Commentary

Non-radiographic axial spondyloarthritis: what is it?

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ABSTRACT

The classification criteria recently developed by the Assessment of Spondyloarthritis International Society (ASAS) highlighted a specific entity: non radiographic axial spondyloarthritis (nr-axSpA). Although more and more widely used in the literature as well as clinical trials, limits and profile of this entity is still under known or debated. Some studies have already compared those forms to classical AS, even in recent forms. They showed that, apart from the difference in the ossification process, and the greater degree and frequency of systemic and MRI inflammation in AS, those two forms of SpA share the same genetic background, clinical patterns, and burden of disease. TNF antagonists seemed as effective in controlling symptoms in patients with nr-axSpA. Concerning the long-term outcome of nr-ax-SpA, only long-term ongoing cohorts of patients with recent nr-axSpA will be able to determine what proportion of patients have persistent non-radiographic disease and what proportion do progress to AS.

Introduction

Spondyloarthritis (SpAs), initially known as 'seronegative spondylarthritides', were recognised in the 1960s and early 1970s as a family of diseases sharing clinical, radiological, genetic, and therapeutic characteristics. This family includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, arthritis related to inflammatory bowel disease, undifferentiated spondyloarthritis, and a subgroup of juvenile idiopathic arthritis (1-4). The clinical features of SpAs consist of axial skeletal involvement, extra-articular features (such as uveitis, Crohn's disease, and ulcerative colitis), peripheral arthritis, and enthesitis. These features are identified simultaneously or sequentially in a single patient or in several family members. SpAs are strongly associated with the genetic marker HLA B27.

Several sets of classification criteria have been developed in order to define homogenous patient subgroups (5-7). However, when used for diagnostic purposes, these criteria sets are of limited value, most notably early in the course of the disease (8, 9). The introduction of new treatment options such as tumour necrosis factor (TNF) antagonists has revolutionised the treatment of SpAs and increased the importance of making an early diagnosis. In patients with AS, the diagnosis is often delayed by 8 to 10 years after symptom onset (9, 10), leading to quality-of-life impairments (11, 12), significant loss of function, and the development of axial ankylosis that might have been preventable with early appropriate care.

Magnetic resonance imaging (MRI) can show abnormalities many years before the first radiographic changes (9). Thus, the classification criteria recently developed by the Assessment of Spondyloarthritis International Society (ASAS) (13-15) use MRI findings to identify patients who have axial spondyloarthritis without radiographic changes (non-radiographic axial spondyloarthritis: nr-axSpA). However, although the existence of nr-axSpA is now widely accepted, few data are available on the features, natural history, and outcomes of nr-axSpA and uncertainty remains about whether nr-axSpA is a full-fledged member of the axial SpA family or a different condition belonging to the same spectrum (16). Here, we review the available data on nr-axSpA and look for some perspectives about the concept. For the review, we performed a PubMed research using the key words "spondyloarthropathy" and "radiographic», leading to 646 results. Then we only included editorials and original articles which specifically focused on this problem of non-radiographic forms.

The ASAS criteria

The modified New York criteria and the ESSG criteria have limitations especially in early disease (17). In 2009, the ASAS group published criteria for axial SpA, including an imaging arm (sacroiliitis on imaging plus ≥1 SpA feature) and a clinical arm (no sacroiliitis on imaging but positive HLAB27 plus ≥2 SpA features). The features are inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/colitis, good response to non steroidal anti-inflammatory drugs, family history of SpA, HLA B27 positivity, or elevated C-reactive protein (13-15). This new criteria set should allow an early diagnosis of ax-SpA. It emphasises the value of MRI in detecting sacroiliac inflammatory changes, the importance of HLA B 27 typing, and the need to separate the main clinical subtypes (axial *vs*. peripheral) (4, 15*)*. This differentiation between axial and peripheral disease is relevant in particular because therapies differ in efficacies (18). The term *spondyloarthritis* was preferred to "spondyloarthropathy" or "spondyloarthritides" to emphasise the inflammatory nature of the diseases (19).

Of course, those new ASAS criteria raise several questions. One of them concerns the place of the former undifferentiated spondyloarthritis (uSpA). Along side AS, uSpA was the most common subtype of the SpA. Inflammatory back pain peripheral arthritis and, less frequently, enthesitis are the main clinical features of those uSpA (19). The most important outcome of uSpA was the risk of progression to AS or other well-defined subsets of SpA. Since IBP is the most impressive clinical finding in uSpA and since these patients are probably most likely to develop into AS, some authors have proposed the term 'predominant axial SpA' (19). Some authors have also suggested the terms of "predominant axial spondyloarthritis", "predominant peripheral spondyloarthritis", and, in case of no real predominance a third group, "spondyloarthritis associated with"psoriasis, inflammatory bowel disease, preceding infection, undifferentiated SpA (18). Finally, the diagnostic performance of the ASAS criteria remains to be evaluated in follow-up studies.

Does recent non-radiographic axial spondyloarthritis differ from AS?

The first study comparing nr-ax SpA to AS was a cross-sectional analysis of patients from the German Spondyloarthritis Inception Cohort (GESPIC) (20). The 226 patients with nr-axSpA (symptom duration <5 years) and the 236 patients with AS (symptom duration <10 years) were not significantly different for age at disease onset; frequency of HLA-B27 positivity; or prevalences of past or current inflammatory back pain, arthritis, enthesitis, psoriasis, or uveitis. Furthermore, the two groups had similar levels of disease activity as assessed using the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), patient global assessment, and pain intensity (20). The proportion of males was higher in the AS group than in the nr-axSpA group, and AS patients had higher values for the Bath Ankylosing Spondylitis Functional Index (BASFI), C-reactive protein (CRP) level and, as expected, mSASSS score (a radiographic score that chiefly evaluates spinal ossification) (20). Similarly, another study comparing 56 patients with AS to 44 patients with nr-axSpA found no differences in demographic, genetic, or clinical variables except for the sex ratio, with a majority of males in the AS group and a majority of females in the nr-axSpA group; the AS patients also had higher CRP levels and greater spinal inflammation by MRI (21). These results were confirmed and completed in a larger population of patients with more recent forms of axial SpA included in a French cohort known as DESIR. (*Devenir des Spondylarthropathies Indifferenciées Récentes*, outcomes of recent-onset undifferentiated SpAs). DESIR is a prospective longitudinal cohort study conducted in France in 708 patients from 25 rheumatology centres to collect comprehensive data on the natural history and prognosis of SpAs, starting at symptom onset (22). The DESIR cohort was established by including consecutive patients aged 18 to 49 years with inflammatory back pain of at least 3 months' but less than 3 years' duration and symptoms suggesting SpA according to a rheumatologist (level of confidence ≥5 on a 0-10 numerical rating scale, where 0 was not suggestive and 10 was very suggestive of SpA). So, "5" (more than half) was the cut-off leading to a more probable diagnosis of SpA than another diagnosis (22). Among the 475 patients fulfilling ASAS criteria for axial SpA at inclusion, factors independently associated with radiographic lesions in these early forms were CRP elevation, sacroiliac joint MRI inflammation, spinal MRI inflammation in smokers, poor response to NSAIDs as defined in the ASAS criteria, and alcohol use (13-15, 22). Again, neither the other usual characteristics (demographic and clinical characteristics) nor the overall disease burden (BASDAI…) differed between the two groups (23).

However, several arguments suggest that nr-axSpA and AS might deserve to be viewed as separate conditions. Robinson *et al*. believe that AS and nr-axSpA are clearly overlapping but different entities (16). Their first argument pertains to the natural history of the two conditions: in longitudinal studies, patients with nr-axSpA do not necessarily progress to AS meeting New York criteria (24, 25), suggesting that nr-axSpA might not be an early stage of AS. In addition, genetic differences between patients with AS and those with nr-axSpA have been suggested. Thus, significant sex-ratio differences have been reported between AS and nr-axSpA (18), and the association with HLA-B27 may be stronger for AS than for other SpA subgroups (20, 26). Nevertheless, all subtypes of axial SpA are now mainly recognised as belonging to the same entity (3). Apart from the difference in the ossification process between AS and nr-axSpA and the greater degree and frequency of systemic and MRI inflammation in AS, the two conditions share the same genetic background, clinical patterns, and burden of disease, even in recent forms.

Are TNF antagonists similarly effective in AS and in nr-axSpA?

If AS and nr-axSpA are the same disease, at least in terms of the clinical symptoms and disease burden, then a reasonable assumption is that the same drugs will be effective in both

conditions, at least until drugs capable of blocking the ossification process become available. However, until recently, the only available data on the efficacy of TNF antagonists came from patients with pure AS. Several studies assessing TNF antagonists in nr-axSpA are under way and one has been published: the ABILITY-1 study comparing adalimumab to a placebo in 185 patients with nr-axSpA showed a significantly higher ASAS40 response rate at week 12 in the adalimumab group (primary criterion 36% *vs*. 15%, $p<0.001$), as well as a larger decrease in MRI inflammation at the spine and sacroiliac joints (26). As previously demonstrated in AS, short symptom duration and CRP elevation were good predictors of responsiveness to adalimumab (26). In a previous smaller placebo-controlled trial, adalimumab showed good clinical efficacy and safety in patients with axial SpA but no radiographically defined sacroiliitis (27). A randomised placebo-controlled trial of infliximab published in 2009 included 40 HLA-B27-positive patients with inflammatory back pain and MRI-determined sacroiliitis, *i.e*. patients with early axial SpA and a high likelihood of eventually progressing to radiographically defined AS (28). Infliximab appeared effective in this patient population, providing a reduction in disease activity by 16 weeks (28): BASDAI score mean reduction -3.41in the infliximab group *vs*. -0.75 in the placebo group ($p=0.002$), BASFI score mean reduction -2.70 n the infliximab group *vs*. -0.47 in the placebo group ($p=0.004$), Finally, a post-hoc analysis of the ESTHER trial found similar response rates in patients with AS (n=20) and in those with nr-axSpA (n=20) after 1 year of etanercept treatment : reduction of BASDAI by 3.3 (95% CI 2.2 to 3.8) *vs*. 3.6 (95% CI 2.8 to 4.4) and reduction of AS Disease Activity Score by 1.8 (95% CI 1.5 to 2.2) *vs*. 1.8 (95% CI 1.5 to 2.1) (29). A communication at the 2012 Annual Scientific Meeting of the American College of Rheumatology reported the week-24 results of a randomised placebo-controlled study evaluating the efficacy and safety of certolizumab pegol in active axial spondyloarthritis meeting ASAS criteria but with either MRI inflammation or systemic CRP elevation (30). Certolizumab pegol was superior over the placebo in improving the signs and symptoms, and no difference in efficacy was detected between the AS group (n=178) and the nr-axSpA group (n=147) (30).

Thus, TNF antagonists seem effective in controlling symptoms in patients with nr-axSpA. A first European drug approval extension for selected forms of nr-axSpA has been granted for adalimumab based on ABILITY-1 results. Available data on the cost effectiveness of those drugs in AS should be reevaluted in those forms of the disease (31).

Is non-radiographic axial spondyloarthritis an early disease stage?

A crucial issue is whether nr-axSpA is usually a pre-radiographic stage of axial SpA or a definite non-radiographic form of axial SpA.

In a 10-year follow-up study of 88 patients who had possible AS but normal or, at the most suspicious radiographic findings, at the sacroiliac joints, 32 patients (59% of the 54 finally available patients and 36% of the 88 original patients) had definite AS at last evaluation (24). In 12 individuals, AS was excluded. The 10 remaining patients had nr-axSpA (24). Similarly, in an inception cohort of 29 patients with axial SpA (inflammatory back pain and MRI inflammation of the sacroiliac joints) with a mean follow-up of 8 years, 21 patients had nr-axSpA and 8 fulfilled modified New York criteria for AS at baseline; at last follow-up, only 3 patients had developed radiographic sacroiliitis, *i.e*. met modified New York criteria for AS (25). Finally, a 2-year follow-up study in 210 patients with early ax-SpA (95 patients with nr-axSpA, 115 with AS) from the Gespic cohort was performed by Poddubnyy *et al*., to assess the progression of sacroiliitis. The rate of progression from nr-axSpA to AS was 11.6% over 2 years. An elevated level of C-reactive protein was a strong predictive factor of progression (32).

Only long-term cohort studies of patients with recent nr-axSpA will be able to determine what proportion of patients have persistent non-radiographic disease and what proportion progress to AS. However, for now, "non-radiographic spondyloarthritis" seems a better term than "pre-radiographic spondyloarthritis".

Conclusion

Non-radiographic axial SpA has been identified as an important subgroup in the SpA spectrum, essentially through the ASAS classification criteria. This subgroup seems very similar to AS, with no detected differences in genetic background, rheumatologic and non-rheumatologic manifestations, disease activity, or disease burden. The absence of ossification in nr-axSpA is of course a major difference with AS, but the probability of remaining free of radiographic disease throughout the lifespan in patients with initial nr-axSpA is unknown. Comparisons of patients with nr-axSpA and AS can be expected to produce major discoveries regarding the genes involved and the mechanisms of the ossifying process. In nr-axSpA, drugs such as TNF antagonists seem useful in controlling the symptoms and restoring good quality of life.

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