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

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Key words: spondyloarthritis, axial spondyloarthritis, ankylosing spondylitis, anti-TNF, magnetic resonance imaging, classification criteria

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.12544

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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
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\textsuperscript{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.

Acknowledgements
PR is funded by the National Health and Medical Research Council (NHMRC) of Australia.

Funding: Nil

Competing Interests: PR has given talks for, consulted for, and received research funding from Abbvie, Janssen, UCB and/or Pfizer. HB has an education grant from UCB and has given a talk for Janssen.

References
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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.

<table>
<thead>
<tr>
<th>Imaging Arm</th>
<th>HLA-B27 Arm</th>
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<tbody>
<tr>
<td>Sacroiliitis on MRI‡ or plain radiograph* and one or more feature of SpA</td>
<td>HLA-B27 plus two or more features of SpA†</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Theory</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Arthritogenic peptide hypothesis</td>
<td>HLA-B27 presents a peptide to CD8 T cells through its classical presentation function contributing to the induction of disease</td>
</tr>
<tr>
<td>Endoplasmic reticulum stress hypothesis</td>
<td>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</td>
</tr>
<tr>
<td>Cell surface homodimer hypothesis</td>
<td>HLA-B27 forms homodimers on the cell surface that interact with innate immune cells to induce disease</td>
</tr>
<tr>
<td>Immunodeficiency hypothesis</td>
<td>HLA-B27 presents an altered type or number of peptides resulting in the immune system inadequately or inappropriately dealing with gut microbes</td>
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