AXIAL SPONDYLOARTHITIS: AN EVOLVING CONCEPT

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ABSTRACT

Axial spondyloarthritis (AxSpA) is the prototype of a family of inter-related yet heterogeneous diseases sharing common clinical and genetic manifestations: the spondyloarthritides (SpAs). The condition mainly affects the sacroiliac joints and axial skeleton, and has a clear classification scheme, wider epidemiological data, and distinct therapeutic guidelines when compared with other SpAs. However, the concept of AxSpA has not been immutable over time and has evolved tremendously on many levels over the past decades. This review identifies the evolution of the AxSpA concept at two levels. First, at the level of classification, the old classifications and rationales leading to the current Assessment of SpondyloArthritis international Society (ASAS) classification are reviewed, and the advantages and drawbacks are discussed. Second, at the therapeutic level, current and future treatments are described and treatment strategies are discussed.

Keywords: Ankylosing spondylitis (AS), axial spondyloarthritis (AxSpA), classification, concept, non-radiographic axial spondyloarthritis, pathophysiology, therapeutic strategies.

BACKGROUND AND OBJECTIVE

Axial spondyloarthritis (AxSpA) is the prototype of a family of inter-related yet heterogeneous diseases sharing common clinical and genetic manifestations: the spondyloarthritides (SpAs). The condition mainly affects the sacroiliac joints and axial skeleton, beginning with insidious-onset inflammatory back pain (IBP). It may also extend to peripheral joints with a pattern of asymmetrical arthritis, predominantly of the lower limbs, and with the frequent presence of enthesitis and dactylitis, and can also be associated with extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease, as well as displaying an association with the human leukocyte antigen B27 (HLA-B27). The prevalence of AxSpA in Western populations is around 0.5%. AxSpA is considered to be a prototype because it has a clear classification scheme, wider epidemiological data, and distinct therapeutic guidelines. However, the concept has not been immutable over time and has evolved tremendously at many levels over the past decades. The objective of this review is to describe the evolution of the AxSpA concept at the levels of classification and therapeutic strategy.

METHODS

A search of the US National Library of Medicine (PubMed) database was performed using the terms “axial spondyloarthritis”, “spondylitis, ankylosing” AND “concept”, with no limits on the date of publication. The search retrieved 166 articles, 33 of which were retained for the analysis according to the following inclusion criteria: pertinence to the review subject, relationship with AxSpA as a concept, relationship with the classification of AxSpA, relationship with the evolution of the treatment of AxSpA, and French or English language. The studies were divided into two categories: classification and treatment. A descriptive analysis of the evolution of these two concepts over time was performed.
The term ankylosing spondylitis (AS) derives from the Greek words ankylosis (bent or crooked) and spondylos (vertebra), and was previously known as Bechterew's disease (1892) and Marie—Strümpell disease (1884-1898). The Egyptian pharaoh Ramses II and some of his descendants were thought to have AS, but this diagnosis was recently ruled out according to findings from computed tomography scans from mummies, with the diagnosis readjusted to diffuse idiopathic skeletal hyperostosis. The first comparatively recent classification was published as the Rome criteria in 1961 and was based on clinical manifestations and sacroiliac plain X-rays, followed by the New York criteria in 1966, which introduced the radiographic grading of the sacroiliac joints. In 1984, the modified New York criteria for AS were published, which introduced the concept of IBP. AS was diagnosed if a mandatory sacroiliitis was found on plain X-rays in addition to the presence of one clinical criterion (either chronic inflammatory low back pain and stiffness, limitation of motion of the lumbar spine, or limitation of chest expansion). Two subsequent European classifications were published in 1990 and 1991, the Amor criteria and the European Spondyloarthropathy Study Group (ESSG) criteria, respectively, but they addressed the SpA as a whole family of diseases, including the undifferentiated form of SpA, rather than the axial form specifically.

Due to the lack of pathognomonic clinical features or laboratory tests, the intermittent nature of the disease, and the wide availability of effective, over-the-counter symptomatic agents (nonsteroidal anti-inflammatory drugs [NSAIDs]), early diagnosis is difficult and the delay between symptom onset and diagnosis by X-rays according to the new criteria is very important, and can be up to 9 years. A new classification system was necessary in order to help earlier identification of the disease. Furthermore, the introduction and standardisation of sacroiliac magnetic resonance imaging (MRI) revolutionised diagnosis of the disease, allowing earlier and more accurate identification of cases. In addition, effective new therapies were available and this increased the importance of an earlier diagnosis. Therefore, the Assessment of SpondyloArthritis international Society (ASAS) published the ASAS classification predominantly for AxSpA in 2009, with the term AxSpA being introduced for the first time (Figure 1).

AxSpA is an umbrella term that encompasses two entities: the first is the well-known AS, in which sacroiliitis is found on plain X-rays according to the modified New York criteria, and it is synonymous with radiographic AxSpA; the second is non-radiographic AxSpA, in which the diagnosis is based on sacroiliitis identified on MRI plus one clinical criterion, or based on a genetic criterion (HLA-B27) plus two clinical criteria (Table 1). The new criteria performed well in a validation study and demonstrated a sensitivity of 82.9% and a specificity of 84.4%, which outperformed the ESSG and Amor criteria even after incorporating ‘sacroiliitis on MRI’ into the earlier criteria. Although the main advantage of the ASAS criteria remains a high sensitivity and an earlier diagnosis leading to an earlier treatment, a major drawback remains the poor sensitivity of the clinical arm, especially in populations with a high prevalence of HLA-B27, in which fibromyalgia cases may be wrongly classified as AxSpA.

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**Figure 1: Evolution of the nomenclature of axial SpA.**

SpA: spondyloarthritides.
Since the introduction of the terms ‘radiographic’ and ‘non-radiographic’ AxSpA, studies and discussions have tried to understand if these diseases have the same genetic, clinical, biological, and prognostic characteristics. These discussions have scientific implications but also regulatory consequences. The two entities share some similar characteristics, such as disease activity and treatment response rates, with a higher response in subgroups with higher objective signs of inflammation. Non-radiographic AxSpA is characterised by a higher prevalence of females and a lower level of C-reactive protein (CRP), reflecting a milder disease. About 12% of the patients with non-radiographic AxSpA progress to AS over a period of 2 years, with elevated CRP and active sacroiliitis on MRI being the strongest predictors for such a progression. The current data consider the two entities to be part of a spectrum of the same disease.

### THERAPY OF AXIAL SPONDYLOARTHRITIS

The ‘window of opportunity’ concept, which is very well established in rheumatoid arthritis (RA), is now under evaluation for AxSpA. In theory, early diagnosis, treatment, and control of inflammation would prevent tremendous symptomatic burden and loss of function during the productive years of life. When looking at the evidence, MRI data support the window of opportunity concept: during tumour necrosis factor (TNF) antagonist therapy, pure inflammatory lesions resolved and no syndesmophytes developed at the same site, whereas complex MRI lesions combining inflammation and fatty infiltration were followed by same-site ossification. Recent-onset symptoms and pure inflammatory MRI lesions, without fatty lesion depositions, seem to be associated with a better outcome.

Another concept ‘borrowed’ from RA is the ‘treat to target’ (T2T) concept. However, unlike the well-established T2T guidance in RA, where clear outcome measures are standardised, the T2T concept for treating SpA is still immature. Clinical evidence of T2T in SpA is still lacking, and practical easy-to-measure outcomes are needed. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is currently used for therapeutic decision-making, with a cut-off score >4 indicating when to start TNF antagonist therapy; however, AS Disease Activity Score (ASDAS) values, incorporating CRP, have a significant influence on radiographic progression in AS and may currently be the best candidate for treatment decisions, as shown recently in the Outcome in Ankylosing Spondylitis International Study (OASIS).

### Table 1: Comparison of the two main classification systems for axial spondyloarthritis.

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<tr>
<td><strong>Clinical criteria</strong></td>
<td>At least one of:</td>
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<tr>
<td>• Chronic inflammatory low back pain and stiffness</td>
<td>Mandatory:</td>
</tr>
<tr>
<td>• Limitation of motion of the lumbar spine</td>
<td>• Chronic back pain and age of onset &lt;45 years</td>
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<tr>
<td>• Limitation of chest expansion</td>
<td>Other SpA features: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn’s disease/ulcerative colitis, good response to NSAIDs, family history of SpA, HLA-B27, elevated CRP</td>
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<tr>
<td><strong>Radiological criteria</strong></td>
<td>Mandatory:</td>
</tr>
<tr>
<td>• Sacroiliitis on plain X-rays (Grade 2 bilaterally or Grade 3-4 unilaterally)</td>
<td>Sacroiliitis on MRI (ASAS criteria) or on plain X-rays (New York criteria) + one other SpA feature</td>
</tr>
<tr>
<td><strong>Genetic criteria</strong></td>
<td>HLA-B27 + two other SpA features</td>
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ASAS: Assessment of SpondyloArthritis international Society; SpA: spondyloarthritides; HLA-B27: human leukocyte antigen B27; NSAID: nonsteroidal anti-inflammatory drug; CRP: C-reactive protein; MRI: magnetic resonance imaging.


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