How important is early diagnosis of ankylosing spondylitis for therapy in clinical practice?

"*It remains to be seen whether early use of biologics will unequivocally halt the new bone formation, which is the main and most debilitating outcome of this disease.*"

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Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting primarily the sacroiliac joints and the spine. AS may be associated with peripheral joint involvement and can also be accompanied by the presence of extra-articular manifestations, such as uveitis, inflammatory bowel disease or skin psoriasis.

For decades, making a diagnosis of AS was dependent on the modified New York criteria, which rely on the combination of clinical symptoms and established radiographic sacroiliitis of at least grade 2 bilaterally or grade 3 unilaterally [1]. However, radiographs are very often normal in the early stages of the disease after the onset of back pain and it may take many years for radiographic sacroillitis to develop [2,3]. As such, the modified New York criteria allow for diagnosis at an advanced stage of disease evolution, a time when structural damage is irreversible. From the clinical standpoint this diagnostic delay is of great significance since the degree of pain and disability that patients experience during this nonradiographic phase is comparable to that reported by patients who have been affected with the disease for many years [4]. The absence of a diagnosis will lead to patients missing out on early and timely initiation of appropriate treatment. Furthermore, early diagnosis is of paramount importance as there are a number of highly efficacious therapies that have become available in recent years.

Early diagnosis in AS

Recently, the Association of Spondyloarthritis International Society (ASAS) has developed more inclusive criteria that allow for the recognition of patients suffering from an axial spondyloarthritis (SpA) at every stage of the disease, even in the presence of normal radiographs. This is because of the inclusion of MRI in addition to x-ray as the imaging tool of choice for the sacroiliac joint (SIJ) and spine. According to these criteria, a patient with low back pain who is younger than 45 years at onset can be classified as having axial SpA if there is imaging evidence of sacroiliitis (either by conventional radiography and/or MRI) plus at least one other clinical feature of SpA. In the absence of sacroiliitis on imaging, the diagnosis can be made if the patient is *HLA-B27* and has at least two other clinical SpA features with a sensitivity of 82% and a specificity of 84.4% [5].

MRI has the capability to identify acute changes, such as those due to active inflammation, and structural changes that reflect an inactive or chronic disease state. Active inflammatory lesions are best visualized by fat-saturated T2-weighted turbo spin-echo sequence or a short tau inversion recovery (STIR) sequence, while chronic lesions are best visualized by T1-weighted turbo spin-echo sequence.

Although the ASAS criteria were initially developed as classification criteria, they are likely to be useful as diagnostic criteria. This may help to prevent diagnostic delay and make an early diagnosis in order to prevent future progression and enable treatment at an early stage. Indeed, there is already published evidence of time to diagnosis and treatment having improved over recent decades. According to Salvadorini *et al.*, the mean of diagnostic delay has been reduced from 12 years in the 1970s to 2 years in the decade from 2000 [6]. This improvement in the time to diagnosis is largely owing to the increased use of MRI.

It is well established that the greater the delay in the diagnostic and treatment of the disease, the more likely that radiographic damage would become apparent. The rate of progression from nonradiographic axial spondyloarthritis to

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AS has been estimated as approximately 10% over 2 years. Poddubnyy *et al.* found a rate of progression of 11.6% over 2 years [7]; Sampario-Barros *et al.* reported 24.3% over 5–10 years [8]; and Mau *et al.* reported 59% after 10 years of follow-up [9].

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Early axial ankylosis is seen more frequently in men than in women. The absence of peripheral arthritis or the presence of uveitis, or *HLA-B27* positivity is associated with multiple syndesmophytes or fusion of multiple vertebrae of the lumbar spine [10]. In a recent study, the combination of severe MRI sacroiliitis and *HLA-B27* positivity was highly predictive of radiographic progression at the SIJ after 8 years. These findings support the concept that MRI is of great utility for the early diagnosis of AS and it also has prognostic value [11]. In another study, the combination of MRI features typical of sacroiliitis in patients with inflammatory back pain who were *HLA-B27* positive was shown to have a 90% probability of being diagnosed as axial SpA in patients with well-established symptoms [12]. Oostven *et al.* investigated 25 *HLA-B27* positive patients, with inflammatory back pain and without definite radiographic evidence of sacroiliitis. They assessed the diagnostic value of MRI in the detection of sacroiliitis. The positive-predictive value of ≥grade 2 sacroiliitis on MRI at study entry for the development of ≥grade 2 sacroiliitis on plain radiograph after 3 years was 60% [13]. On the other hand, a longitudinal study investigated MRI, computed tomography and radiographic changes in the SI joints over 1 year in 34 patients with early inflammatory back pain and no correlation between MRI scores and radiographic changes at follow-up was found [14]. This may have been owing to the short follow-up period, as it is expected that 2 years is the minimum time period for radiographic progression to become apparent [15]. Nevertheless, MRI could detect significant inflammatory and destructive changes in the sacroiliac joint over the 1-year follow-up period.

Although the late stage of the disease is the major concern, it is important to note that not all AS patients will progress to spinal fusion and some patients will only develop mild radiographic sacroiliitis. For this reason it is important to identify those patients with the worst prognosis at an early stage. Amor *et al.* reported seven variables that are correlated with disease severity: hip arthritis; erythrocyte sedimentation rate >30 mm/h; poor efficacy of NSAIDs; limitation of lumbar spine; sausage-like finger or toe; oligoarthritis and onset ≤16 years. If none of these factors are present at diagnosis a mild outcome can be predicted (sensitivity: 92.5%; specificity: 78%). If a hip is involved or if three factors are present, a severe outcome is predictable (sensitivity: 50%) and a mild disease practically excluded (specificity: 97.5%) [16].

> "*MRI is of great utility for the early diagnosis of ankylosing spondylitis...*"

Clinicians and researchers are increasingly focusing on the identification and application of biomarkers for disease activity, prognosis and response to therapy. Several biomarkers have been identified as candidates reflecting disease activity such as the C-reactive protein (CRP), an acute phase reactant that is elevated in approximately 50% of patients with SpA [17]. CRP is regulated by IL-6 and both biomarkers correlate with MRI features of inflammation. Moreover, IL-6 was shown to predict MRI response to anti-TNF-α therapy independently of CRP [18].

TNF-blocking agents in the management of AS

The objectives for treatment in AS are to relieve pain, stiffness and fatigue, and to maintain posture and good physical functioning. Aside from physical therapies, the two main therapeutic options currently available are the nonsteroidal anti-inflammatory and TNF-blocking agents, by far the most efficacious drugs in AS.

Anti-TNF therapy has been shown to reduce disease activity by 50% in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50) in up to 50% of the patients [19–21]. Importantly, this response is better when patients are treated early on in the disease course. A recent study reported a BASDAI 50 response being achieved in 80% of patients with a disease duration of less than 3 years compared with 14.3% of patients with a disease duration of more than 10 years in patients without radiographically defined sacroiliitis treated with adalimumab. Similarly, in the same study, a better improvement in the ASAS 40 was achieved in patients with shorter disease duration. In total, 73% of patients with a disease duration of less than 3 years achieved

an ASAS 40 response compared to none of the patients with a disease duration of >10 years [22]. Furthermore, the level of response appears higher in patients with shorter disease duration (3 years) in the nonradiographic stage. The same authors described patients with nonradiographical SpA with disease duration of approximately 3 years. Significantly more patients in the adalimumab group achieved ASAS 40 at week 12 compared with patients in the placebo group (36 vs 15%; $p < 0.001$) [23]. A third study used infliximab in a small population of patients with poor prognosis early axial SpA of less than 2-year duration. All were *HLA-B27* positive with evidence of active bone marrow edema on MRI of the SIJs and the majority were reported to have normal baseline radiography. The level of response in the infliximab-treated group as shown by the ASAS40 criteria (61.1 vs 17.6%; $p = 0.009$) was superior to that reported in more established AS populations [24], suggesting a higher and enhanced chance of response in early disease.

A small number of imaging studies have shown that inflammatory lesions suggestive of disease activity are more commonly found during the first 10 years of disease compared with the late stages. This is true particularly at the SIJ level [25]. Short disease duration, an elevated CRP and a high MRI score have been reported as important predictors of response to anti-TNF treatment (probability of 99%) [25]. This clinical response is mirrored on the resolution of MRI-determined lesions in the spine and sacroiliac joints [24,26,27].

However, despite the ample evidence for clinical efficacy of these drugs in AS it remains to be demonstrated whether TNF-blocking therapies lead to modification of the disease progression. Preliminary MRI data suggest that there is a relationship between resolution of inflammatory lesions and development of inactive or 'fatty' vertebral corner lesions [28]. Furthermore, there is also some evidence suggesting that these 'fatty' lesions may be the forerunner of new bone formation or syndesmophytes at vertebral corners [29]. However, unequivocal evidence of radiographic progression being halted post-anti-TNF is lacking and new syndesmophytes are detected even in patients who receive continuous treatment [30,31], although there may be a retardation on the rate of progression [32]. Since the inflammation is more active in the early stages, early treatment may prevent the appearance of new inflammatory lesions, and thus indirectly the appearance of new syndesmophyte. Likewise, early treatment might lead to a reduction of the radiologic progression and is supposed to positively influence long-term outcome. Longitudinal studies with larger inception cohorts are needed to address these issues.

Conclusion

The increased use of MRI in recent decades in the study of AS and the rest of the SpA and its inclusion in the new ASAS classification criteria has been of great utility in the identification of early disease. This has contributed to a significant reduction in the time to diagnosis and has allowed for the introduction of therapy at a much earlier stage of the evolution of the disease. Preliminary data suggest that response to treatment is enhanced in the earlier stages and this may contribute to slow the rate of radiographic progression. It remains to be seen whether early use of biologics will unequivocally halt the new bone formation, which is the main and most debilitating outcome of this disease.

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