The gestalt of spondyloarthritis: From early recognition to long-term imaging outcomes

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Chapter 8

Is active sacroiliitis on MRI associated with radiographic damage in axial spondyloarthritis? Real-life data from the ASAS and DESIR cohorts

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ABSTRACT

Objectives: To assess any association between bone marrow edema on MRI of the sacroiliac joints (MRI-SIJ) according to local readings in daily practice and the development of structural damage on radiographs of the SIJ (X-SIJ) in axial spondyloarthritis (axSpA).

Methods: Patients with axSpA from the Assessment of the SpondyloArthritis international Society (ASAS) and DEvenir des Spondylarthopathies Indifférenciées Récentes (DESIR) multicentre cohorts were included. MRI-SIJ and X-SIJ were obtained at baseline, and X-SIJ at follow-up after a mean 4.6 years (ASAS) and 5.1 years (DESIR). All images were scored by local readers. Structural damage in the X-SIJ was defined according to the modified New York criteria. The percentage of structural net progression (number of 'progressors' minus the number of 'regressors' divided by the total number of patients) was assessed and the effect of bone marrow edema on MRI-SIJ on X-SIJ damage evaluated by multivariable logistic regression.

Results: In total, 125 (ASAS-cohort) and 415 (DESIR-cohort) patients had baseline MRI-SIJ and complete X-SIJ data available. According to local readings, progression and 'improvement' in X-SIJ was seen in both the ASAS- and DESIR-cohort, yielding a net progression that was higher in the former than in the latter (19.2% and 6.3%). In multivariable analysis, baseline bone marrow edema on MRI-SIJ was strongly associated with X-SIJ structural progression in both ASAS (odds ratio=3.2 [95% CI: 1.3; 7.9]), and DESIR (odds ratio=7.6 [95% CI: 4.3; 13.2]).

Conclusion: Inflammation on MRI-SIJ is associated with future radiographic progression according to local readings despite an expected increased imprecision invoked by local readings.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a term used to describe patients with SpA with predominant axial manifestations including those with (radiographic axSpA; r-axSpA) and without (non-radiographic axSpA; nr-axSpA) evidence of radiographic damage at the sacroiliac joint (SIJ) level (according to the modified New York criteria; mNY).[1]

Over the years, several studies have been assessing the rate of progression from nr-axSpA to r-axSpA (i.e. from mNY-negative to mNY-positive).[2-8] Overall, progression is known to be a slow process in axSpA, but some features have been shown to associate with an increase in SIJ damage accrual, especially objective inflammatory markers, such as elevated CRP and presence of inflammation at the local level as measured by subchondral bone marrow edema (BME) on MRI of the SIJ (MR-SIJ).[2, 3, 5, 9, 10]

To partially control for the well-known limitations of the mNY method (i.e. poor reliability due to substantial interobserver variation) and to arrive at the most reliable and unbiased progression rate, researchers have been relying on scores provided by trained central readers (often more than one) when assessing SIJ radiographic progression and predictors thereof.[11, 12] Indeed, central reading (especially when more than one reader contributes with scores) has been shown to increase the chances of finding subtle associations.[13] On the other hand, central reading findings are not easy to transfer to clinicians' daily clinical practice where central imaging interpretation is not available.

The effect of BME on MRI-SIJ on SIJ radiographic progression using imaging data provided by (untrained) local readers, has not been tested thus far. Therefore, the question remains whether the practicing clinician can use the imaging data available in daily clinical practice, though possibly less reliable, to make prognostic decisions when confronted with a positive MRI-SIJ, as suggested by studies with dedicated central reading procedures.

We aimed to test the possible effect of MRI-SIJ inflammation on structural damage in radiographs of the SIJ (X-SIJ), when both are assessed by local readers as in daily clinical practice.

METHODS

Patients and study design

Patients with axSpA according to their treating rheumatologist from the Assessment of the SpondyloArthritis international Society (ASAS) cohort (clinicaltrials.gov ID: NCT00328068) and from the DEvenir des Spondylarthopathies Indifférenciées Récentes (DESIR) cohort (clinicaltrials.gov ID: NCT01648907), with baseline MRI-SIJ and complete (i.e. baseline and follow-up) X-SIJ data available were included. Details on the inclusion criteria of the above-mentioned cohorts have been previously reported.[14, 15] Importantly, they differ in the duration of symptoms allowed for inclusion, which was not restricted in the ASAS cohort, but was limited to 3 years in DESIR.

Both studies were conducted according to good clinical practice guidelines and were approved by the appropriate local medical ethical committees. Written informed consent was obtained from participating patients before inclusion.

Data collection

Information on age, symptom duration (in years), gender, HLA-B27 status (positive/negative) and on CRP (mg/L) was collected at baseline in both cohorts. In addition, in DESIR, data on disease activity (BASDAI), smoking status (smoker/non-smoker) and treatment with non-steroidal anti-inflammatory drugs (yes/no) was also collected. MRI-SIJ and X-SIJ were obtained at baseline, and X-SIJ at follow-up (ASAS: mean (S.D.) 4.6 (0.8) years; DESIR: 5.1 (0.2) years) and evaluated by a local reader (i.e. rheumatologist and/or radiologist). Images were taken unblinded to other imaging information and clinical characteristics. Readers had the option to view the baseline image when scoring the follow-up image. BME at MRI-SIJ was assessed either without a formal definition (i.e. according to the reader overall judgement; ASAS-cohort) or according to the ASAS definition (DESIR-cohort) as present/absent.[16, 17] Structural damage in the X-SIJ was defined according to the mNY criteria (positive/negative).[18]

Statistical analysis

The percentage of structural net progression was defined as the number of 'progressors' (change from mNY-negative to mNY-positive) minus the number of 'regressors' (change from mNY-positive to mNY-negative) divided by the total number of patients. Net progression was assessed separately in the entire population of each cohort and in subgroups according to the CRP and BME status at baseline. The effect of baseline MRI-SIJ BME on X-SIJ damage at follow-up was evaluated in two types of logistic regression models adjusted for potential baseline confounders selected *a priori* based on clinical grounds: i) including only variables common to both cohorts (i.e. gender, HLA-B27, CRP, symptom duration); and ii Including all common variables plus the ones only available in DESIR (i.e. BASDAI, smoking status and treatment with non-steroidal anti-inflammatory drugs). All models were fit including all axSpA patients irrespective of the mNY status at baseline.

RESULTS

In total, 125 (out of 445) and 415 (out of 708) axSpA patients were included from the ASAS and DESIR cohorts, respectively. Patients that were included were more likely to be HLA-B27 positive and to have radiographic sacroiliitis and BME on MRI-SIJ at baseline than those that did not, in the DESIR cohort but were similar in the ASAS cohort (Supplementary Table S1 and S2 available at *Rheumatology* online).

Included patients from the ASAS cohort had longer mean symptom duration (6.7 vs 1.5 years) and were also more likely to be HLA-B27 positive (70% vs 64%), to have BME on MRI-SIJ (66% vs 40%) and elevated CRP (38% vs 30%) at baseline as compared with patients from the DESIR cohort.

Radiographic progression

From the total 125 patients in the ASAS cohort, 35 (28%) changed from mNY-negative to mNY-positive (positive change) after a mean of 4.6 years, while 11 (8.8%) changed in the opposite direction (negative change), resulting in a net percentage of progression of 19.2%. In DESIR, positive change occurred in 49 (11.8%) out of the total 415 patients after a mean of 5.1 years; and negative change in 23 (5.5%), yielding a net progression of 6.3%. In Fig. 1, net progression is shown in subgroups of patients according to the presence of objective signs of inflammation at baseline. In both cohorts, progression was much higher if BME on MRI-SIJ was present regardless of CRP elevation.

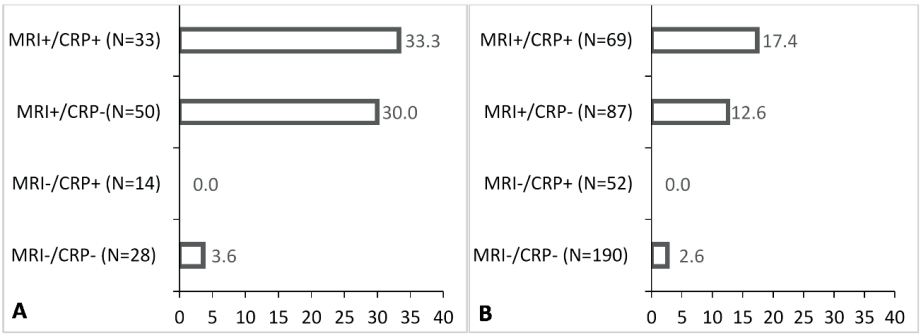

Figure 1. Net progression from mNY-negative to mNY-positive according to baseline objective inflammatory markers.
(A) ASAS cohort: N=125; (B) DESIR: N=398 (17 patients miss baseline CRP). MRI, magnetic resonance imaging; CRP, c reactive protein; mNY, modified New York criteria; SIJ, sacroiliac joints.

Effect of MIR-SIJ inflammation on X-SIJ progression

In the multivariable analysis (including only variables common to both cohorts), BME on MRI-SIJ was found to be an independent predictor of the development of radiographic damage both in the ASAS (odds ratio=3.2 [95% CI: 1.3; 7.9]), and DESIR (odds ratio=7.6 [95% CI: 4.3; 13.2]) cohort (Table 1). The results were similar also in the model adjusted for variables only available in DESIR (odds ratio=6.6 [95% CI: 3.7; 11.6]).

Table 1. Effect of inflammation on MRI-SIJ at baseline on the development of X-SIJ structural damage at follow-up

Predictor \ Outcome	mNY aOR (95% CI)
Sacroiliitis on MRI-SIJ (ASAS-cohort) (N=125)	**3.2 (1.3; 7.9) ***
Sacroiliitis on MRI-SIJ (DESIR-cohort) (N=398)	**7.6 (4.3; 13.2) ***

* Adjusted for gender, HLA-B27, CRP, symptom duration. MRI-SIJ, magnetic resonance imaging of the sacroiliac joints; X-SIJ, radiograph of the SIJ; mNY, modified New York criteria; c reactive protein; aOR, adjusted odds ratio.

DISCUSSION

In this study we analysed data from two independent multicentre cohorts conducted in daily practice with readings of MRI-SIJ and X-SIJ performed by local rheumatologists or radiologists. We have shown axSpA patients with inflammation on MRI-SIJ at baseline were 3-7-fold more likely to develop radiographic damage after 4.6-5.1 years. We were able to find this relationship despite the fact that local readers may not be necessarily well trained, and that the scores are usually based on one reader only, two factors that increase variation in scores. On the other hand, local readers were unblinded to the time order of images, which may increase precision, but also has the risk of expectation bias.

The assessment of SIJ radiographic progression based on the mNY grading system is challenging. Researchers have been implementing strategies to handle the well-known poor reliability of this method.[11, 12] The use of scores from at least one trained central reader being one of the most common.[2, 3, 5] Central reading reduces (but does not eliminate) the 'noise' and increases the likelihood of capturing true progression (i.e. the signal). Although the 'noise' is expectedly bidirectional (if readers are blinded to time-order) it is not unreasonable to assume that it explains the captured 'improvements' of structural damage.[13]

The above-mentioned concept of 'signal' to 'noise' ratio remained overlooked for several years. Only recently, researchers from the German Spondyloarthritis Inception Cohort acknowledged that 'improvements' should not be ignored when calculating progression.[5] In this cohort 3 (1.4% of the total) axSpA patients that were mNY-positive at baseline 'improved' after 2 years (i.e. became mNY-negative). Also, in DESIR, 'improvements' were seen in 7 patients (1.6% of the total) after 2 years and in 3 (0.7%) after five years with central reading.[2, 3] These studies, even within the same cohort, differ from each other in the method to obtain the scores (e.g. how to combine data from different readers) as well in the method to calculate 'net progression', but they all unequivocally show that improvements (i.e. noise) can still be seen even with central reading.

Thus, it is not surprising that when relying on local (untrained) readers, as in the current study, figures for improvements and potentially for worsening were even higher compared with studies with central readings. 'Improvements' were seen in 9% and 6% of all axSpA patients from the ASAS and DESIR cohorts, respectively, even though readers had the possibility to access the baseline scoring when judging the follow-up images. Yet, it was neither assessed in ASAS nor in DESIR, whether the same or different readers scored baseline and follow-up images, and whether or not readers reviewed baseline images (MRI/radiographs) at the time of scoring follow-up radiographs. After taking measurement error into account, the 'net progression' was higher in the ASAS (19%) than in the DESIR cohort (6%), which may be partly explained by prognostic dissimilarities between the two populations (i.e. patients from the ASAS cohort had higher likelihood of features known to associate with structural progression: e.g. elevated CRP and HLA-B27 positivity).[2, 5] Overall, it would be expected that a low signal/noise ratio of scoring radiographs could compromise the ability to detect significant associations, especially, because the predictor of interest (i.e. BME on MRI-SIJ) is not free of measurement error either, though to a lesser extent compared to radiographs.[17] Notwithstanding, and despite all the

noise, it is remarkable that inflammation on MRI-SIJ is still clearly associated with the development of radiographic damage in both cohorts (with different populations – adding to external validity).

The results from this study should be interpreted with some caution. Unblinded readings as done in daily practice may lead to a higher rate of progression (expectation bias). However, given the rather high rate of 'improvements' of X-SIJ at follow-up, unblinded readings appeared not to be a major confounder in this regard in both cohorts. Moreover, the association between baseline BME on MRI-SIJ and the later development of radiographic damage was found at the group level. This means that, on average, patients with BME on MRI are 3-7 times more likely to develop structural damage in a setting that the rheumatologist encounters in daily practice. However, our data do not support (and we do not claim) that finding inflammation on MRI-SIJ at the individual-patient level implies definite progression in that individual patient. Of note, this limitation applies in the same way to studies with central reading assessments.

In summary, our data from the two multicentre cohorts show, for the first time, that at the group level SIJ inflammation on MRI is associated with the later development of structural progression in radiographs according to local readings in clinical practice.

SUPPLEMENTARY DATA

Supplementary data are published online on the website of Rheumatology (Oxford)

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