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Axial Spondyloarthritis

About the Reviewer

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Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease characterised by inflammatory or structural changes that mainly affect the axial skeleton, such as erosions and new bone formation in the sacroiliac joints and spine. Under classification criteria developed by the Assessment of SpondyloArthritis international Society (ASAS), the term axSpA describes both patients with established ankylosing spondylitis (AS) and those with nonradiographic axSpA.[1,2]

This paper is intended as an educational resource for healthcare professionals. It discusses the diagnosis and classification of axSpA, the relationship between axSpA and AS, epidemiology, treatment options, and whether we may be able to more accurately predict prognosis and modify the disease process with therapeutic interventions in axSpA.

Ankylosing spondyloarthritis and axial spondyloarthritis

Ankylosing spondyloarthritis (AS) is a chronic inflammatory rheumatic disease, with an estimated prevalence of 0.9–1.4% worldwide.[3-5] However, it is likely that prevalence data underestimate the true number of individuals affected: radiography is insensitive for diagnosing early disease and is relatively insensitive to changes over time, limiting its utility in the diagnosis of AS.[6] Moreover, plain film radiologic diagnosis is subject to intra- and interobserver variability in interpreting radiographic sacroiliitis.[6]

The disease mainly affects the axial skeleton, with or without concomitant peripheral involvement such as peripheral arthritis or enthesitis, leading to structural and functional impairments and a substantial decrease in quality of life.[3,4] AS belongs to the spondyloarthritis (SpA) group of related but phenotypically distinct disorders, including psoriatic arthritis, arthritis/spondylitis associated with inflammatory bowel disease, reactive arthritis, and juvenile spondyloarthropathy; AS is regarded as the disease prototype.[7]

The modified New York criteria stipulate radiographic changes in the sacroiliac (SI) joints of at least grade II bilaterally or grade III or IV unilaterally.[7] In many patients with AS, the appearance of radiographic changes leading to definite sacroiliitis appears relatively late after the onset of symptoms (usually inflammatory back pain) and inflammation of SI joints, resulting in a long diagnostic delay of 5–10 years.[7] The diagnostic delay is also due to a relatively low awareness of AS among physicians dealing with chronic back pain patients, because AS may account for as few as 5% of cases with chronic back pain.[8] Even if AS is considered in a back pain patient, the finding of normal SI joints on radiographs in early disease often lead the physician to rule out AS in the differential diagnosis. Whilst the modified New York criteria can effectively identify patients with established AS, they are not applicable in early disease when radiographic sacroiliitis is not yet present, nor do they identify patients who do not develop radiographic sacroiliitis.[8] The challenge of diagnosis is compounded by the fact that while radiographic sacroiliitis will be present in the majority of patients after 5–10 years of symptoms, a small percentage of patients will never develop radiographic changes despite having inflammatory back pain for many years.[8]

In SpA patients without definite radiographic changes, magnetic resonance imaging (MRI) can visualise active inflammation of the SI joints.[7] Although not all SpA patients develop radiographic sacroiliitis, many patients with active inflammation of the SI joints on MRI despite normal radiographic findings go on to develop radiographically-defined sacroiliitis and thus evolve to AS.[7] This led to the concept of axial (ax)SpA, in which all cases of SpA with predominantly axial involvement are considered to belong to one disease continuum, with and without radiographic damage.[9]

The prevalence of axSpA

The US national prevalence estimates of axSpA are based on a representative sample of 5103 US adults aged 20–69 years who were examined in the National Health and Nutrition Examination Survey (NHANES) program 2009–2010.[10] NHANES used two published sets of classification criteria: the Amor criteria and the European Spondylarthropathy Study Group (ESSG) criteria (the most widely utilised in previous population-based studies of SpA).[10] The overall age-adjusted prevalence of definite and probable SpA by the Amor criteria was 0.9%, corresponding to an estimated 1.7 million adults; according to the ESSG criteria, the age-adjusted prevalence of SpA was 1.4%, corresponding to an estimated 2.7 million adults. The study notes that SpA prevalence estimates are in the range of SpA prevalence estimates reported elsewhere in population-based surveys, showing SpA to be at least as prevalent as rheumatoid arthritis, yet SpA remains an under-recognised condition. The study adds that the US SpA prevalence estimates may be lower than actual rates because the NHANES 2009–2010 data collection did not capture a complete set of the elements specified in the SpA criteria sets. Thus, SpA may affect even more people in the US population.

In the classification criteria developed by the Assessment of Spondyloarthritis International Society (ASAS), axSpA refers to both patients with established AS and those with nonradiographic (nr)-axSpA.[1] The two conditions share similar clinical, imaging, and laboratory features, but patients with nr-axSpA do not have radiographic sacroiliitis and are considered to have an earlier form of AS, although not all will progress if left untreated.[11]

Differentiating between AS and nr-axSpA

AS and nr-axSpA are differentiated by conventional radiography findings (namely, the presence or absence of definite structural changes in the SI joint). These two groups also differ according to the extent of inflammation: patients with AS have significantly higher signs of inflammation, as measured by spinal inflammatory lesions on MRI, higher serum levels of C-reactive protein (CRP) and a higher median Ankylosing Spondylitis Disease Activity Score (ASDAS), compared to patients with nr-axSpA.[12] Registry and clinical trial data demonstrate that both patients with early established AS and patients with nr-axSpA have comparable clinical manifestations and burden of disease, requiring treatment irrespective of the presence of radiographic damage.[7,13,14] Specifically, registry data from the German SpA Inception Cohort (GESPIC) compared patients with AS and nr-axSpA and also a cohort of patients meeting ASAS criteria for axSpA,[7] while the clinical trial data involved both AS[13] and nr-axSpA patients.[14]

Recent findings from the RAPID™-axSpA study reveal a high disease burden of axSpA on household and workplace productivity in the overall study population (with on average >1 week of paid work and 2–3 weeks of household duties or social activities affected per month, at study baseline) and a similarly high burden reported by patients with AS and nr-axSpA.[15] Notably, while conventional radiography fails to detect definite structural changes in the SI joints in patients with nr-axSpA, over half of these patients have MRI-detected spinal inflammation.[12]

Under the current ASAS classification criteria for axSpA, diagnosis depends on either clinical characteristics or imaging features.[1] MRI-detected sacroiliac inflammation is the major imaging-based diagnostic criteria; positivity for human leukocyte antigen B27 (HLA-B27) is the key clinical-based diagnostic criteria. MRI scans of SI joints are defined as positive (i.e., indicative of axSpA) in the presence of either inflammatory lesion(s) on a single imaging slice, or when one lesion is detectable in more than one consecutive imaging slice.[16]

Imaging and treatment

ASAS/EULAR recommendations on the management of AS have recently been updated; the project group unanimously agreed that these recommendations can equally be applied to patients with ax-SpA.[17] NSAIDs, including Coxibs, are recommended as first-line treatment for the majority of patients with AS; NSAIDs have proven to be highly effective against the major symptoms of axSpA (pain and stiffness) and may have disease-modifying properties including retarding progression of structural damage in the spine[18] and continuous NSAID treatment is preferred for patients with persistently active, symptomatic disease.[17] Interestingly, NSAID therapy improved MRI evidence of inflammatory spinal lesions due to axSpA (treatment resulted in fewer lesions) in one study[19] but not in another.[20] Clinical data have shown that high doses (NSAID index ≥50) or continuous intake of NSAIDs over two years slow radiographic progression to a greater extent compared with low doses (NSAID index <50) or on-demand treatment strategies in axSpA.[21,22] This beneficial effect of intensive NSAID therapy was especially evident in patients with established AS and those with increased levels of acute phase reactants at the start of treatment,[21,22] although the effect of high or continuous doses of NSAIDs is less evident in patients with nr-axSpA, which is thought to be because many do not have pre-existing radiographic damage or high levels of CRP.[21] No recommendation has been made as yet in regard to intensive NSAID therapy in nr-axSpa.

Tumour necrosis factor (TNF) blockers are the only treatments indicated in patients with persistently high disease activity despite intensive NSAID therapy.[17] There are now five biologics approved for the treatment of patients with active AS in many countries, all directed against TNFα: infliximab, etanercept, adalimumab, certolizumab pegol and golimumab. Adalimumab and certolizumab pegol are also approved for use in the EU in adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant of, NSAIDs.[23] Adalimumab has gained regulatory approval for nr-axSpA in 50 countries including the European Union and Hong Kong.[24]

TNF inhibitor therapy effectively reduces MRI-proven inflammation in the SI joint and the spine in patients with axSpA[25-27] and recent evidence shows that they can also inhibit radiographic progression in AS,[28,29] with therapeutic advantages linked to early initiation of TNF inhibitors and prolonged duration of treatment.[29] An analysis of combined data from 2 placebo-controlled randomised trials with infliximab and etanercept, respectively, revealed that AS patients with extensive active inflammation in the spine at the initiation of anti-TNF therapy were more likely to have major clinical responses than the patients with low-grade or no inflammation.[30]

Predictors of a positive response to TNF inhibitors

The analysis identified 4 covariables as predictors of a positive response to anti-TNF therapy: disease duration, CRP, Bath Ankylosing Spondylarthritis Functional Index (BASFI), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The likelihood of achieving BASDAI 50 significantly decreased for every year of disease duration: 73% of patients with ≤10 years' disease duration achieved BASDAI 50 at the end of the study compared with only 31% of those with >20 years of disease (p=0.003). High CRP levels at baseline correlated with TNF-α inhibitor response (OR 1.02, 95% CI 1.002 to 1.05); moreover, the likelihood of responding to anti-TNF therapy in patients with high CRP increased with a short disease duration (5 years) to 90% and in patients with a long disease duration from 30% to 70%. Having a lower BASFI increased the likelihood of attaining BASDAI 50: 70% of the patients achieved BASDAI 50 when BASFI was <4.5 compared with 36% when BASFI was ≥6.5 (p=0.017). Similarly, after 52 weeks of adalimumab therapy, patients with nr-axSpA who were HLA-B27 positive and had active inflammatory changes shown by MRI were more frequently BASDAI 50 (75.0%) or ASAS40 (62.5%) responders.[14]

In the 52-week adalimumab data, predictors of good response to anti-TNF therapy in patients with axSpA without radiographically-defined sacroiliitis include the combination of MRI features indicating active inflammation with elevated serum CRP at onset (>6 mg/L), younger age (≤30 years) and short disease duration (≤3 years).[14] Outcomes from a study involving HLA-B27 positive patients with MRI-determined early sacroiliitis indicate that MRI-proven inflammation at baseline might be a predictor of favourable response to anti-TNF therapy in axSpA; after 16 weeks of infliximab, 56% of patients achieved ASAS partial remission.[31]

A group of European researchers developed matrix- and algorithm-based prediction models, in an attempt to identify AS subpopulations likely to respond optimally to anti-TNF therapy.[32] They report that a combination of six variables (CRP, HLA-B27 genotype, BASFI semi-quantitative evaluation, age, enthesitis and choice of therapy) adequately predicted clinical improvement following therapy and subsequent disease states. These data may help clinicians choose more appropriate therapies for patients in daily practice.

Evidence from the ABILITY-1 trial indicates that adalimumab is a potential treatment option for nr-axSpA patients regardless of whether they fulfil the imaging or clinical arm of the ASAS axial SpA criteria.[33] At baseline, study participants fulfilled ASAS criteria for AS, had a BASDAI score of ≥4, total back pain score of ≥4 (on a 10 cm visual analogue scale), an inadequate response to NSAIDs and were without radiographic disease. At week 12, significantly more patients in the adalimumab group achieved ASAS40 compared with patients in the placebo group (36% vs 15%; p<0.001) and adalimumab was also associated with significant clinical improvements in ASDAS and BASDAI responses, as well as improvements in quality of life measures. Clinical remission was achieved by a greater number of patients in the adalimumab group compared with those in the placebo arm, whether defined by ASAS partial remission or ASDAS inactive disease. Adalimumab was also associated with significant improvements in objective measures of inflammation (as assessed by CRP and the Spondyloarthritis Research Consortium of Canada [SPARCC]) MRI scores for both SI joints and spine). The better maintenance of spinal mobility seen with adalimumab compared with placebo could mean that in axSpA, a therapeutic window exists in support of the early use of anti-inflammatory treatment (with NSAIDs and anti-TNF agents) before irreversible bony changes have developed. This is supported by a clinical investigation showing that early inflammatory lesions resolve following anti-TNFα therapy and are not associated with the development of new syndesmophytes.[34]

CLINICAL EFFICACY OF ADALIMUMAB IN axSpA

Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two[14]

Summary: This was the first randomised placebo-controlled trial of anti-TNF therapy to involve patients with axSpA without radiographically-defined sacroiliitis refractory to conventional treatment.

Methods: Forty-six patients with active axSpA were randomised to receive subcutaneous adalimumab 40 mg (n=22) or placebo (n=24), every other week for 12 weeks, followed by an open-label extension that continued up to week 52 (completed by 38 patients). The diagnosis of axial SpA without radiographically-defined sacroiliitis was based on the presence of chronic low back pain (>3 months' duration), an age at symptom onset of <50 years, and the fulfillment of at least 3 of the following 6 criteria, including at least 2 of the first 3 criteria: 1) inflammatory back pain; 2) HLA-B27 positivity; 3) an MRI showing active inflammation of the spine or sacroiliac joints; 4) a history of a good response to NSAID treatment; 5) the presence (current or past) of 1 or more extraspinal manifestations (anterior uveitis, peripheral arthritis, or enthesitis); and 6) a family history of SpA.

Results: At week 12, an ASAS40 response was achieved by 54.5% of the adalimumab group and by 12.5% of the placebo-treated patients (p=0.004). Patients who were initially treated with placebo achieved a similar degree of efficacy after switching to adalimumab at week 12, with 54.2% of patients originally randomised to placebo achieving ASAS40 after 40 weeks. Efficacy was maintained in all patients until week 52. Younger age (≤30 years) at study entry and an elevated CRP concentration at baseline (>6 mg/L) were the best predictors of achieving an ASAS40 response. No serious adverse events occurred during the 12-week placebo-controlled phase. During the open-label extension, 8 serious adverse events were reported in 5 patients; none of the events was considered to be related to adalimumab.

Specialist's Comments: See next study.

Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1)[33]

Summary: ABILITY-1 was the first large international study to use the new ASAS criteria. The patient population had a significant burden of disease. Adalimumab treatment resulted in significant improvement of disease activity across all outcome measures including imaging data.

Methods: Patients met ASAS criteria for axSpA, had a BASDAI score of ≥4, total back pain score of ≥4 (10 cm visual analogue scale) and inadequate response, intolerance or contraindication to NSAIDs. Patients were randomised to adalimumab (n=91) or placebo (n=94).

Results: Significantly more patients in the adalimumab group achieved ASAS40 at week 12 compared with patients in the placebo group (36% vs 15%; p<0.001). Adalimumab also resulted in significantly higher percentages of patients achieving clinical improvements based on other ASAS responses (ASAS20, 52% vs 31% for placebo, p=0.004; ASAS5/6, 31% vs 6%, p≤0.001), ASDAS (ASDAS clinically important improvement, 37% vs 13%; ASDAS major improvement, 19% vs 3%, p≤0.001 for both comparisons) and BASDAI 50 (35% vs 15%, p≤0.001) at week 12. Significantly higher percentages of adalimumab-treated patients also achieved states of disease remission (ASAS partial remission 16% vs 5%, p=0.01; ASDAS inactive disease, 24% vs 4%, p≤0.001). Significant improvements in physical function and quality of life were observed with adalimumab, according to the Health Assessment Questionnaire modified for Spondyloarthropathies (HAQ-S) (–0.3 from baseline vs –0.1 with placebo; p=0.025) and the Short Form-36 physical component summary scores (5.5 vs 2.0 with placebo; p=0.001). Inflammation in the spine and SI joints on MRI significantly decreased after 12 weeks of adalimumab treatment. Shorter disease duration (<5 years), younger age (<40 years), elevated baseline CRP (>3.0 mg/dL) or higher MRI SI joint scores (≥2) on the SPARCC index were all associated with better responses to adalimumab at week 12. The safety profile was consistent with what is known for adalimumab in AS and other immune-mediated diseases.

Specialist's Comments: These studies highlight the importance of diagnosing SpA early (before any radiological sacroiliitis) as anti-TNF treatment shows promising effects in early disease. Shorter disease duration and younger age are also considered as markers for better treatment response. Anti-TNF treatment improves disease activities (BASDAI), functional status (BASFI) as well as biochemical markers (CRP) and is considered to be a safe drug. The first study also showed sustained effectiveness during long-term (52 weeks) anti-TNF therapy. In daily practice, it would be important to use Magnetic Resonance Imaging and HLA-B27 to diagnose SpA if lumbosacral radiographs fail to show any change in patients with inflammatory back pain. In addition, one should consider using anti-TNF treatment for those with poor response to conventional NSAID therapy.

Sustained clinical remission in patients with non-radiographic axial spondyloarthritis after two years of adalimumab treatment[35]

Summary: Two-year follow-up data (week 104) reported for ABILITY-1 showed sustained responses, with about half of the patients treated with adalimumab in remission at 2 years (defined as either ASDAS inactive disease [ASDAS <1.3] or ASAS partial remission). The outcomes support the efficacy of adalimumab in patients with SpA who do not meet AS diagnostic criteria.

Methods: This analysis involved the MRI^{+}/CRP^{+} nr-axSpA subpopulation (n=107), defined as patients who had a positive baseline MRI (SPARCC score ≥2 for either the SI joints or spine) or an elevated CRP at baseline.

Results: Sustained remission rates (clinical remission achieved at weeks 52, 80 and 104) were similar between patients with symptoms lasting <5 versus ≥5 years (sustained ASDAS inactive disease 38% vs 31%; sustained ASAS partial remission 26% vs 29%). Most of the patients in remission at 104 weeks had also been in remission after 52 and 80 weeks of treatment. Eight serious infections, 1 case of lupus-like syndrome and 2 deaths (suicide and cardiopulmonary failure due to opiate toxicity) were attributed to adalimumab exposure. No malignancies or demyelinating diseases were reported.

Specialist's Comments: The long-term efficacy (≤104 weeks) and safety of anti-TNF therapy in axSpA is shown in this study. In active SpA patients, it would be important to continue the therapy, as discontinuation is associated with a high disease relapse rate. The drug is regarded safe although certain precautions need to be taken before and during therapy. Despite its effectiveness, anti-TNF treatment is expensive. Regular monitoring of pain scores/BASDAI would be necessary during the treatment course. In patients with persistently high pain scores/BASDAI, it would be justified to have another reassessment axial MRI before considering switching to another anti-TNF agent.

OVERALL CONCLUSIONS – Dr Chung

The concept of SpA consists of a spectrum of disease where AS represents the more advanced disease and nr-axSpA represents the earlier stage. The diagnosis of disease has also evolved from sole reliance on lumbosacral radiographs to more liberal use of MRI and HLA-B27 during the initial assessment. Despite these advancements, the treating physician would still need a high degree of alertness in order to diagnose early. We recommend using clinical features of inflammatory back pain as an initial screening measure. It is hoped that earlier use of anti-TNF therapy could reduce long-term radiographic damage and ankylosis, and preserve the functional status.

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