SPONDYLOARTHRITIS: Sacroiliac joints' radiographic progression: speed and determinants

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STANDFIRST

Non-radiographic axial spondyloarthritis (nr-axSpA) and radiographic axial spondyloarthritis (r-axSpA) are considered to represent different spectra of the same disease. Accumulating data suggest that the transition rate from nr-axSpA to r-axSpA in patients with early disease is low and identify inflammation, smoking and HLA-B27 positivity as factors associated with transition.

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Within the disease spectrum of axial spondyloarthritis (axSpA), patients are currently distinguished into two groups: radiographic axSpA (r-axSpA) or ankylosing spondylitis, which is characterized by the presence of substantial radiographic damage of the sacroiliac joints (fulfilling modified New York criteria for radiographic sacroiliitis); and non-radiographic axSpA (nr-axSpA), which is characterized by the absence of definite radiographic changes of the sacroiliac joints. Over time, as symptom duration increases, there is a decrease in the nr-axSpA to r-axSpA ratio, i.e. if subgroups of axial SpA patients with different disease durations are compared, subgroups with shorter disease duration are expected to have lower nr-axSpA to r-axSpA ratios of patients than subgroups with longer disease duration, supporting the concept of axSpA as a single disease. Over time, a proportion of axial SpA patients might never develop definite radiographic damage, whereas others will experience a shift from nr-axSpA to r-axSpA.[1] The celerity of this shift and its predisposing factors are still unclear. In a newly published prospective study of patients with early axSpA, Dougados et al[2] report new data regarding the rate of transition from nr-axSpA to r-axSpA as well as factors that might be associated with this transition; these data have implications for both clinical practice and research studies.

Patients with a high chance of progressing to r-axSpA might require different treatment strategies in order to prevent this irreversible change; however, there is still no evidence that the drugs currently available to treat axSpA[3] (including NSAIDs, TNF blockers, and a recently approved IL-17 blocker) are actually capable of achieving this goal, and it is possible that this can only be achieved by drugs with different mechanisms of action: namely, drugs targeting bone metabolic pathways.[4]

Previous studies have attempted to determine the percentage of patients who progress from nr-axSpA to r-axSpA over time[5, 6]; however, these studies had important

methodological limitations and included a small number of patients. A third study, performed using the German Spondyloarthritis Inception Cohort (GESPIC), has provided the most relevant data so far.[7] This study included 95 patients with a mean disease duration of 3.2 years and reported that 12% patients with nr-axSpA progressed to r-axSpA over 2 years. However, this finding required confirmation in other studies and in patients with a shorter disease duration.

The new study by Dougados et al.[2] determined the rate of progression from nr-axSpA to r-axSpA in 326 patients from the *Devenir des Spondylarthopathies Indifférenciées Récentes* (DESIR) cohort, which included patients with a mean symptom duration of 1.5 years. Only 5% patients progressing from nr-axSpA to r-axSpA over 2 years, which is less than half the rate observed in the GESPIC cohort[7]. If one just compares the progression rates found in these two studies, it could be concluded that the rate of progression from nr-axSpA to r-axSpA is lower in patients with a shorter disease duration. However, interpretation of these data should take two critical methodological issues into account.

First, the inclusion criteria of these two studies were not the same. In the GESPIC cohort[7], all patients with nr-axSpA had a definite clinical diagnosis of axSpA according to the local rheumatologist, and patients fulfilled the European Spondyloarthropathy Study Group (ESSG) criteria. By contrast, patients in the DESIR cohort[2] had inflammatory back pain and a high probability (>50%) of having axSpA according to the opinion of the treating rheumatologist, but not all of them had definite axSpA or necessarily fulfilled axSpA criteria according to any classification system. Therefore, if only those patients in the DESIR cohort with definite axSpA had been included in the Dougados et al. study[2], the observed rate of progression could have been increased.

Second, in both studies, readers scored the radiographs in a random order: that is, without knowing their chronological order. In the GESPIC cohort[7], some patients initially classified as r-axSpA later switched to nr-axSpA, but this regression was an uncommon event

(2.6%). However, in the DESIR cohort[2], the percentage of regressors was even higher than the percentage of progressors (5.7% versus 4.9%) and almost the double of the percentage of regressors in the GESPIC cohort (5.7% versus 2.6%). These results suggest that the known phenomenon of measurement error that is inherent to any type of radiographic scoring may have had more influence in the observed progression rate in the DESIR study[2] than in the GESPIC study[7]. Such measurement error has previously been related to the moderate inter-reader reliability when assessing radiographs of sacroiliac joints.[8] In patients with rheumatoid arthritis, chronological reading of radiographs is preferable to random reading due to decreased variability when estimating progression rate, therefore increasing the efficiency of the reading.[9] Based on these considerations, we wonder whether chronological reading would have been a more appropriate method to determine the progression rate from nr-axSpA to r-axSpA in both the DESIR and GESPIC cohorts.

Dougados et al.[2] also investigated predisposing factors for radiographic progression of the sacroiliac joints, which they defined as progression by at least one grade in at least one sacroiliac joint during the 2-year follow-up period. The potential predisposing factors investigated in this study were: age, gender, smoking status, HLA-B27 positivity, serum C-reactive protein (CRP) levels, MRI inflammation of the sacroiliac joints, clinical disease activity measured by the Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) and treatment (NSAID and TNF-blocker therapy). Among them, the characteristics that were found to be independently and significantly associated with radiographic progression of the sacroiliac joints were: smoking at baseline (OR=3.3, 95% CI 1.0–11.5); HLA-B27 positivity (OR=12.6, 95% CI (2.3–274); and a positive MRI of sacroiliac joints at baseline according to Assessment of Spondyloarthritis International Society (ASAS)–Outcome Measures in Rheumatology (OMERACT) definition (OR=48.8, 95% CI 9.3–904).

The results of Dougados et al.[2] are partially consistent with previously reported data. A study by Bennett et al[10] found that severe sacroiliac joint inflammation on MRI and HLA-B27 positivity were associated with the development of r-axSpA in a group of patients with inflammatory back pain; however, this study only included 40 patients. By contrast, no clear association between HLA-B27 positivity or smoking status and radiographic progression of the sacroiliac joints was observed in the GESPIC cohort.[7] However, at the spinal level, smoking has been clearly associated with radiographic progression in the same cohort.[1] Additionally, the Dougados et al.[2] study did not observe an independent association with serum CRP levels, which were the strongest predictor of sacroiliac joint radiographic progression in the GESPIC cohort[7]. As mentioned above, these discrepancies could be explained by the differences in the inclusion criteria.

Overall, we think that accumulating evidence supports the concept that nr-axSpA and r-axSpA are spectra of the same disease. The percentage of patients who shift from nr-axSpA to r-axSpA is not easy to determine, mainly due to methodological difficulties, particularly the variability in reading and rating radiographic changes of the sacroiliac joints. However, based on the data from the DESIR and GESPIC cohorts[2,7], the transition rate from nr-axSpA to r-axSpA during the early years of the disease seems to be quite low (5–12% during 2 years of follow-up). Furthermore, among the possible factors associated with this important shift, inflammation (elevated serum CRP levels or MRI inflammation of the sacroiliac joints), HLA-B27 positivity and smoking have been identified (Figure 1). We will need to wait for studies with longer follow-up in order to clarify whether this low rate changes or remains stable over time, and also to confirm whether these characteristics are robust prognostic factors of the progression of structural damage of the sacroiliac joints.

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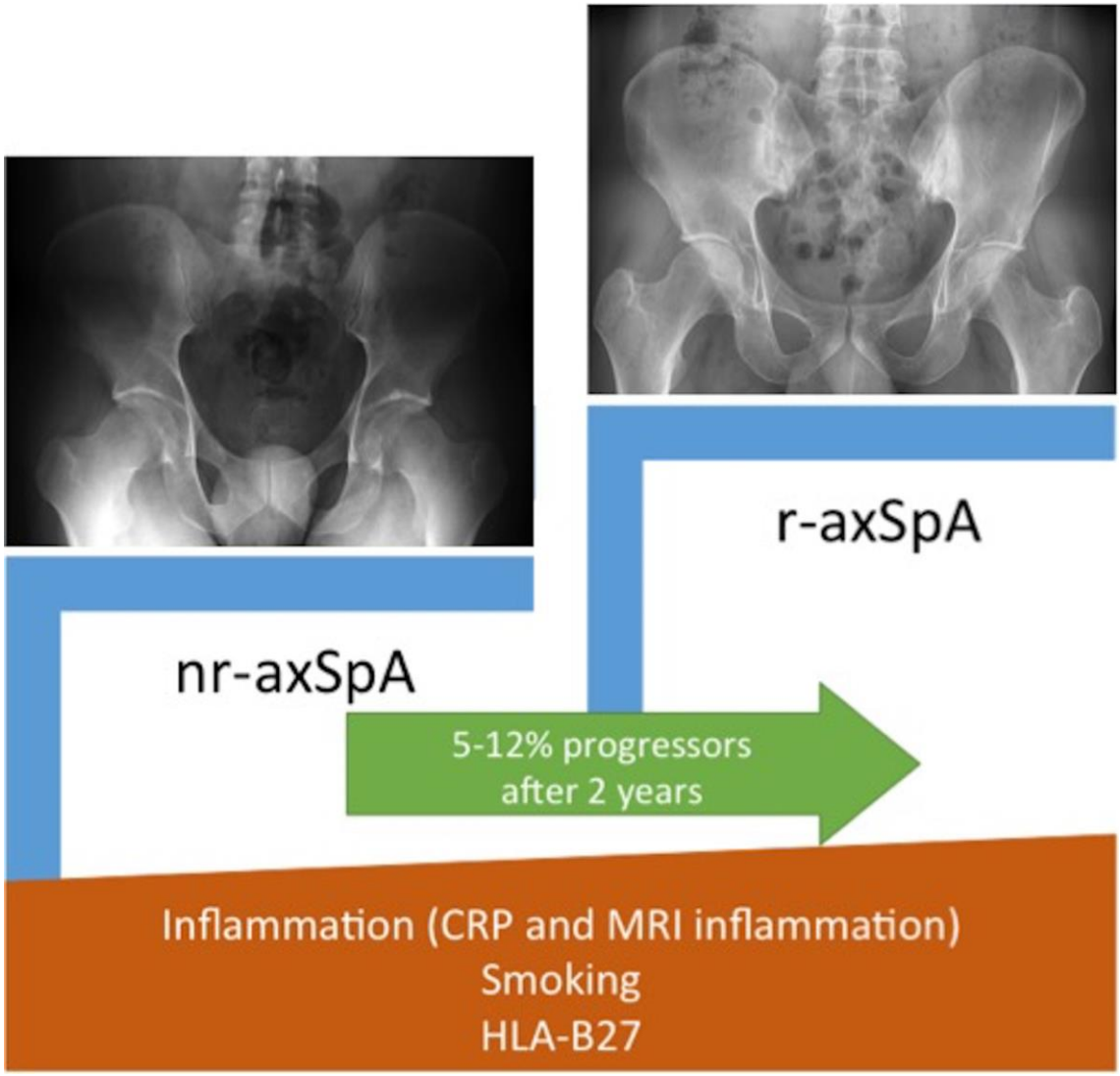
Author contributions
Both authors researched data for the article and contributed to discussion of content, writing the article, and reviewing and editing the manuscript before submission.

Competing interests statement
The authors declare no competing interests.

Figure 1. Rate of progression from non-radiographic to radiographic axial spondyloarthritis and predisposing factors for this shift. CRP, C-reactive protein; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis. Pelvic radiographs are shown; in the left panel the sacroiliac joints do not fulfil the radiographic criterion of the modified New York criteria for ankylosing spondylitis; in the right panel the sacroiliac joints have significant damage fulfilling modified New York criteria for ankylosing spondylitis.



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