the diagnosis of sacroiliitis was not included in the new ASAS criteria for AxSpA. Despite its inability to demonstrate the characteristic bone marrow edema visible on MRI and associated radiation exposure, CT imaging is considered superior to conventional radiography, and even to MRI, for the detection of erosions and joint space alteration in sacroiliitis [19]. Thus, in patients with suspected AS but without clear evidence of sacroiliitis on conventional X-ray films, CT of SIJs can be useful in various situations especially when MRI is contraindicated or impossible to perform, e.g., the presence of metallic implants in a patient or a patient who is claustrophobic.

BONE SCINTIGRAPHY

As summarized in a recent literature review, scintigraphy of SIJs, with its overall sensitivity of about 50% to detect sacroiliitis, has a limited yield in the diagnosis of both advanced and early AS [20].

MANAGEMENT OF PATIENTS WITH AS

OUTCOME MEASURES

Improving patients' functional status and quality of life as well as preventing structural damage are the main goals of treatment in AS. In this regard, validated and easy-to-use outcome measures should help in the assessment of clinical trial findings, and also serve as landmarks in the management of each individual patient. The recently suggested Ankylosing Spondylitis Disease Activity Score (AS-DAS) includes laboratory parameters of inflammation (serum C-reactive protein or erythrocyte sedimentation rate) and self-reported level of well-being; it is also a quick measure to use. Thus, it is considered superior to the traditional Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). MRI, reflecting the activity of both AS and early AxSpA in the majority of patients, has the potential to be validated in the future as one of the outcome measures of the disease.

PHARMACOLOGIC TREATMENT

While the non-pharmacologic approach to the treatment of AS patients such as balneotherapy and climatotherapy has always been popular [21], recent advances in the study of AS as well as progress in the technology of drug synthesis have opened a new era in the pharmacologic treatment of the disease. NSAIDs are still the first-line in the treatment of patients with AS. The recently recognized ability of NSAIDs to prevent the radiographic progression of the disease represents their main advantage over other therapies, including biologic. However, continuous therapy with NSAIDs is necessary to reach optimal effects. Yet it should be noted in the light of growing apprehension regarding prolonged treatment with NSAIDs that the rate of serious adverse events in AS patients on daily NSAID treatment was less than 1% per year in a recent large 2 year study [16].

Anti-TNFα therapy has become the standard of care of AS patients during the last decade. This class of medicines has shown superb efficacy in AS patients regarding both clinical and MRI-seen signs and symptoms of the disease, which led to its worldwide approval as treatment for patients with active AS in whom NSAIDs failed. The efficacy of the TNFa blockade is particularly impressive in patients with early stages of AS with more than 50% reaching remission [22]. The ability of TNFa blockers to slow structural disease progression in AS patients, however, has not been convincingly shown. Several two-year studies failed to demonstrate slower syndesmophyte growth in AS patients treated with a TNFa blocker. One recent long-term observation study suggested that continuous (more than 4 years) anti-TNFa treatment is needed to slow the radiographic progression of the disease [23]. Management of AS patients who failed treatment with anti-TNFa blockers is difficult. Pamidronate, rituximab and secukinumab have

ASAS = Assessment in SpondyloArthritis international Society

NSAIDs = non-steroidal anti-inflammatory drugs

demonstrated some clinical efficacy in small trials and can be considered in AS patients resistant to other treatments.

In summary, we are witnessing an impressive breakthrough in the understanding, diagnosis and management of ankylosing spondylitis. With more than 2500 AS-related scientific articles published within the last 5 years and numerous basic and clinical ongoing studies in this field, the hope is that in the near future the mystery of this ancient disease may be unraveled.

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References

1. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009; 60: 717-27.
2. Bennett AN, McGonagle D, O'Connor P, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008; 58: 3413-18.
3. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
4. Slobodin G, Reyhan I, Avshovich N, et al. Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis. *Clin Rheumatol* 2011; 30 (8): 1075-80.
5. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. *Ann Rheum Dis* 2011; 70: 1921-5.
6. Bremander A, Petersson IF, Bergman S, Englund M. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. *Arthritis Care Res* (Hoboken) 2011; 63: 550-6.
7. Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort. *Ann Rheum Dis* 2012; 71: 809-16.
8. Taurog JD, Dorris M, Satumtira N, et al. Spondyloarthritis in HLA-B27/human beta2-microglobulin-transgenic rats is not prevented by lack of CD8. *Arthritis Rheum* 2009; 60: 1977-84.
9. Dhaenens M, Fert I, Glatigny S, et al. Dendritic cells from spondyloarthritis-prone HLA-B27-transgenic rats display altered cytoskeletal dynamics, class II major histocompatibility complex expression, and viability. *Arthritis Rheum* 2009; 60: 2622-32.
10. Evans DM, Spencer CC, Pointon JJ, et al. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet* 2011; 43: 761-7.
11. Francois RG, Neure L, Sieper J, Braun J. Immunohistological examination of open sacroiliac biopsies of patients with ankylosing spondylitis: detection of tumor necrosis factor-alpha in two patients with early disease and transforming growth factor beta in three more advanced cases. *Ann Rheum Dis* 2006; 65: 713-20.
12. Appel H, Maier R, Wu P, et al. Analysis of IL-17+ cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. *Arthritis Res Ther* 2011; 13: R95.
13. Appel H, Ruiz-Heiland G, Listing J, et al. Altered skeletal expression of sclerostin and its link to radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2009; 60 (11): 3257-62
14. Barliakos 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; 66: 9101-5.
15. Pedersen SJ, Sørensen IJ, Lambert RG, et al. Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondylarthritis treated with tumor necrosis factor α inhibitors: a study of radiographic progression, inflammation on magnetic resonance imaging, and circulating biomarkers of inflammation, angiogenesis, and cartilage and bone turnover. *Arthritis Rheum* 2011; 63: 3789-800.
16. Wanders A, van der Heijde D, Landewe R, et al. Nonsteroidal anti-inflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005; 52: 1756-65.
17. Weber U, Lambert RG, Østergaard M, Hodler J, Pedersen SJ, Maksymowych WP. The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010; 62: 3048-58.
18. Jarrett SJ, Sivera F, Cawkwell LS, et al. MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. *Ann Rheum Dis* 2009; 68: 1466-9.
19. Devauchelle-Pensec V, D'Agostino MA, Marion J, et al. Computerized tomography scan facilitates the diagnosis of sacroiliitis in patients with suspected spondyloarthritis: Results of the ECHOSPA cohort. *Arthritis Rheum* 2012; 64: 1412-19.
20. Song IH, Carrasco-Fernández J, Rudwaleit M, Sieper J. The diagnostic value of scintigraphy in assessing sacroiliitis in ankylosing spondylitis: a systematic literature research. *Ann Rheum Dis* 2008; 67: 1535-40.
21. Codish S, Dobrovinsky S, Abu Shakra M, Flusser D, Sukenik S. Spa therapy for ankylosing spondylitis at the Dead Sea. *IMAJ Isr Med Assoc J* 2005; 7: 443-6.
22. Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27 positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009; 60: 946-54.
23. Barliakos X, Haibel H, Listing J, Sieper J, Braun J. Radiographic progression in ankylosing spondylitis – results after up to 8 years of anti-TNF treatment. *Ann Rheum Dis* 2011; 70 (Suppl 3): 344.

"I have nothing new to teach the world. Truth and non-violence are as old as the hills. All I have done is to try experiments in both on as vast a scale as I could"

Mahatma Gandhi (1869-1948), leader of Indian nationalism in British-ruled India. Employing non-violent civil disobedience, Gandhi led India to independence and inspired movements for non-violence, civil rights and freedom across the world

"Courage is what it takes to stand up and speak; courage is also what it takes to sit down and listen"

Winston Churchill (1874-1965), British Conservative politician, orator and statesman known for his leadership of the United Kingdom during the Second World War. Widely regarded as one of the greatest wartime leaders of the past century, he served as Prime Minister twice