Advances in classification, basic mechanisms and clinical science in ankylosing spondylitis and axial spondyloarthritis

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Abstract

The field of spondyloarthritis has seen huge advances over the past 5 years. The classification of axial disease has been redefined by the axial spondyloarthritis criteria that incorporate disease captured before radiographic damage is evident as well as established erosive sacroiliac joint disease. Our knowledge of genetics and basic immunological pathways has progressed significantly. In addition, revolutionary progress has been achieved with the availability of tumour necrosis factor inhibitors for treating patients with moderate to severe disease. In parallel a number of novel biomarkers have been identified that show significant promise for the future. Advances in magnetic resonance imaging have helped define positive disease. We have identified that T1 and short tau inversion recovery sequences are best for the diagnosis of axial spondyloarthritis and gadolinium contrast is not additive for diagnosis. Progress has been made in identifying potential agents and strategies that reduce radiographic progression. A number of referral strategies aimed at appropriate identification of patients have been trialed and found to be effective. There is still substantial work ahead but the advances of the last 5 years have made a huge and tangible difference at the clinical coalface and we suggest this trend will continue.

In the last five years the field of spondyloarthritis (SpA) has seen significant progress. New classification criteria have been proposed and there have been significant advances in basic science and therapeutics. This progress is welcome as for decades little progress was made in treating this disease. This review aims to cover the significant advances in ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA), a term now being used to encompass AS and other forms of axial SpA.

Classification

The classification of SpA has been, and continues to be, an area of significant interest and controversy [1, 2]. We currently lack a thorough understanding of the basic mechanisms of disease pathogenesis. Therefore diagnosis and classification remains, at this present time, based primarily on signs and symptoms.

Initial classification criteria for SpA as a whole included the Amor criteria [3] and European Spondyloarthritis Study Group (ESSG) criteria [4]. These criteria were designed to capture the entire spectrum of SpA, not purely axial disease. When measured against physician diagnosis as gold standard the Amor and ESSG criteria have sensitivity and specificity of 87 - 90% each [5]. These criteria had some scope to capture SpA earlier in its disease course, but their more general nature meant they were unable to specifically identify early axial SpA. The New York criteria, and then the modified New York (mNY) criteria capture established long standing AS by virtue of the requirement for limitation in movement and erosive sacroiliac joint damage [6].

There were always clearly patients who did not meet the mNY criteria but had active debilitating axial SpA, and a proportion of these patients progress to mNY AS [7]. With the stimulus of the introduction of tumour necrosis factor (TNF) inhibitors as effective treatments, a new classification system was proposed by Assessment of SpondyloArthritis International Society (ASAS) that aimed to capture both early and established disease [8]. This introduced the concept of axial spondyloarthritis (axSpA) that includes two groups. The first is patients with mNY AS and the second is patients who do not meet the mNY criteria but have classifiable disease called non-radiographic axial spondyloarthritis (nr-axSpA). Patients can meet criteria for axSpA in two ways (see Table 1): (1) By virtue of having plain film evidence of erosion (the same as for the mNY criteria) or magnetic resonance imaging (MRI) evidence of sacroiliac joint inflammation *and* one feature of SpA from a list of 11, such as psoriasis or anterior uveitis ("Imaging arm"); or (2) By being Human Leucocyte Antigen (HLA)-B27 positive *and* having two features of SpA, from a list of 10 ("HLA-B27 arm").

The ASAS axSpA criteria (both arms combined) against a physician gold standard have a sensitivity and specificity of 83% and 84% respectively. The imaging arm alone has a sensitivity of 66% and a specificity of 97%. This clearly demonstrates that positive imaging, be that with plain film or MRI has high specificity but lacks sensitivity when assessed against physician gold standard. An interesting longitudinal study that performed MRI and sacroiliac joint biopsies in patients with early SpA and followed them up demonstrated that the sensitivity for MRI may not be as high as thought, the study suggested 31%. Although correlation between histological sacroiliac joint

inflammation and clinical symptoms is not something the SpA community has any experience with, so the actual clinical relevance of this finding is unclear [9].

The introduction of the axSpA criteria has demonstrated that there is a set of patients with disease that will not progress to mNY AS, as these cohorts have lower HLA-B27 carriage rates and more females compared to cohorts of established AS [1, 10]. It has enabled the identification of early disease that previously was not well captured and precipitated trials of effective agents such as anti-TNF in early disease, demonstrating excellent efficacy [11]. Therefore it seems the field is moving towards the use of the term 'axial spondyloarthritis' instead of 'ankylosing spondylitis' to describe the wider axial disease group. However AS will continue to be used to describe the more advanced form and provide homogenous groups for biological research.

Basic Science - Genetics

The genetics of AS has come a long way since the discovery of HLA-B27 in 1973 [12-14]. The advent of large scale array based genotyping, the genome wide association study (GWAS) and significant international collaboration now means there are 41 independent genetic associations for AS [15-18]. The salient features of these associations is the clustering in immunological pathways such as the IL-23, antigen processing and presentation and lymphocyte development and activation [19]. In addition a genetic interaction has been identified between *HLA-B27* and a gene that encodes an enzyme called endoplasmic reticulum aminopeptidase (ERAP1), this enzyme

processes peptides prior to presentation on the cell surface on MHC class I molecules. Variants of ERAP1 only increase the risk of AS when *HLA-B27* is present. In addition the same interaction is observed with *HLA-B40*, another AS associated HLA-B allele [20]. These interactions strongly suggest that the mechanism by which *HLA-B27* contributes to AS development is through its antigen presentation function [19]. Whether it is presenting the wrong antigen, not presenting an antigen or changing the mix of presented antigens is wholly unclear [21]. In fact a newer theory suggests that *HLA-B27* may contribute to disease pathogenesis in the setting of an 'immunodeficient' state. A summary of the current theories of how HLA-B27 might contribute to SpA pathogenesis is shown in Table 2.

The other interesting and important finding from the significant body of recent genetic research is the significant sharing of risk variants between immune mediated diseases such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis and systematic lupus erythematosus [22]. This sharing is both concordant, and discordant, in that variants, can at times be protective for one disease but increase risk for another disease. An excellent example is the *TNFRSF1A* variants that reduces risk in AS but increases risk for multiple sclerosis [23].

Basic Science – Immunology

Advances in genetic research has allowed for concurrent evolution in understanding the basic immunology underpinning the pathogenesis of SpA. GWAS studies have identified susceptibility genes common to SpA and associated conditions including psoriasis and inflammatory bowel disease

(IBD). Polymorphisms in these commonly shared genes implicate innate immunity, antigen presentation and interleukin-23 (IL-23) modulated pathways in SpA disease development [24].

IL-23-signalling appears pivotal in the pathogenesis of SpA. Human data demonstrates increased production and sensitivity to IL-23 and expansion of both adaptive and innate IL-23-responsive cells, within joints and the periphery of patients with various forms of SpA [25-28]. However the initial inflammatory and/or microbial stimulus resulting in IL-23 production, where anatomically this might occur, and how IL-23 drives SpA in genetically prone individuals has been puzzling.

Understanding the mechanisms of IL-23 signalling and subsequently the pathogenesis of SpA, have been hindered by the lack of appropriate SpA animal models. However a recent publication by Sherlock et al. utilising minicircle DNA technology to systemically overexpress IL-23 in B10.RIII mice resulted in the subsequent identification of a previously undescribed lineage of IL-23 responsive, resident entheseal T cells. This has been widely acknowledged as a significant advance [29]. The entheseal cells identified are CD3+CD4-CD8+IL-23R+RORγt+ and show up-regulated expression of both IL-17 and IL-22 (IL-23-dependent cytokines). This model provides an elegant link between enthesitis and systemic expression of IL-23, allowing further postulation that disease initiation in SpA may be linked to IL-23 produced at a distant site. Intriguingly the mice where also shown to develop a psoriasis-like phenotype in the setting of the IL-23 overexpression, further linking Ps with IL-23 and SpA. In addition the CD3+CD4-CD8+IL-23R+RORγt+ cells were

shown to produce IL-22 and subsequently activate STAT-3 dependent osteoblast-mediated bone remodelling at the enthesis [29]. This IL-22 and STAT-3-dependent osteoproliferative effect at the enthesis, recapitulates the characteristic disease phenotype seen in human SpA.

Leading on from this work IL-23 signalling involving gut, joints and skin in SpA, has been investigated in a further new animal model of SpA. Ruutu et al demonstrated that BALB/c ZAP-70^{W163C}-mutant SKG mice systemically exposed to â-1,3-glucan (curdlan) develop a disease closely resembling human SpA [30]. After curdlan administration SKG mice develop both axial and peripheral SpA, 50–60% develop small intestine inflammation reminiscent of human Crohn's disease, 25% develop unilateral uveitis and all the mice develop psoriasis-like skin inflammation. Inhibition of IL-23 in the curdlan treated SKG mice, suppresses the development of SpA (both axial and peripheral arthritis) and the ileitis. Interestingly IL-23 is secreted by the gut in response to curdlan and promotes ER stress and proinflammatory cytokine production locally whilst altering intestinal mucosal barrier integrity [31].

These recent data highlight that the development of SpA may be driven by microbial stimuli and likely involve multiple IL-23-mediated downstream pathways at various tissue sites, in genetically predisposed individuals [32]. The field remains enthusiastic towards the development of therapeutics targeting IL-23-responsive cells or their generation to improve clinical outcomes for patients with SpA.

Clinical Science

The introduction of anti-TNF agents into clinical practice was a landmark in the treatment of axSpA. Since that time there have been a number of compounds trailed that have shown promise, and a number that have not. Originating from the discovery of the involvement of IL-17 and IL-23 in SpA monoclonal antibodies to these agents have been trialed in axSpA patients [33, 34]. Both of these agents have shown promise in phase 2 trials. However one caveat with the use of anti-IL-17 in axSpA is the observation that it worsens inflammatory bowel disease (IBD) [35]. Around 60-70% of axSpA patients have either overt or subclinical IBD and therefore this may substantially curtail the use of this agent for axSpA treatment unless a biomarker or other means to stratify patients is found. Unfortunately trials of anti-CD20 therapy (rituximab) only showed efficacy in those who had not failed anti-TNF therapy in a small trial [36]. This suggests that failure of anti-TNF agents marks a slightly different biological sub-type of disease. A trial of the co-stimulatory blocking agent CTLA-Ig (abatacept) in 30 patients failed to show a major response [37]. Two agents targeting IL-6 agents (tocilizumab and sarilumab) and an anti-IL-1 agent (anakinra) have also been tested in small trials and failed to show significant efficacy [38-40]. Although sustained responses have been noted in individual patients to anakinra [41] and in sarilumab (personal observation, P. Robinson). In addition the phosphodiesterase 4 inhibitor, apremilast showed encouraging results in phase 2 trials. Currently in trial is the janus kinase inhibitor tofacitinib in AS and aminopeptidase inhibitors are in preclinical development [42]. Therefore it is likely a number of new therapeutics will make it to the clinic in the next 5 - 10 years.

Magnetic Resonance Imaging

MRI is the technological advance that enables the recognition of axSpA at an early stage or in those who do not have erosive disease. Research has shown that T1 and short tau inversion recovery (STIR) sequences are best to demonstrate axSpA and that gadolinium contrast is not additive in making the diagnosis and is therefore not justified [43, 44]. Definitions of a positive sacroiliac joint scan have been proposed and include 2 discrete STIR lesions on the same slice or 1 STIR lesion that is observed on more than one slice [45]. A positive spinal MRI is currently defined as 3 or more corner inflammatory lesions (osteitis) with each lesion having to be present on at least 2 slices [46]. Work on including structural lesions like erosions in the ASAS definition is in progress [47]. Finally research examining the value of scanning the entire spine in addition to the sacroiliac joints in the diagnosis of nr-axSpA has shown there is little additive value in the spine imaging [48]. However it should be noted that in daily clinical practice the purpose of an MRI is not only to include or exclude SpA but to diagnose chronic back pain.

Referral Strategies

Referral strategies aimed at effective identification and referral of suspected axSpA have been trailed in multi-centre randomized trials. These have shown in those patients with chronic back pain the presence of one item such as inflammatory back pain or HLA-B27 identifies 25 - 42% of patients [49-52]. Increasing the complexity the referral algorithm did not significant improve

identification rates in one large German trial [50]. Large scale campaigns aimed at the public are also effective at increasing referral rates [53].

Biomarkers

A number of biomarkers have shown some promise in identification of both axSpA from non-axSpA and poor prognosis disease in those with axSpA. These include vascular endothelial growth factor, matrix metalloprotein 3, sclerostin, citrullinated vimentin, dikkopf-1 and antibodies to MHC class II-associated invariant chain [54-60]. Whilst identification of individual biomarkers is important, evaluating the capacity of panels of multiple biomarkers is required. Evaluation of these biomarker panels in a number of independent and longitudinal cohorts would determine their prognostic value in the clinical setting.

Radiographic progression and the potential window of opportunity

Observational cohort studies have shown that smoking, an elevated CRP, pre-existing syndesmophytes and being male all increase the risk of radiographic progression [61].

First described in 1973 with a drug called phenylbutazone, the potential for non-steroidal anti-inflammatory drugs (NSAIDs) to reduce radiographic progression has gained more credence with the increasing evidence base [62]. A 2 year randomized trial of celecoxib noted a significant difference in radiographic progression of the spine in those who took celecoxib regularly compared to those with took it as required. Supporting this is an additional observational report of NSAIDs ability to retard radiographic damage from the

GESPIC cohort [63]. A re-analysis of the celecoxib trial demonstrated that those with an elevated CRP had the most benefit from continuous NSAID therapy in regard to radiographic progression [64].

There is substantial circumstantial evidence that early effective treatment of inflammatory disease in axSpA could reduce radiographic progression - analogous to the 'window of opportunity' in rheumatoid arthritis [65]. This stems from the substantial longitudinal MRI studies of anti-TNF drug therapy. In addition two observational studies have suggested that anti-TNF reduces radiographic progression over the long term [66, 67]. Therefore combined NSAID and anti-TNF therapy may be effective at significantly slowing or halting radiographic progression in patients. However definitively demonstrating this is challenging, primarily because of the very slow baseline rate of radiographic progression. This is demonstrated by the difference observed in the 2 year celecoxib trial in the PRN dosing group (those that progressed the fastest), they progressed a mean of 1.5 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) units, although the standard deviation was 2.5 mSASSS units [68]. One mSASSS unit is erosion of one corner of a vertebrae, sclerosis or squaring of a vertebrae [69]. This demonstrates the low average progression rate but a high level of variance between individuals, thereby requiring large sample sizes over a long time. The effect of newer agents on radiographic progression is unknown but will be of substantial interest. Their effect will help determine whether it is just suppression of inflammation or a specific biological action that helps reduce radiographic progression.

Conclusion

The advances in therapeutics have brought back to rheumatology clinics a huge cohort of patients who often felt there was little to be gained from visiting a rheumatologist. There are also a number of additional novel agents in the pipeline that may also join TNF inhibitors in the clinic in the near future. With huge recent gains made in both genetics research and in basic mechanisms of pathogenesis, coupled with improved classification criteria and diagnostic tools the future looks bright.

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References

1. Robinson PC, Wordsworth BP, Reveille JD, Brown MA. Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. Ann Rheum Dis. 2013;72:162-4.
2. Nash P, Mease PJ, Braun J, van der Heijde D. Seronegative spondyloarthropathies: to lump or split? Annals of the Rheumatic Diseases. 2005;64 Suppl 2:ii9-13.
3. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. Rev Rhum Mal Osteoartic. 1990;57:85-9.

4. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991;34:1218-27.
5. Taylor WJ, Robinson PC. Classification criteria: peripheral spondyloarthropathy and psoriatic arthritis. Curr Rheumatol Rep. 2013;15:317.
6. 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;27:361-8.
7. Mau W, Zeidler H, Mau R, Majewski A, Freyschmidt J, Stangel W, et al. Clinical Features and Prognosis of Patients with Possible Ankylosing-Spondylitis - Results of a 10-Year Follow-Up. J Rheumatol. 1988;15:1109-14.
8. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, 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.
9. Gong Y, Zheng N, Chen SB, Xiao ZY, Wu MY, Liu Y, et al. Ten years' experience with needle biopsy in the early diagnosis of sacroiliitis. Arthritis Rheum. 2012;64:1399-406.
10. Robinson PC, Brown MA. The genetics of ankylosing spondylitis and axial spondyloarthritis. Rheum Dis Clin North Am. 2012;38:539-53.
11. Robinson PC, Bird P, Lim I, Saad N, Schachna L, Taylor AL, et al. Consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA). Int J Rheum Dis. 2014.
12. Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A 27. Lancet. 1973;1:904-7.
13. Caffrey MF, James DC. Human lymphocyte antigen association in ankylosing spondylitis. Nature. 1973;242:121.
14. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM. High association of an HL-A antigen, W27, with ankylosing spondylitis. N Engl J Med. 1973;288:704-6.
15. Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, Leo P, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. Nat Genet. 2013;45:730-8.
16. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet. 2007;39:1329-37.
17. Reveille JD, Sims AM, Danoy P, Evans DM, Leo P, Pointon JJ, et al. Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet. 2010;42:123-7.
18. Evans DM, Spencer CC, Pointon JJ, Su Z, Harvey D, Kochan G, 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.
19. Robinson PC, Brown MA. Genetics of ankylosing spondylitis. Mol Immunol. 2014;57:2-11.
20. Cortes A, de Bakker P, Brown MA. Fine-Mapping Major Histocompatibility Complex Variation Associated With Ankylosing Spondylitis Susceptibility. Arthritis & Rheumatism. 2013;65:S723.

21. Haroon N, Inman RD. Endoplasmic reticulum aminopeptidases: Biology and pathogenic potential. Nat Rev Rheumatol. 2010;6:461-7.
22. Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insights into common pathways and complex relationships among immune-mediated diseases. Nat Rev Genet. 2013;14:661-73.
23. Gregory AP, Dendrou CA, Attfield KE, Haghikia A, Xifara DK, Butter F, et al. TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis. Nature. 2012;488:508-11.
24. Reveille JD. Genetics of spondyloarthritis--beyond the MHC. Nat Rev Rheumatol. 2012;8:296-304.
25. Wang WW, Wang ZM, Liu YY, Qin YH, Shen Q. [Increased level of Th17 cells in peripheral blood correlates with the development of hepatocellular carcinoma]. Zhonghua zhong liu za zhi [Chinese journal of oncology]. 2010;32:757-61.
26. Kenna TJ, Davidson SI, Duan R, Bradbury LA, McFarlane J, Smith M, et al. Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive gamma/delta T cells in patients with active ankylosing spondylitis. Arthritis Rheum. 2012;64:1420-9.
27. Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum. 2009;60:1647-56.
28. Wendling D. IL-23 and IL-17 in ankylosing spondylitis. Rheumatol Int. 2010;30:1547.
29. Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. Nature medicine. 2012;18:1069-76.
30. Ruutu M, Thomas G, Steck R, Degli-Esposti MA, Zinkernagel MS, Alexander K, et al. Beta-glucan triggers spondyloarthropathy and Crohn's-like ileitis in SKG mice. Arthritis Rheum. 2012.
31. Benham H, Rehaume LM, Hasnain SZ, Velasco J, Baillet AC, Ruutu M, et al. IL-23-mediates the intestinal response to microbial beta-glucan and the development of spondyloarthritis pathology in SKG mice. Arthritis & rheumatology. 2014.
32. Costello M-E, Elewaut D, Kenna T, Brown MA. Microbes, the Gut and Ankylosing Spondylitis. Arthritis Research & Therapy. 2013;15:214.
33. Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382:1705 - 13.
34. Poddubnyy D, Hermann KG, Callhoff J, Listing J, Sieper J. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). Ann Rheum Dis. 2014;73:817-23.
35. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012;61:1693-700.
36. Song IH, Heldmann F, Rudwaleit M, Listing J, Appel H, Braun J, et al. Different response to rituximab in tumor necrosis factor blocker-naive patients

with active ankylosing spondylitis and in patients in whom tumor necrosis factor blockers have failed: a twenty-four-week clinical trial. Arthritis Rheum. 2010;62:1290-7.
37. Song IH, Heldmann F, Rudwaleit M, Haibel H, Weiss A, Braun J, et al. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. Ann Rheum Dis. 2011;70:1108-10.
38. Sieper J, Inman R, Badalamenti S, Radin A, Braun J. Sarilumab for the treatment of ankylosing spondylitis: results of a phase 2, randomized, double-blind, placebo-controlled, international study (ALIGN). Annals of the Rheumatic Diseases. 2012;71(Suppl 3): 111.
39. Sieper J, Porter-Brown B, Thompson L, Harari O, Dougados M. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. Ann Rheum Dis. 2013;73:95-100.
40. Haibel H, Rudwaleit M, Listing J, Sieper J. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. Ann Rheum Dis. 2005;64:296-8.
41. Bennett AN, Tan AL, Coates LC, Emery P, Marzo-Ortega H, McGonagle D. Sustained response to anakinra in ankylosing spondylitis. Rheumatology (Oxford). 2008;47:223-4.
42. Zervoudi E, Saridakis E, Birtley JR, Seregin SS, Reeves E, Kokkala P, et al. Rationally designed inhibitor targeting antigen-trimming aminopeptidases enhances antigen presentation and cytotoxic T-cell responses. Proc Natl Acad Sci U S A. 2013;110:19890-5.
43. de Hooge M, van den Berg R, Navarro-Compan V, van Gaalen F, van der Heijde D, Huizinga T, et al. Magnetic resonance imaging of the sacroiliac joints in the early detection of spondyloarthritis: no added value of gadolinium compared with short tau inversion recovery sequence. Rheumatology (Oxford). 2013;52:1220-4.
44. 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.
45. Rudwaleit M, Jurik AG, Hermann KG, Landewe R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis. 2009;68:1520-7.
46. Hermann KG, Baraliakos X, van der Heijde DM, Jurik AG, Landewe R, Marzo-Ortega H, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. Ann Rheum Dis. 2012;71:1278-88.
47. Weber U, Lambert RG, Pedersen SJ, Hodler J, Ostergaard M, Maksymowych WP. Assessment of structural lesions in sacroiliac joints enhances diagnostic utility of magnetic resonance imaging in early spondylarthritis. Arthritis Care Res (Hoboken). 2010;62:1763-71.
48. Weber U, Zubler V, Zhao Z, Lambert RG, Chan SM, Pedersen SJ, et al. Does spinal MRI add incremental diagnostic value to MRI of the sacroiliac joints alone in patients with non-radiographic axial spondyloarthritis? Ann Rheum Dis. 2014.
49. Sieper J, Srinivasan S, Zamani O, Mielants H, Choquette D, Pavelka K, et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the

Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. Ann Rheum Dis. 2013;72:1621-7.
50. Poddubnyy D, Vahldiek J, Spiller I, Buss B, Listing J, Rudwaleit M, et al. Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol. 2011;38:2452-60.
51. Braun A, Saracbasi E, Grifka J, Schnitker J, Braun J. Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? Ann Rheum Dis. 2011;70:1782-7.
52. Hermann J, Giessauf H, Schaffler G, Ofner P, Graninger W. Early spondyloarthritis: usefulness of clinical screening. Rheumatology (Oxford). 2009;48:812-6.
53. Harrison AA, Badenhorst C, Kirby S, White D, Athens J, Stebbings S. Comparison of rates of referral and diagnosis of axial spondyloarthritis before and after an ankylosing spondylitis public awareness campaign. Clin Rheumatol. 2014;33:963-8.
54. Baraliakos X, Baerlecken N, Witte T, Heldmann F, Braun J. High prevalence of anti-CD74 antibodies specific for the HLA class II-associated invariant chain peptide (CLIP) in patients with axial spondyloarthritis. Ann Rheum Dis. 2013.
55. Baerlecken NT, Nothdorft S, Stummvoll GH, Sieper J, Rudwaleit M, Reuter S, et al. Autoantibodies against CD74 in spondyloarthritis. Ann Rheum Dis. 2013.
56. Appel H, Ruiz-Heiland G, Listing J, Zwerina J, Herrmann M, Mueller R, et al. Altered Skeletal Expression of Sclerostin and Its Link to Radiographic Progression in Ankylosing Spondylitis. Arthritis Rheum-Us. 2009;60:3257-62.
57. Heiland GR, Appel H, Poddubnyy D, Zwerina J, Hueber A, Haibel H, et al. High level of functional dickkopf-1 predicts protection from syndesmophyte formation in patients with ankylosing spondylitis. Ann Rheum Dis. 2012;71:572-4.
58. Poddubnyy D, Conrad K, Haibel H, Syrbe U, Appel H, Braun J, et al. Elevated serum level of the vascular endothelial growth factor predicts radiographic spinal progression in patients with axial spondyloarthritis. Ann Rheum Dis. 2013.
59. Maksymowych WP, Landewe R, Conner-Spady B, Dougados M, Mielants H, van der Tempel H, et al. Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondylitis. Arthritis Rheum. 2007;56:1846-53.
60. Bay-Jensen AC, Karsdal MA, Vassiliadis E, Wichuk S, Marcher-Mikkelsen K, Lories R, et al. Circulating citrullinated vimentin fragments reflect disease burden in ankylosing spondylitis and have prognostic capacity for radiographic progression. Arthritis Rheum. 2013;65:972-80.
61. Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum. 2012;64:1388-98.
62. Boersma JW. Retardation of ossification of the lumbar vertebral column in ankylosing spondylitis by means of phenylbutazone. Scand J Rheumatol. 1976;5:60-4.
63. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic

spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012;71:1616-22.
64. Kroon F, Landewe R, Dougados M, van der Heijde D. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. Ann Rheum Dis. 2012;71:1623-9.
65. Robinson PC, Brown MA. The window of opportunity: a relevant concept for axial spondyloarthritis. Arthritis Research & Therapy. 2014;16:109.
66. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65:2645-54.
67. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. Ann Rheum Dis. 2013.
68. Wanders A, Heijde D, Landewe R, Behier JM, Calin A, Olivieri I, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum. 2005;52:1756-65.
69. 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;64:127-9.

Table 1: Assessment of SpondyloArthritis International Society axial spondyloarthritis classification criteria (adapted from ref [8])

Patients need to have back pain or at least 3 months and have an age of onset of that back pain of less than 45 years.	
Imaging Arm	HLA-B27 Arm
Sacroiliitis on MRI‡ or plain radiograph* and one or more feature of SpA	HLA-B27 plus two or more features of SpA†
SpA features: Inflammatory back pain, arthritis, heel enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, Good response to non-steroidal anti-inflammatory agents, Family history of SpA, HLA-B27, elevated CRP	
‡ Lesions demonstrated on short tau inversion recovery (STIR) indicative of acute inflammation. *As per the modified New York criteria grading of at least unilateral grade 3 or bilateral grade 2 sacroiliitis. † Excluding HLA-B27 as an SpA feature	

Table 2: Theories of how HLA-B27 could cause disease in axial spondyloarthritis

Theory	Explanation
Arthritogenic peptide hypothesis	HLA-B27 presents a peptide to CD8 T cells through its classical presentation function contributing to the induction of disease
Endoplasmic reticulum stress hypothesis	Properties of HLA-B27 results in protein misfolding in the endoplasmic reticulum and causes stress, subsequently inducing disease through IL-23 production and subsequent modulation of downstream pathways
Cell surface homodimer hypothesis	HLA-B27 forms homodimers on the cell surface that interact with innate immune cells to induce disease
Immunodeficiency hypothesis	HLA-B27 presents an altered type or number of peptides resulting in the immune system inadequately or inappropriately dealing with gut microbes