Arthritis 2

Spondyloarthritis

Maxime Dougados, Dominique Baeten

Spondyloarthritis is a group of several related but phenotypically distinct disorders: psoriatic arthritis, arthritis related to inflammatory bowel disease, reactive arthritis, a subgroup of juvenile idiopathic arthritis, and ankylosing spondylitis (the prototypic and best studied subtype). The past decade yielded major advances in the recognition of spondyloarthritis as an entity, the classification of the disease, and understanding of the genetic and pathophysiological mechanisms of disease-related inflammation and tissue damage. In parallel, new clinical and imaging outcomes have allowed the assessment of various therapeutic modalities. Blockers of tumour necrosis factor are a major therapeutic advance, but the exact roles of physiotherapy, and treatment with non-steroidal anti-inflammatory drugs and other biological treatments are unknown. The major challenges with direct relevance for clinical practice for the next decade are the development of techniques for early diagnosis, therapeutic modulation of structural damage, and, ultimately, induction of long-term, drug-free remission.

Lancet 2011; 377: 2127–37

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This is the second in a **Series** of three papers about arthritis

Paris-Descartes University, Medicine Faculty, UPRES EA 4058, AP-HP, Cochin Hospital, Department of Rheumatology B, Paris, France (Prof M Dougados MD)**; and University of Amsterdam, Academic Medical Centre, Clinical Immunology and Rheumatology, Amsterdam, Netherlands** (D Baeten MD)

Correspondence to:
Prof Maxime Dougados, René Descartes University, Department of Rheumatology, Hôpital Cochin, 27 Rue du Faubourg Saint Jacques, Paris, 75014, France
m.doug@cch.aphp.fr

Introduction

In 1974, Moll and colleagues[1] established the concept of a group of inter-related disorders originally termed seronegative spondarthritides. The group of diseases now called spondyloarthritis consists of psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease, a subgroup of juvenile idiopathic arthritis, and ankylosing spondylitis—the prototype of spondyloarthritis.[2] The various clinical forms include spinal (axial) features, peripheral arthritis, enthesopathy, and extra-articular features such as uveitis, psoriasis, and inflammatory bowel disease. The clinical rationale for grouping these diseases is that they are simultaneously or sequentially identified in the same patient or in a family member. Furthermore, clinical characteristics such as eye involvement and enthesopathy are similar whatever the diagnosis.[1,2] A strong argument, based on work in animals, in favour of grouping these diseases is that HLA-B27 transgenic rats develop the various clinical features that are noted in human beings with spondyloarthritis.[3]

One subject of debate at present is whether the clinical approach, including diagnosis, classification, and management, should be focused on a specific disease subtype (eg, ankylosing spondylitis) or on the overall group of spondyloarthritis. In the 1970s, several sets of criteria were proposed to classify patients with a specific spondyloarthritis subtype, such as the modified New York criteria for ankylosing spondylitis.[4] These criteria have important restrictions in clinical practice: they focus exclusively on the axial features, omitting the other clinical features of the disease. In 1990, Amor and colleagues[5] proposed the first set of classification criteria for the entire group of spondyloarthritis, allowing a patient to be classified as having spondyloarthritis whatever the presenting symptoms. A different set of criteria for the entire group of spondyloarthritis was developed by the European Spondyloarhropathy Study Group,[6] with inflammatory back pain and peripheral arthritis as major entry criteria. Recognition of the drawbacks of criteria focused on a specific subtype, the Assessment of Spondyloarthritis International Society (ASAS) did a large cross-sectional study to propose new criteria on the basis of the two main clinical features identified in daily practice—eg, axial symptoms and peripheral involvement.

In the first set of criteria focusing on patients presenting with axial symptoms (panel),[7] the term axial spondyloarthritis was proposed for the entire range of axial diseases irrespective of structural damage. These criteria emphasise three important points: the relevance of the clinical features identified whatever the presenting symptoms, the value of new imaging techniques to detect sacroiliac changes, and the contribution of HLA-B27 typing.

One important advance is the use of MRI to assess sacroiliac changes. Plain radiographs can detect only structural changes such as joint erosion and

Search strategy and selection criteria

We searched The Cochrane Library and Medline for work published in the past 5 years (2005–10), as well as the abstracts of the American (American College of Rheumatology) and European (European League Against Rheumatism) congresses of Rheumatology published during the past 2 years (2009–10). We used the search terms "spondyloarthropathy", "spondylarthropaty", "spondyloarthritis", "spondylarthritis", "ankylosing spondylitis", and "psoriatic arthritis". We limited our search to published work in English. We also searched the reference lists of articles identified by this search strategy and in particular the articles that summarised systematic research on a specific topic. Review articles and book chapters are cited to provide readers with more details and more references than we can accommodate in this paper.

Panel: ASAS classification criteria for axial spondyloarthritis in patients with back pain for 3 months or more and age at onset younger than 45 years

Sacroiliitis on imaging* plus one or more features of spondyloarthritis†
or
HLA-B27 plus two or more other features of spondyloarthritis†

ASAS=Assessment of Spondyloarthritis International Society. *Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with spondyloarthritis or definite radiographic sacroiliitis according to modified New York criteria. †Inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to non-steroidal anti-inflammatory drugs, family history for spondyloarthritis, HLA-B27, or elevated C-reactive protein (a spondyloarthritis feature in the context of chronic back pain).

subchondral-bone sclerosis seen at the late stage of the disease; this restriction is also the case for CT, although with higher sensitivity and specificity but greater exposure to radiation. Unfortunately, the medical term used to describe such chronic changes focuses on inflammation—eg, sacroiliitis—despite the fact that plain radiographs cannot detect inflammation. By contrast, MRI allows the visualisation of synovial fluid, synovitis within the sacroiliac joint, and subchondral-bone oedema. The relevant abnormalities detected with MRI have been described and clearly defined,[8] allowing inclusion of active inflammatory lesions of sacroiliac joints with definite bone-marrow oedema and osteitis on MRI in the new criteria for axial spondyloarthritis.[7] Whether such a definition—eg, MRI findings at the sacroiliac joints—is optimum remains an open question since data suggest that inflammatory lesions of the posterior structures of the spine as well as the spinal fatty Romanus lesions (fatty changes at vertebral corners) are also suggestive of spondyloarthritis.[9,10] More importantly, however, these criteria were developed in a well defined cross-sectional study population (eg, age <45 years and with back pain for at least 3 months) and have not yet been validated for diagnostic use in prospective studies in clinical practice.

The second set of criteria proposed by ASAS is focused on patients presenting with peripheral rheumatological involvement (eg, peripheral arthritis, enthesopathy, dactylitis) without axial symptoms.[11] These criteria (figure 1) also emphasise the importance of the different clinical features, HLA-B27 typing, and imaging of sacroiliac joints despite the absence of spinal symptoms. Sacroiliac abnormalities at imaging raise the question of which of the investigations should be done when spondyloarthritis is suspected, whatever the presenting symptoms. Clinicians agree on the use of HLA-B27 typing, although it is only useful in cases with an a-priori high suspicion, and a negative result does not preclude the presence of spondyloarthritis. The findings of the study[12] used to develop the criteria also suggest that in a case of peripheral rheumatological presentation, the systematic radiological (eg, plain radiographs and MRI) assessment of the sacroiliac joints might be of interest even in the absence of any axial features. Similarly, a systematic assessment of different entheses allows differentiation between spondyloarthritis patients and controls even in the absence of clinical enthesopathy.[13–15]

Enthesopathy, inflammation at the bone insertion sites of ligaments and tendons, is an important ASAS criterion. The main peripheral clinical location is the heel (inferior part at the insertion of plantar fascia on the calcaneus and posterior part at the insertion of Achilles tendon on the calcaneus). The recognition of spondyloarthritis and the use of these new criteria should allow clinical trials in patients with early disease and thereby the assessment of treatments to alter the course of the disease. Whether these criteria will also shorten the diagnostic delay remains to be investigated prospectively. Another interesting approach to reduce the diagnostic delay is the development of early referral strategies, since patients with back pain are usually first seen by primary care physicians.[16] Defining better strategies and techniques for early diagnosis remains one of the major challenges in spondyloarthritis for the next decade.

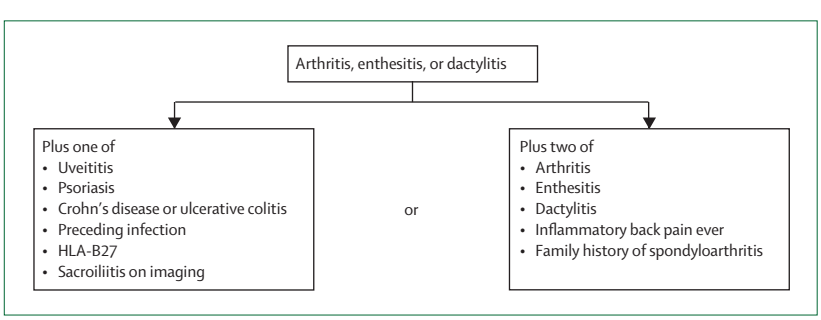

Figure 1: **ASAS criteria for peripheral spondyloarthritis in patients with peripheral features only**
Adapted from Rudwaleit and colleagues.[11] ASAS=Assessment of Spondyloarthritis International Society.

Pathophysiology

Advances in the classification of spondyloarthritis show that progress in the understanding of genetics (eg, the gene for HLA-B27), the pathophysiology of inflammation (eg, lesions on MRI), and structural damage (eg, sacroiliitis on plain radiographs) affect clinical practice in the context of classification and diagnosis. Basic understanding of the pathophysiology of the disease is even more relevant for outcome measurement and targeted treatment.

Through familial aggregation studies[17] investigators have estimated that genetic risk factors contribute to 80–90% of the susceptibility to ankylosing spondylitis. The stronger concordance rates between monozygotic (50–75%) versus dizygotic (15%) twins confirms that familial aggregation is related to genetic rather than environmental factors.

The major genetic risk factor is HLA-B27, an MHC class I molecule. This association is present in many genetically diverse populations and across all major HLA-B27 subtypes. Whereas HLA-B2706 and HLA-B2709 have long been thought to be protective, the finding of ankylosing spondylitis in carriers of these alleles that encode these molecules suggests a hierarchy of association of different HLA-B27 subtypes with ankylosing spondylitis.[18] Whether the effect of the specific aminoacid substitutions in the peptide binding groove of HLA-B2706 and HLA-B2709 can explain the differential association in vivo remains to be established.[19]

The presence of HLA-B27 in 80–90% of patients with ankylosing spondylitis and the spontaneous spondyloarthritis-like disease in HLA-B27 transgenic rats suggest a direct and dominant effect of the gene encoding this molecule.[3] However, only a small proportion of people in the general population who harbour HLA-B27 (5–6% in white people) develop ankylosing spondylitis, and HLA-B27 explains only 20–40% of the genetic susceptibility to ankylosing spondylitis—suggesting the contribution of additional genes. Genome-wide associations studies (GWASs) have allowed the identification of several of these additional genes (table).

A definite association has been identified with the genes for endoplasmic reticulum aminopeptidase 1 (*ERAP1*), interleukin 23 receptor (*IL23R*), and the gene deserts on chromosome 2p15 and 21q22.[20,21] Besides these definite associations, GWAS findings suggested potential associations with genes for tumour necrosis factor (TNF) receptor 1 (*TNFSF1A*), the signalling molecule TNF receptor 1-associated death domain protein (*TRADD*), the TNF superfamily cytokine *TNFSF15*, interleukin 1α (*IL1A*), interleukin 1 receptor 2 (*IL1R2*), the vascular morphogenesis protein gene anthrax toxin receptor 2 (*ANTXR2*), and the innate immune receptor caspase recruitment domain family, member 9 (*CARD9*).[20–25] Other candidate genes such as non-B27 MHC genes, the familial Mediterranean fever-related *MEFV*, and signal transducer and activator of transcription 3 (*STAT3*) need additional confirmation.

The strong genetic predisposition also applies to other spondyloarthritis subtypes as suggested by a recurrence rate of disease in 12% of the first-degree relatives of spondyloarthritis patients. Accordingly, genes encoding HLA-B27 and interleukin 23 receptor are associated with different spondyloarthritis subtypes. Additionally, genes such as *IL23R* also confer risk for spondyloarthritis-associated disorders such as Crohn's disease and psoriasis (table). The absence of familial clustering of distinct phenotypic features of the subtypes suggests a dominant shared genetic factor in all spondyloarthritis forms, with additional genetic and environmental factors contributing to the phenotypic diversity.[26] Reinforcing this idea, HLA-B27 transgenic rats develop not only spondylitis but also the full spondyloarthritis clinical range with peripheral arthritis, colitis, uveitis, and skin disease, with environmental factors such as the gut flora and additional genetic factors determining the exact phenotype.[27,28]

	Gene	Function	Associated with		
			Ankylosing spondylitis	Psoriasis*	Inflammatory bowel disease*
6p21.3	*HLA-B*	Antigen presentation	Yes	..	..
5q15	*ERAP1*	Aminopeptidase	Yes	Probable	..
1p31.2	*IL23R*	Cytokine receptor	Yes	Yes	Yes
2p15	..	..	Yes	..	..
21q22	..	..	Yes	..	..
12p13.2	*TNFRSF1A*	Cytokine receptor	Probable	..	Yes
16q22	*TRADD*	Signalling	Probable	..	..
9q32	*TNFSF15*	Inflammatory cytokine	Probable	..	Yes
2q14	*IL1A*	Inflammatory cytokine	Probable	..	..
2q12	*IL1R2*	Cytokine receptor	Probable	..	..
9q34	*CARD9*	Innate immune defence	Probable	..	..
4q21.3	*ANTXR2*	Vascular morphogenesis	Probable	..	..

*Some factors are also associated with psoriasis or inflammatory bowel disease.

Table: **Overview of the locus, gene, and function of definite and probable genetic risk factors for ankylosing spondylitis**

The traditional pathophysiological framework for spondyloarthritis is the arthritogenic-peptide theory, which proposes that HLA-B27 presents self-peptides that resemble pathogen-derived peptides to CD8-restricted T lymphocytes. Circumstantial evidence for this hypothesis is provided by the triggering of spondyloarthritis by gastrointestinal or urogenital infections, and the presence of HLA-B27-restricted CD8-T-cell clones that are reactive against bacterial antigens[29] as well as against self-proteins from cartilage[30] in the inflamed joint. However, this hypothesis has been seriously challenged by two independent reports that CD8 T cells are not needed for disease in HLA-B27 transgenic rats.[31,32] Moreover, the anticartilage responses in human beings are not disease-specific, suggesting common secondary autoimmune responses rather than primary pathophysiological processes. In more general terms, the scarce evidence for HLA-B27-restricted autoimmune-T-cell responses, the absence of shared genetic risk factors for autoimmune diseases such as *PTPN22* polymorphisms, and the absence of known disease-specific autoantibodies question whether spondyloarthritis is a genuine autoimmune disease driven by T-cell or B-cell reactivity towards self-antigens.

Two additional hypotheses have emerged to explain the role of HLA-B27 (figure 2). Both hypotheses argue for an autoinflammatory rather than autoimmune origin since HLA-B27 has a role in triggering innate immune responses rather than its canonical role of antigen presentation. If correct, this hypothesis might have important implications because it predicts, for example, that inflammation will happen at sites of

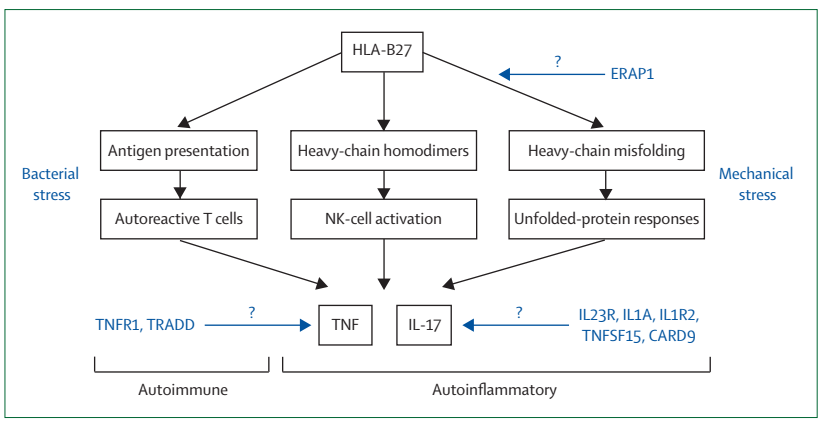

Figure 2: **Potential roles of HLA-B27 in triggering the pathogenesis of spondyloarthritis**
The three main hypotheses relate to the presentation of arthritogenic peptides to autoreactive T lymphocytes, the formation of heavy-chain homodimers (which activate natural killer cells), and the misfolding of HLA-B27 in the endoplasmic reticulum leading to an unfolded-protein response. The role of ERAP1 has not been assessed. Upon bacterial or mechanical stress, these pathways can lead to the abnormal production of proinflammatory cytokines such as tumour necrosis factor and interleukin 17. Investigators do not completely understand the role of additional genetic associations. ERAP1=endoplasmic reticulum aminopeptidase 1. NK=natural killer. TNFR1=TNF receptor 1. TRADD=TNF receptor 1-associated death domain protein. IL23R=interleukin 23 receptor. IL1A=interleukin 1α. IL1R2=interleukin 1 receptor 2. TNFSF15=TNF superfamily cytokine 15. CARD9=caspase recruitment domain family, member 9.

bacterial or mechanical stress, and that T-cell or B-cell directed treatments might not be effective in spondyloarthritis.

The first hypothesis proposes that β2 microglobulin-free HLA-B27 heavy chains can assemble into disulphide-linked homodimers expressed at the cell surface that can be directly recognised by the killer immunoglobulin-like receptors KIR3DL2 independently of the bound peptide.[33] Titres of natural killer and T cells expressing KIR3DL2 are raised in HLA-B27-positive patients and can be directly activated by ligation of the homodimers.[34] The second hypothesis proposes that the Cys 67 residue of the B pocket leads to HLA-B27 heavy-chain misfolding in the endoplasmic reticulum before assembly into complexes with β2 microglobulin and peptide.[35,36] The resulting unfolded-protein response (UPR) induces an altered responsiveness and cytokine production of inflammatory cells to a range of innate immune stimuli.[37–39] However, overexpression of human β2 microglobulin to reduce the UPR in HLA-B27 transgenic rats exacerbated rather than prevented arthritis and spondylitis, whereas colitis was unchanged.[28] Although investigators still debate to what extent β2 microglobulin overexpression really down-regulates UPR, this discrepancy emphasises that the non-mutually exclusive functions of HLA-B27 might differ between models and between distinct features of spondyloarthritis.

The altered cellular responsiveness induced by the UPR accords with the predilection of spondyloarthritis for tissues exposed to either bacterial or mechanical stress. Bacterial stress is shown by the association with inflammatory bowel disease, gastrointestinal infections, and abnormal Toll-like receptor expression and function.[40,41] The role of mechanical stress is emphasised by imaging and pathological findings that inflammation happens mainly at the synovio-entheseal complex.[42] Taken together with the prominent infiltration with innate immune cells at affected sites,[43,44] the stress hypothesis proposes that inflammation in spondyloarthritis is induced by abnormal innate immune responsiveness to mechanical or bacterial danger signals and should thus be seen as an autoinflammatory rather than autoimmune disorder.[45]

Two cytokines are of particular interest in the propagation and perpetuation of inflammation in spondyloarthritis. First, a key role for TNF has been shown through the effectiveness of TNF blockers. This role fits with the genetic associations with *TNFR1* and the TNFR1 signalling molecule TRADD; however, how TNF drives spondyloarthritis is unclear. Many models of TNF overexpression lead to sacroiliitis, with one model giving TNFR1 signalling to stromal cells a prominent role.[46] However, these models differ fundamentally from spondyloarthritis by their polyarticular, erosive character without osteoproliferation. The low titres of soluble TNF in spondyloarthritis synovitis[47] and spinal deformities in mice overexpressing transmembrane TNF[48] warrant further investigation of the forms of TNF and TNF receptors in the disease process.

The second cytokine of interest is interleukin 23. Besides the genetic association with *IL23R*, evidence is emerging that the HLA-B27 induced UPR augments the production of interleukin 23.[39] Altered interleukin-23 production or signalling in spondyloarthritis could lead to abnormal interleukin-17 responses, certainly in view of the data that TNFSF15, CARD9, and the DR3-TRADD pathways can also affect responses of T-helper-17 (Th17) cells. Early demonstration of interleukin-17 overexpression in spondyloarthritis[49] could, however, not be confirmed by independent studies on blood, synovial fluid, and gut.[47,50–52] Keeping in mind that interleukin 23 has several functions and targets many cells besides Th17 cells, these expression studies need to be extended to functional studies in vitro and in vivo. Investigators have yet to clarify the potential role of interleukin 1, as suggested by the genetic associations, and interleukin 6 in the induction of a Th17 response, and more generally in the pathophysiology of spondyloarthritis. Emerging data from clinical trials aiming to block interleukins 1, 6, 17, or 23 will be crucial to understand the role of these cytokines.

Genetic risk factors, and the related hypotheses, fall short of explaining the second major feature of spondyloarthritis: the prominent tissue remodelling that leads to osteoproliferation and ankylosis. Three major hypotheses have emerged.

First, the typical structural features cannot be explained by the presumption that the disease is non-erosive. Imaging and histological studies clearly show that bone destruction and erosions are prominent

features of both axial and peripheral spondyloarthritis.[53,54] Accordingly, cellular and molecular pathways of cartilage and bone destruction are activated at the sites of pathology and, as in rheumatoid arthritis, are largely dependent on TNF.[55–58]

In line with these findings, the second emerging hypothesis is that the structural features of spondyloarthritis relate to important pathways of endochondral-bone formation. In a model of spontaneous ankylosing enthesitis, signalling by bone morphogenetic proteins was the key pathway driving the structural changes and active signalling of the proteins was identified in target tissues of human spondyloarthritis.[59] In TNF transgenic mice, activation of Wnt signalling by targeting the inhibitor Dickkopf-related protein 1 reversed the process of bone destruction and induced fusion of sacroiliac joints.[60,61] Several inhibitors of the Wnt pathway seem to be dysfunctional in human spondyloarthritis and are associated with new bone formation.[62,63] Further functional analyses of bone morphogenetic proteins, Wnt, and other tissue-remodelling pathways are of paramount importance because they could be attractive targets for treatment.

The third emerging possibility is that osteoproliferation in spondyloarthritis is, at least partly, uncoupled from inflammation. Two hypotheses have been proposed to account for this uncoupling. The first hypothesis claims that osteoproliferation can be explained by the intermittent nature of the inflammation.[64] In an early disease phase, TNF would simultaneously drive destruction and inhibit remodelling by the Wnt pathway by upregulating Dickkopf-related protein 1 (figure 3). On downregulation of TNF in a later phase, the brake on Wnt-mediated remodelling would be released and the early erosions would trigger reactive osteoproliferation. The relation between early inflammation and subsequent new bone formation is, however, still highly debatable in human ankylosing spondylitis because although inflammation is associated with a greater likelihood new bone formation, most syndesmophytes are located at sites without detectable inflammation.[65,66] Moreover, this hypothesis cannot explain why new bone formation is independent of osteoclasts in various models[67,68] or why TNF blockade does not prevent ankylosing enthesitis.[69] The second hypothesis proposes that direct activation of stromal pathways, including the pathways of bone morphogenic protein, leads to new tissue formation independent of inflammation or early erosive changes.[70] Mechanical stress at synovio-entheseal complexes might then induce distinct and unrelated pathways of inflammation and tissue remodelling.

Although both hypotheses are not mutually exclusive (figure 3), the relative contribution of both mechanisms and the exact relation between inflammation and stromal-cell activation has major clinical implications: the first hypothesis predicts that early anti-inflammatory treatment will prevent structural damage whereas the second hypothesis predicts that separate assessment and therapeutic targeting of stromal pathways is needed for optimum management of spondyloarthritis.

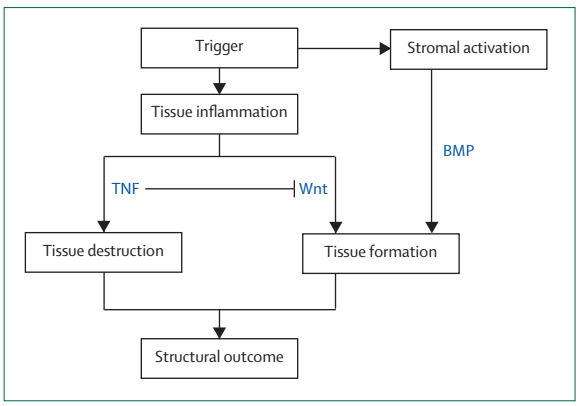

Figure 3: **Connection between inflammation and endochondral-bone formation in spondyloarthritis**
Mechanical or other triggers might cause tissue inflammation, which is initially characterised by TNF-driven tissue destruction and inhibition of Wnt-mediated repair processes. Resolution of inflammation might reduce the inhibition of Wnt signalling and lead to reactive osteoproliferation. The same initiating trigger might also directly activate stromal cells and induce an inflammation-independent pathway of endochondral-bone formation, in which BMP signalling is thought to have a key role. The structural outcome as well as the effect of anti-inflammatory treatments on the structural outcome will be determined by the relative contributions of these pathways as well as by the type, severity, and duration of inflammation. BMP=bone morphogenic protein. TNF=tumour necrosis factor.

Outcome assessment

The optimum management of patients necessitates systematically addressing five points related to the possible clinical presentations (axial, peripheral, enthesopathy, and extra-articular): does the patient really have the disease, is the disease active, is the disease severe, is the disease potentially severe, and is the disease refractory? One of the major challenges in spondyloarthritis remains the development of sensitive and specific imaging or biological markers for early diagnosis.

Activity in spondyloarthritis is a reference to the inflammation caused by the disease, which is commonly assessed in daily practice with the Bath ankylosing spondylitis disease activity index (BASDAI).[71] This index consists of questions related to the patient's self-assessment (eg, fatigue, axial symptoms, peripheral symptoms, enthesopathy, and duration and intensity of morning stiffness). To improve the objective properties of such an index, an ankylosing spondylitis disease activity score (ASDAS) has been developed that includes not only four questions from the BASDAI, but also the level of acute phase reactants.[72] Preliminary data suggest that the ASDAS is more discriminative than BASDAI when in assessment of TNF blockers.[73] However, clinicians must further assess the usefulness of this new composite index in daily practice.

Apart from clinical assessment, the activity of the disease could also be assessed by MRI of the spine and sacroiliac joints. Several scoring systems at present assess the reliability, validity, and responsiveness of the technique.[74–76] Investigators are yet to clarify if the inflammatory abnormalities of the posterior elements of the spine should be included[77,78] or even if a whole-body MRI should be preferred.[79,80] Whatever the scoring system, axial disease activity measured by MRI as well as other imaging modalities (eg, ultrasonography for enthesopathy) are useful additional outcome measures in clinical trials;[81–86] but their added value in daily clinical practice is unknown.

The severity of spondyloarthritis is a reference to irreversible structural damage caused by the disease, often due to tissue remodelling and its functional consequences. For clinical studies, several outcomes have been proposed to show severity: death, job loss, functional impairment, range of motion, and hip involvement. Radiological scoring systems assess structural damage at the axial level (eg, mainly new bone formation because of syndesmophytes).[87,88] The scoring system recommended at present is the modified stoke ankylosing spondylitis scoring system,[88] which consists of cervical and lumbar assessments. The addition of the thoracic spine might improve the sensitivity to change.[89] This new system is very useful in clinical research but it remains unclear whether it should be used routinely in clinical practice.

A further factor in the optimum management of the disease relates to prediction of the natural course of the disease at an early stage in an individual patient. This notion is clinically highly relevant because structural damage and functional impairment in spondyloarthritis are largely irreversible. If the hypothesis that early inflammatory and erosive lesions trigger subsequent osteoproliferation is correct, highly efficient anti-inflammatory treatments should be started as early as possible. However, preliminary data suggest that axial inflammatory lesions detected with MRI are not highly predictive for subsequent ossification.[63,64] If the structural damage is independent of inflammation but relates to stromal remodelling pathways, it would make a case for additional treatments targeting stromal remodelling irrespective of disease activity and before irreversible structural damage. Long-term follow-up of patients presenting with recent inflammatory back pain in different European cohorts will help to delineate which patients are at risk for long-term structural damage.

Whether the disease is refractory is important to guide the decision for second-line treatments such as anti-TNF. For axial spondyloarthritis, the present recommendation from ASAS and the European League Against Rheumatism is to define a patient as refractory when active disease persists despite the intake of at least two courses of non-steroidal anti-inflammatory drugs (NSAIDs) taken at an optimum dose for at least 2 weeks without needing to be classified a failure of a disease-modifying antirheumatic drug. For peripheral arthritis, a refractory disease is defined by an active disease despite current or past intake of disease-modifying antirheumatic drugs.[90] To disseminate and facilitate the implementation of such methods, ASAS has recently published a guide to assess spondyloarthritis.[91]

Treatment

The objectives of treatment of spondyloarthritis are to improve the condition of the patient (eg, pain, functional disability) as well as to prevent subsequent clinical deterioration. ASAS has provided recommendations for both the management of spondyloarthritis in general[90] and the use of TNF blockers in particular.[92]

A recent Cochrane systematic review of published work[93] concluded that an individual home-based or supervised exercise programme is better than no intervention, that supervised group physiotherapy is better than home exercises, and that combined in-patient spondyloarthritis-exercise therapy with subsequent group physiotherapy is better than group physiotherapy alone. Despite the modality of physiotherapy, another important question is related to the characteristics of the patients who should benefit most from this therapy. In particular, the benefit of such therapy during the painful inflammatory flares of the disease or at a very early stage has not been investigated.

NSAIDs are the cornerstone of pharmacological intervention for ankylosing spondylitis, rapidly reducing pain and stiffness after 48–72 h. Despite this dramatic symptomatic effect, NSAIDs might be also effective on some other outcome measures. These drugs might substantially reduce the level of acute-phase reactants compared with placebo, but with questionable relevance of the recorded size of effect.[94] The investigators of one study[95] also suggest that NSAIDs can delay radiological progression of spine disease when given continuously as a daily dose over 2 years, compared with an on-demand treatment schedule.[95] Although this finding suggests that a systematically continuous daily intake of NSAIDs might be of benefit, the converse argument is the potential long-term gastrointestinal and cardiovascular toxic effects of such therapy, in particular in patients recognised as having more comorbidities than the general population.[96]

Conventional disease-modifying antirheumatic drugs such as sulfasalazine, methotrexate, and leflunomide which have been shown to be effective in the treatment of rheumatoid arthritis, have no proven efficacy for either the axial or enthesopathic features of spondyloarthritis, but some efficacy for peripheral arthritis and other extra-articular features such as psoriasis, uveitis, and inflammatory bowel disease.[97–99]

Thalidomide has some efficacy in axial spondyloarthritis in open uncontrolled studies, possibly because of its anti-TNF effect, but is thought too toxic for widespread

use.[100–102] Although some clinical effectiveness of pamidronate, a bisphosphonate with potential anti-inflammatory and antierosive effects, has been reported,[103] further placebo-controlled studies are needed before this treatment can be recommended.

The major clinical and therapeutic advance in spondyloarthritis care is the successful use of TNF blockade in active, refractory disease.[104–107] Registration studies in early, preradiographic axial spondyloarthritis as well as in undifferentiated peripheral spondyloarthritis are ongoing.

A couple of issues are of particular relevance for daily clinical practice. First, TNF blockade is highly effective in targeting the different disease features—eg, not only axial disease but also peripheral arthritis, enthesitis, and extra-articular features such as psoriasis or uveitis.[108–111] TNF blockade also has a substantial effect on general symptoms such as fatigue and substantially improves the overall function and quality of life. Long-term follow-up studies suggest that effectiveness is maintained for several years of treatment. Second, short-term and long-term studies suggest a safety profile of TNF blockade in spondyloarthritis that is similar to that of rheumatoid arthritis and inflammatory bowel disease, and reactivation of tuberculosis remains the major concern.[112] Third, the various TNF blockers seem to be equally potent for the treatment of axial, peripheral, and extra-articular features, with the exception that etanercept has no proven efficacy in inflammatory bowel disease. As to safety, large registries suggest that the risk for tuberculosis and possibly also herpes zoster might be lower with etanercept than with the monoclonal anti-TNF antibodies infliximab and adalimumab.[113–115] Finally, by contrast with rheumatoid arthritis and Crohn's disease, there is no recommendation at present in axial spondyloarthritis to combine TNF blockers with drugs such as methotrexate or azathioprine.

Despite its major therapeutic effectiveness, TNF blockade also has important limitations. First, 20–40% of the patients do not respond well to treatment and clinical, biological, or imaging findings that predict a better response at the group level lack specificity to make reliable predictions in individual patients.[116,117] In case of failure of a first TNF blocker, trying a second drug is justified since many patients do still respond to a different anti-TNF.[118,119] Second, TNF blockade does not induce longlasting remission since almost all patients relapse within 6–12 months of interruption of treatment.[120] Third, TNF blockade seems to halt joint destruction,[121] but fails to substantially slow new bone formation in spondyloarthritis.[122–124] It remains unclear whether this effect is related to the fact that TNF blockade was started too late in the disease course in these studies or to the fact that new bone formation is uncoupled from TNF-driven inflammation in spondyloarthritis. These three caveats suggest that there is still an important unmet need for highly effective anti-inflammatory treatments as well as for remission-inducing and structure-modifying therapies.

Several other biological agents have been tested in small proof-of-concept trials[125–129] in ankylosing spondylitis and psoriatic arthritis on the basis of their efficacy in related diseases such as rheumatoid arthritis and psoriasis. B-cell depletion by the anti-CD20 antibody rituximab did not show similar efficacy in ankylosing spondylitis as in rheumatoid arthritis, although some response was noted in TNF-blocker naive patients in an open study.[125,126] T-cell targeted therapies have also not been very successful in spondyloarthritis. Despite the role of T cells in psoriasis, psoriatic arthritis did not respond to the anti-CD11a monoclonal antibody efalizumab[127] and showed only slight clinical improvement with the anti-LFA3 antibody alefacept[128] and the CTLA4-Ig construct abatacept.[129] These findings are thus consistent with the pathophysiological concept that spondyloarthritis might be an autoinflammatory rather than a T-cell or B-cell driven autoimmune disease.

The genetic associations have raised interest in blockade of cytokines other than TNF. Interleukin-1 blockade with the interleukin-1 receptor antagonist anakinra did not show consistent efficacy in ankylosing spondylitis,[130] the human anti-interleukin 12/interleukin 23 monoclonal antibody ustekinumab had slight but significant (p=0·0002) efficacy in psoriatic arthritis.[131] Trials with interleukin-6 and interleukin-17 blockade are underway.

Future prospects

From the present state of the art in spondyloarthritis, several important clinical and pathophysiological issues seem unsolved: the development and validation of better clinical or biological markers for early diagnosis and for prognosis, clarification whether the subtypes of spondyloarthritis are driven by different pathophysiological processes or rather represent different phenotypes of a single pathological entity, deciphering the functional role and the interaction of genes emerging from GWAS, in-depth understanding of the cellular and molecular mechanisms of tissue remodelling and their interaction with inflammation, and the development of newer anti-inflammatory therapies, including the clinical assessment of interleukin-6 blockade and interleukin-17 blockade, as well as treatments targeting tissue remodelling. In view of the present research efforts, our understanding of these issues will probably develop rapidly over the coming years.

Contributors

The authors contributed equally to the preparation of this paper.

Conflicts of interest

MD has received consultancy fees, speaker's fees, and his department has received research grants from Abbott, Aventis, Pfizer, Roche, Sanofi, Shering Plough, and UCB. DB has received consultancy fees, speaker's fees, and research grants from Abbott, Centocor, Novartis, Pfizer, Shering Plough, and UCB.

Acknowledgments

We thank Kris A Reedquist for critical reading of our paper.

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