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CLINICAL SCIENCE

Sacroiliac radiographic progression over 10 years in axSpA: data from the DESIR inception cohort

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ABSTRACT

Objectives To evaluate sacroiliac radiographic progression over a 10-year follow-up and determine the baseline factors associated with such progression in patients with recent-onset axial spondyloarthritis (axSpA, <3 years).

Methods This analysis was performed in the DESIR cohort (NCT01648907). The radiographic status of the patients (radiographic axSpA (r-axSpA) vs non-radiographic axSpA (nr-axSpA)) was based on the modified New York (mNY) criteria. Information on mNY criteria on the pelvic radiographs was obtained in four reading waves over a 10-year period. Images were blinded and centrally read by 3 trained readers. The % of mNY net progressors (ie, number of 'progressors' minus number of 'regressors' divided by the total number of patients) was assessed in completers (ie, pelvic radiographs at baseline and 10 years). The yearly likelihood of mNY+ was estimated using an integrated analysis (ie, including all patients with at least one available mNY score ('intention-to-follow' population) using a generalised estimating equations model and time-varying tumour necrosis factor (TNF) use as a confounder. Baseline predictors of mNY+ during 10 years were evaluated.

Results Completers included 294 patients, while intention-to-follow included 659 participants. In the completers, the net % progression (from nr-axSpA to r-axSpA) was 5.8%. In the intention-to-follow population, the probability of being mNY+ was estimated to increase 0.87% (95% CI 0.56 to 1.19) per year (ie, 8.7% after 10 years) while when introducing TNF inhibitors (TNFi) as a time-varying covariate, the probability was 0.45% (95% CI 0.09 to 0.81) (ie, 4.5% after 10 years). Baseline bone marrow oedema (BME) on MRI of the sacroiliac joints (SIJ) was associated with being mNY+ over time OR 6.2 (95% CI 5.3 to 7.2) and OR 3.1 (95% CI 2.4 to 3.9) in HLA-B27+ and HLA-B27−, respectively). Male sex, symptom duration >1.5 years, Axial Spondyloarthritis Disease Activity Score ≥2.1 and smoking (only in HLA-B27 positives) were also associated with being mNY+ over 10 years. BME was not found to be a mediator of the HLA-B27 effect on mNY+ at 10 years.

Conclusions The yearly likelihood of switching from nr-axSpA to r-axSpA in patients after 10 years of follow-up was low, and even lower when considering TNFi use.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Information about the likelihood of radiographic sacroiliitis over time in patients with recent-onset axial spondyloarthritis (axSpA) is scarce, but previous data have suggested a shift from non-radiographic axSpA (nr-axSpA) to radiographic axSpA (r-axSpA) over 5 years of 5.1% of patients.

WHAT THIS STUDY ADDS

⇒ This study confirms that the likelihood of radiographic progression at the sacroiliac level in patients with axSpA with <3 years of onset is quite low after 10 years of follow-up (<10% likelihood of switch from nr-axSpA to r-axSpA over 10 years), and even lower when adjusting for time-varying tumour necrosis factor inhibitors (TNFi) exposure (<5% over 10 years); however, the causal effect of TNFi exposure cannot be demonstrated in this setting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Local inflammation (eg, bone marrow oedema at the sacroiliac joints (SIJ) on MRI) was found as the main predictor of SIJ radiographic progression, especially in HLA-B27+ patients, highlighting the importance of HLA-B27 as a critical factor for the severity of axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic and musculoskeletal disease that primarily affects the axial skeleton, in particular the sacroiliac joints (SIJ).[1] Axial structural damage may arise over time because of persistent inflammation, which may lead to complete ankylosis, but previous data have suggested that such radiographic progression occurs slowly in the SIJ.[2]

Ankylosis of the spine has been reported to be the leading source of functional limitation in patients with established axSpA.[3] Determining the likelihood of structural progression at SIJ level is important for several reasons: first, because this is usually the first area to be involved and structural damage of the SIJ has been reported to predict spinal structural involvement[4]; however, poorer functional status has also been reported in patients with structural damage of the SIJ, independently of damage in the spine,[5] suggesting that SIJ involvement could have on its own a functional impact in patients with axSpA. Furthermore, despite the

broad use of biologics (namely TNF inhibitors (TNFi), ie, very efficacious drugs significantly reducing inflammation), and their resulting major improvements in the quality of life of patients with axSpA, some patients continue to present structural damage despite treatment. It seems therefore important to be able to determine which factors are associated with radiographic progression among patients receiving the standard of care.

Finally, information about the likelihood of radiographic sacroiliitis over time and the factors that contribute to it is scarce. In 2017, data on sacroiliac radiographic progression after 5 years of follow-up in the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort were published,[2] showing a shift from non-radiographic to radiographic axSpA in only 5.1% of patients and a change of at least one grade of sacroiliitis in the radiographs in 13.0% of patients.

Based on these remarks, and as the 10-year data of the DESIR axSpA inception cohort became available, we decided to conduct an analysis aiming to evaluate radiographic progression over a 10-year follow-up and determine the baseline factors associated with such progression in this population.

METHODS

Patients

A total of 708 patients with early inflammatory back pain (IBP) have been included in the DESIR cohort (NCT01648907), the French multicentric prospective inception cohort of patients with axSpA.[6] The cohort has been described elsewhere, but briefly, consecutive adult patients aged <50 years with IBP involving the thoracic, lumbar spine or buttock area for >3 months but <3 years and symptoms suggestive of axSpA according to the rheumatologist's assessment (score ≥5 on a Numerical Rating Scale of 0–10, where 0=not suggestive and 10=very suggestive of axSpA) were included in the cohort. Patients fulfilled either the Calin or Berlin criteria for IBP. Exclusion criteria for DESIR included conditions that might interfere with the validity of the informed consent and/or prevent optimal compliance (eg, alcoholism, psychiatric disorders) and a history of TNFi (eg, the only biologic and targeted synthetic disease-modifying antirheumatic drugs approved for SpA at the time) usage at baseline. Visits were scheduled every 6 months, for the first 2 years and yearly thereafter. The present analysis includes the first 10 years of data, while a follow-up until 20 years is currently ongoing. As DESIR is an inception cohort, during the 10-year follow-up some patients ended up receiving a different diagnosis than axSpA and were therefore excluded from this study. The database used for this analysis was locked in July 2022.

Clinical data

By using a standardised case report form, data were collected with questionnaires, physical examination, ongoing treatments and laboratory tests according to the DESIR protocol.

At baseline, age, gender, smoking status, HLA-B27 and duration of axial symptoms have been collected. At every visit the following parameters were collected: Bath Ankylosing Spondylitis Disease Activity Index,[7] Bath Ankylosing Spondylitis Functional Index,[8] C reactive protein (CRP), Axial Spondyloarthritis Disease Activity Score (ASDAS)[9] and treatment including intake of non-steroidal anti-inflammatory drugs (NSAIDs) assessed by the Axial Spondyloarthritis Assessment international Society (ASAS)-NSAID score[10] and TNFi.

Imaging

Modalities

Pelvic radiographs were performed at baseline, 1 year, 2 years, 5 years and 10 years of follow-up. An MRI of the SIJ (MRI-SIJ) was performed at baseline and at 10 years for all patients, and, per protocol, at years 1, 2 and 5 only in patients followed in Parisian centres (9 out of 27).

Scoring

Over the years, four central reading sessions (called 'central reading waves'), with trained central readers (blinded for chronological order, other imaging modalities and clinical information) have been conducted in DESIR. It is worth noticing that a dedicated 'Imaging Task Force' exists and meets before and during every reading wave to decide on the optimal methods to approach the next central reading wave and plan the subsequent analysis.

Description of the central reading waves:

- Wave 1 (central reading of baseline imaging): included two central readers per modality. For continuous variables, the mean of the two readers was used. For dichotomous outcomes, in case of disagreement between the readers one adjudicator was used for the final score.
- Wave 2 (central reading of baseline, and years 1 and 2 imaging): in this wave, patients with at least imaging at 2 years were included. Two readers and one adjudicator per modality evaluated the images: for continuous variables, the mean of the two readers was used. For dichotomous outcomes, in case of disagreement between the readers one adjudicator was used for the final score.
- Wave 3 (central reading of baseline, and years 2 and 5): patients with available images at least at baseline and year 5 images were included. Three readers per modality evaluated all the images: for continuous variables, the mean of the three readers was used. For dichotomous outcomes, in case of disagreement between the readers, the score reported by two out of the three readers was used for the final score.
- Wave 4 (central reading of baseline, and years 5 and 10): patients with at least baseline and year 10 images were included. Three readers per modality evaluated all the images: for continuous variables, the mean of the three readers was used. For dichotomous outcomes, in case of disagreement between the readers, the score reported by two out of the three readers was used for the final score.

For pelvic radiographs, each reader evaluated each SIJ according to the modified New York (mNY) grading method (0: normal; 1: suspicious changes; 2: minimal abnormalities; 3: unequivocal abnormalities and 4: severe abnormalities (complete ankylosis)).[11] Since each SIJ can obtain a score from 0 to 4, a 'total mNY score' (expressed as a continuous variable) could be calculated, with a range from 0 to 8 (4 grades per SIJ). A radiographic sacroiliitis was defined as at least unilateral grade 3 or bilateral grade 2.

For MRI-SIJ, the imaging was considered positive according to the ASAS definition.[12 13]

For each imaging modality, scores from readers from each reading wave were combined: for continuous outcomes (ie, SIJ mNY grading), the mean of the available scores was calculated; for binary outcomes (ie, mNY criteria yes/no and positive MRI-SIJ yes/no), the score of the adjudicator was used in case of disagreement in waves 1 and 2, while in waves 3 and 4, the score agreed by at least two out of the three readers was retained.

For MRI, in this present analysis only baseline and year 5 information (positive MRI-SIJ yes/no) were used, with the final score being agreed in at least two out of the three readers.

Imaging outcomes

For SIJ radiographic progression at 10 years, several outcomes were evaluated:

1. Switch from nr-axSpA at baseline to r-axSpA (according to the mNY radiographic criteria definition).
2. Worsening of at least one grade in at least one SIJ.
3. Worsening of at least one grade in at least one SIJ, but with a 10-year grade of at least two in the worsened joint.
4. Change in the total mNY score (expressed as a continuous variable).

Statistical analysis

Populations definitions

- The 'completers' population included all patients who had pelvic radiographs available both at baseline and 10 years and scored by all readers of wave 4.
- The 'intention-to-follow' population included all patients who had at least one radiographic score from at least one reader from any of the reading waves available.

Analysis

Evaluation of radiographic progression over the 10-year follow-up:

1. Net progression analysis in the completers population: in this analysis, the different definitions for radiographic progression listed above were used, including only the 'completers' population. In order to reduce measurement error, 'net radiographic progression' was calculated, that is, the proportion of 'progressors' (% of patients with *worsening*, ie, fulfilling the radiographic progression definitions presented above—1–3) as well as the proportion of 'regressors' (% of patients with improvement) was determined.[14] 'Improvement' was specified for each radiographic progression definition: (a) switching from r-axSpA at baseline to nr-axSpA at 10 years; (b) reduction of at least one grade in at least one SIJ and (c) reduction of at least one grade in at least one SIJ with a baseline score of at least 2 in the improved joint. Then, the 'net' percentage of progressors was defined as the number of 'progressors' minus the number of 'regressors' (numerator) and divided by the total number of the study population (denominator).
2. Estimation of the yearly probability to fulfil the mNY radiographic criteria over 10 years: in order to make use of all available imaging data from all waves, an integrated analysis was conducted. This assumption-free method has shown to not jeopardise the precision of the estimated of change in imaging parameters, while possibly yielding an increase in the statistical power for detecting changes with low incidence. Another important advantage of this method is that, as opposed to the completers analysis, all individual scores are included (each timepoint score from each wave from each reader), resulting in the inclusion of all patients that have ever had imaging assessed, referred as 'intention-to-follow' population, which almost corresponds to the complete DESIR population, thereby minimising selection bias.[15] Multilevel ('central reading wave', 'reader' and 'time') generalised estimated equations (GEE) model was used. The model estimated the percentage of mNY-positivity per year. As TNFi use has been recently reported as potentially inhibiting radiographic progression[16 17] in axSpA, especially at the SIJ level,[18] we decided to additionally test the impact of TNFi use on the mNY-positivity over time. We first tested whether progression was significantly different in TNFi ever versus never users (by testing for interaction). In case of a significant interaction, further analyses were stratified by TNFi use. In case of a non-relevant interaction, the model was adjusted for TNFi, as a time-varying variable.
3. Determining the effect of baseline bone marrow oedema (BME) on radiographic progression over the 10-year follow-up.
   To this end, we estimated the probability to fulfil the mNY radiographic criteria over 10 years of follow-up with a GEE multilevel (levels='central reading wave', 'reader' and 'time') model using the 'intention-to-follow' population, and including in the model the following variables at baseline: gender, smoking status (ever vs never), HLA-B27, positive MRI-SIJ, ASDAS ≥2.1 and symptom duration as potential explanatory variables; interactions were explored, namely with HLA-B27, as this parameter was previously found to interact with BME in DESIR.[2] In order to further explore the causal pathway of mNY+, that is, the potential role of BME as a mediator of the HLA-B27 effect on mNY status at 10 years, we performed a mediation analysis. This analysis could only be performed in patients with complete data for HLA-B27 status at baseline and for MRI sacroiliitis at M60 (ie, BME, using wave 4) and for the mNY radiographic status at M120 (two out of three readers, wave 4).

All analysis were conducted using R (packages: 'geepack', 'margins', 'ggeffects' and 'mediation').

RESULTS

At baseline, 708 patients were included in the DESIR cohort. Over the 10-year follow-up, 45 patients were excluded for an alternative diagnosis (6.4%), and 3 patients died.

The 'completers' population included 294 patients while the intention-to-follow population had in total 659 participants. Baseline characteristics of both populations are presented in table 1: both populations were mostly comparable, slightly predominantly females, mean 34 years of age, 1.5 years of symptom duration, <25% of mNY criteria fulfilment and a mean ASDAS of 2.6. However, HLA-B27 (66% vs 58%), MRI-SIJ-positivity (42% vs 36%) and abnormal CRP (ie, >5 mg/L) (35% vs 28%) were more frequent in the 'completers' population.

Over the 10-year follow-up, in the intention-to-follow population, 244 patients (37.0%) were exposed to TNFi.

Evaluation of radiographic progression over the 10-year follow-up

1. Net radiographic progression in the 'completers' population:
   Switch from nr-axSpA at baseline to r-axSpA: among the 294 completers, 17 patients switched from nr-axSpA to r-axSpA, while no patient switched from r-axSpA to nr-axSpA, yielding a net progression rate of 5.8% ((17 progressors−0 regressors)/294 total) (figure 1A).
   Worsening of at least one grade in at least one SIJ: 43 (14.4%) patients fulfilled this definition, while 1 (0.3%) patient showed an improvement of at least one grade in one SIJ, resulting in a net progression of 14.3% (43.1/294) for this definition (figure 1B).
   Worsening of at least one grade in at least one SIJ, but with a 10-year grade of at least two in the worsened joint: among the 294 completers, 34 patients fulfilled this definition of

Table 1 Baseline characteristics of the analysis populations in the DESIR cohort

Baseline characteristics	Completers* N=294	Intention-to-follow† N=659
Male gender‡	142 (48%)	304 (46%)
Age (years)	34.3 (8.6)	33.6 (8.6)
BMI (kg/m^2)	23.9 (4.1)	24.0 (4.1)
Symptom duration (years)	1.5 (0.9)	1.5 (0.9)
HLA-B27-positivity	194 (66%)	390/658 (59%)
Family history of SpA	126/279 (45%)	277/622 (45%)
Fulfilment of ASAS classification criteria	208 (71%)	416 (63%)
Radiographic sacroiliitis (mNY criteria) (w1)	69 (24%)	141/644 (22%)
MRI-SIJ ASAS positive (w1)	118/278 (42%)	233/619 (38%)
Abnormal CRP	98/283 (35%)	190/638 (30%)
BASDAI (0–10)	4.3 (2.0)	4.4 (2.0)
ASDAS	2.6 (0.9)	2.7 (0.9)
BASFI (0–10)	2.9 (2.3)	3.0 (2.3)

**Completers population*=all patients who had pelvic radiographs available and scored both at baseline and 10 years.
†'*Intention-to-follow*' *population*=all patients who had at least one imaging score from at least one reader from any of the central reading waves available.
‡Numeric variables are presented as mean and SD; categorical variables as number and percentage.
ASAS, Axial Spondyloarthritis Assessment international Society; ASDAS, Axial Spondyloarthritis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; MRI-SIJ, MRI of the sacroiliac joints; SpA, Spondyloarthritis; w1, first central reading wave in DESIR.

progression, with no patient improving according to this definition, yielding a net progression of 11.6% (figure 1C).
Change in total mNY score with a range from −8 to 8: baseline mean (SD) total mNY score in the completers was 1.3 (1.72) and increased to 1.63 (1.97) at 10 years (figure 1D).

2. *Estimation of the yearly probability of fulfilling the mNY radiographic criteria over 10 years*: in the intention-to-follow population, that is, including all imaging from all waves from all patients with at least one available imaging score, the probability of being mNY+ was estimated to increase 0.87% (95% CI 0.56 to 1.19) per year, resulting in a progression of 8.7% after 10 years.
Over the 10-year follow-up, 244/659 (37.0%) patients from the intention-to-treat population were treated with TNFi.
Interestingly, in patients that were treated with TNFi, at some point during follow-up and compared with those never treated with TNFi, the estimated probability of being mNY+ was 0.35% (95% CI −0.11 to 0.82) vs 0.64% (95% CI 0.16 to 1.12) per year, resulting in a 3.5% vs 6.4% progression after 10 years (figure 2), but the interaction between TNFi exposure (ever/never) and time was not statistically significant (p=0.340). When introducing TNFi as a time-varying adjustment covariate, the probability of being mNY+ was estimated to yearly increase by 0.45% (95% CI 0.09 to 0.81), that is, 4.5% after 10 years.
3. *Determining the effect of baseline BME on radiographic progression over the 10-year follow-up*: the HLA-B27 status modified the association between BME on MRI-SIJ at baseline and mNY-positivity over 10 years (interaction p<0.001). Baseline BME on MRI-SIJ (on central reading) was associated with being mNY+ over time in both HLA-B27+ and HLA-B27− patients, but the association was stronger in the

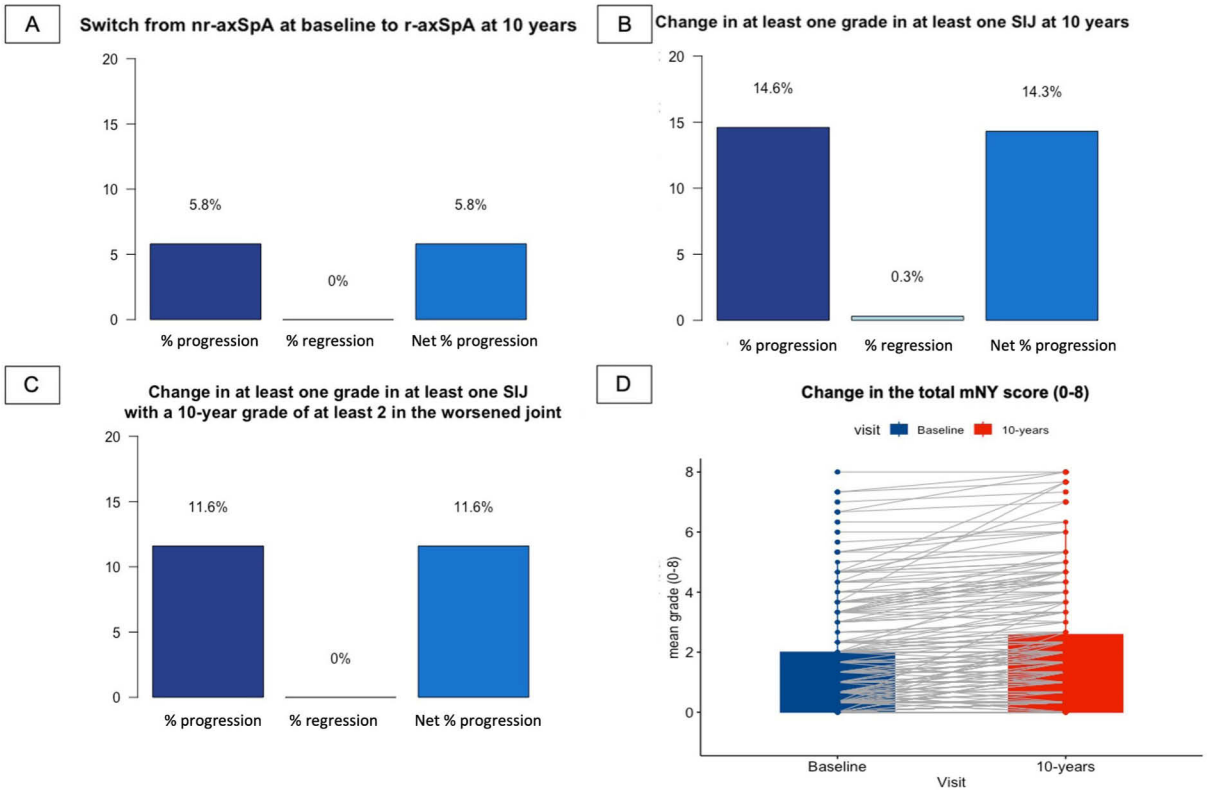

Figure 1 Representation of the different definitions of radiographic progression at the SIJs. The 'net' percentage of progressors was defined as the number of 'progressors' minus the number of 'regressors' (numerator) and divided by the total number of the study population (denominator). mNY, modified New York; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis; SIJ, sacroiliac joint.

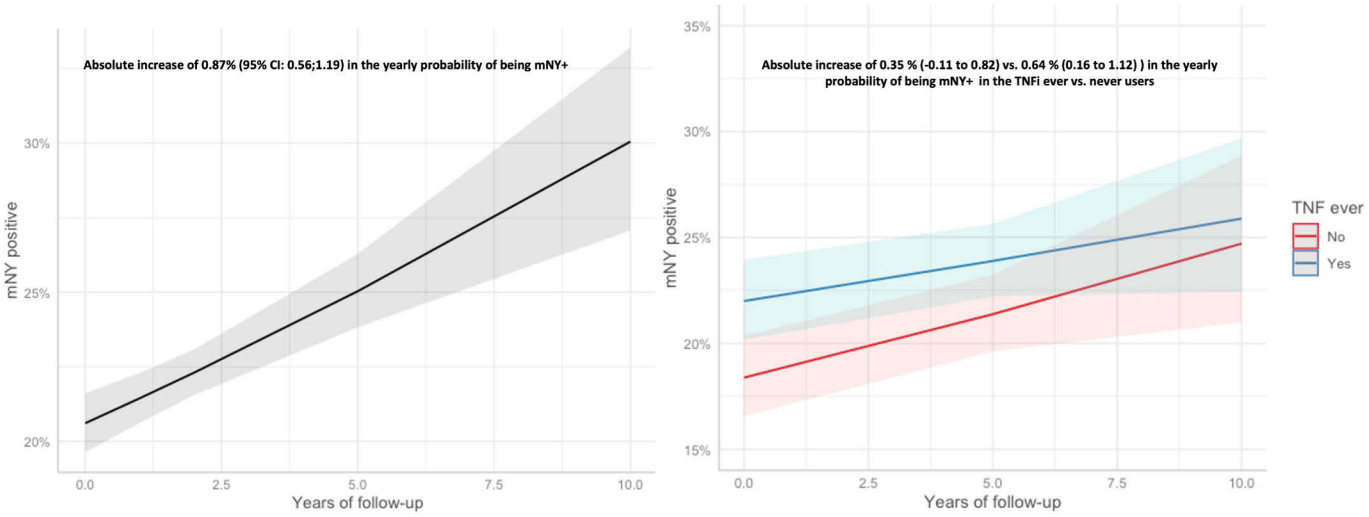

Figure 2 Graphic representation of the estimated probability of radiographic sacroiliitis per year over 10 years of follow-up. Yearly probability of being modified New York (mNY)+ was estimated by a generalised estimating equations multilevel (levels='reader', 'time' and 'wave') model in the intention-to-treat population (ie, all patients with at least one radiographic score available in at least one of the four central reading waves of DESIR). TNF, tumour necrosis factor.

former: OR 6.15 (95% CI 5.26 to 7.19) and OR 3.07 (95% CI 2.44 to 3.88), respectively.

In addition, male sex, symptom duration >1.5 years, ASDAS ≥2.1 and also smoking (only in HLA-B27 positives) were also associated with being mNY+ over 10 years (figure 3).

The mediation analysis was performed in the 103 patients fulfilling the criteria for this analysis and revealed that being positive for HLA-B27 at baseline was associated with an 11% absolute increase in the probability of being mNY+ at 10 years, with none of this effect mediated by the presence of BME (MRI sacroiliitis) at 5 years. Furthermore, this 11% increase was not found to be significant in this analysis (table 2) with the reduced sample size.

DISCUSSION

This is the first study describing the 10-year structural progression at the sacroiliac level in an axSpA inception cohort.

In our study, the 10-year radiographic SIJ progression was significant but of limited magnitude (5.8% net progressors from mNY− to mNY+), especially when observed in the 'completers population', and almost identical as the one observed at 5 years[2]; however, when using the integrated multilevel analysis, which allowed us to include all available imaging results from several reading waves to estimate the 10-year probability of mNY positivity, the overall 10-year probability increased to 8.7% (95% CI 5.6 to 11.9). Interestingly, when adjusting for time-varying TNFi use, such probability decreased to a 4.5% (95% CI 0.9 to 8.1) likelihood of progression after 10 years. Finally, local inflammation of the SIJ measured on MRI was highly predictive of a SIJ progression, especially in HLA-B27+ patients.

Radiographic progression (especially at the spine level) has classically been a major concern in the management of axSpA, as it can lead to irreversible structural damage and functional impairment. However, this analysis confirms our recent clinical impression that contradicts historical findings on radiographic progression in axSpA: low progression rates are observed in patients who are diagnosed and treated early in their disease. Nevertheless, the proportion of patients in DESIR who presented radiographic damage of the SIJ at baseline (ie, with onset of symptoms <3 years) (ie, 20%) has already been presented and discussed elsewhere,[2] is comparable to what had been reported in the literature[19 20] and shows that structural damage can already be found early in the disease.

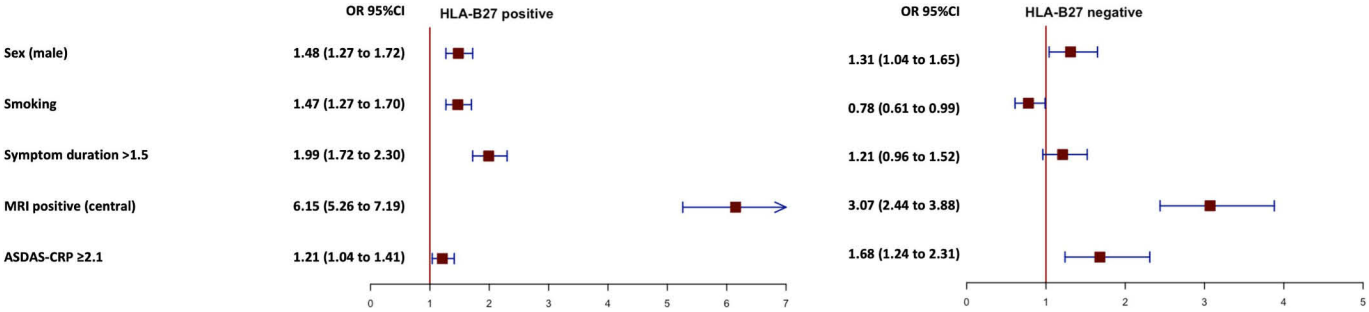

Figure 3 Baseline factors associated with radiographic progression over the 10-year follow-up. Baseline predictors of radiographic progression over 10 years of follow-up were estimated with a generalised estimating equations multilevel (levels='reader', 'wave' and 'time') model using the 'intention-to-follow' population (ie, all patients with at least one radiographic imaging score in at least one of the four waves of central reading in DESIR), and including in the model: gender, smoking, HLA-B27, positive MRI of the sacroiliac joints (MRI-SIJ), Axial Spondyloarthritis Disease Activity Score (ASDAS) >2.1 and symptom duration as explanatory variables. HLA-B27 status significantly modified the association between bone marrow oedema on MRI-SIJ at baseline and modified New York-positivity over 10 years (interaction p<0.01).

Table 2 Mediation analysis (for BME at 5 years as mediator of the HLA-B27 effect on mNY status at 10 years) (n=130)*

	Estimate	95% CI lower	95% CI upper
Total effect	0.11	−0.05	0.26
Average indirect effect	0	0	0
Average direct effect	0.11	−0.05	0.26
Proportion mediated	0	0	0

*Only patients with complete data for HLA-B27 at baseline and MRI-SIJ sacroiliitis at 5 years (BME evaluation, wave 4 of central reading) and mNY status at 10 years (wave 4 of central reading) could be included in this analysis.
BME, bone marrow oedema; mNY, modified New York; SIJ, sacroiliac joints.

With regard to progression at the SIJ level, prospective longitudinal studies evaluating the proportion of patients switching from non-radiographic to radiographic status are scarce: Sampaio-Barros *et al* found a 24% progression rate over 10 years in a study evaluating patients with 'undifferentiated SpA',[21] but more recent data from the German Spondyloarthritis Inception Cohort (GESPIC) cohort[20] integrating both progression and regression in scores yielded an estimate of 9% progression to r-axSpA after 2 years.

A more recent analysis of the Swiss Quality Management cohort used one of our proposed definitions to assess radiographic progression at the SIJ level, that is, a worsening in at least one grade of mNY in at least one SIJ, and found an overall 4.5% proportion of progressors per 2-year period[22]; but more interestingly, they also found a 'protective' effect of TNFi exposure during the radiographic interval (2 years) (OR 0.21, 95% CI 0.07 to 0.65). The magnitude of the protective effect in their study seems much larger than our findings, but this may be due to the different analysis of the exposure, which was time-varying in our case but only using the information available at the study visits versus a rather quantitative approach in their analysis, suggesting a trend for an additive inhibitory effect for each additional year of TNFi treatment.

Our study shows an increased proportion of progressors estimated in the intention-to-follow, compared with the 'completers' population progression rate. By using all available imaging scoring data, the integrated multilevel analysis should better reflect the true evolution of radiographic progression at the SIJ, by including more patients, while ensuring internal validity.[15 23]

Finally, it is important to consider the way the DESIR recruitment was organised: the launch of the cohort was preceded by an extensive national advertising campaign, which included press conferences, press releases and interviews at local radio and TV stations. This collective effort by the French Rheumatology community and endorsed by the French Society of Rheumatology was made to try to recruit a sample of patients that would genuinely reflect real-world incident axSpA, as opposed to the typical axSpA seen in tertiary centres. Therefore, lower progression rates as well as lower TNFi prescription rates in DESIR compared with cohorts of patients with axSpA recruited only in tertiary care centres are to be expected.

This analysis has several strengths and weaknesses worth being addressed. First, radiographic SIJ scores have been reported to have poor interobserver reliability,[24] and although trained central readers have shown better reliability compared with local readers, a combined score by our three central readers ('2 out of 3' score) is still fallible in terms of measurement error, as is suggested by the finding of 'improvement' of SIJ damage under fully blinded conditions in a proportion of patients. The almost inexistence of 'regressors' in this analysis enhances the validity of the scorings, although it could appear as unexpected; this could be explained by the fact that the three central readers are very experienced readers having been involved in several central reading exercises of SpA images (clinical trials, other SpA cohorts, etc).

Second, while DESIR is an observational cohort, it is an inception axSpA cohort conducted in a country with a national security health system, and a policy of fully reimbursed access to biologics, resulting in 37% of patients receiving a TNFi in this analysis over the 10 years; therefore, these results might not reflect the pure natural course of the disease, but might be considered as an indirect indicator of the beneficial outcomes derived from timely diagnosis and early access to powerful anti-inflammatory drugs (eg, TNFi). Indeed, in our study, the likelihood of radiographic SIJ progression over 10 years was lower in patients exposed to TNFi. These results reflect the course of the disease in patients treated with standard of care in France. Nevertheless, it is important to highlight that this present analysis was not designed to address the structural effectiveness of TNFi, which would require a separate analysis to overcome prescription bias over time, for example, emulating a target trial, and applying statistical methods such as inverse-probability weighting; nevertheless, even with such methodological approach, given the low progression rates, the causal effect will be challenging to demonstrate. In any case, for the present results, the TNFi effect needs to be interpreted with caution, as the causal effect of TNFi exposure cannot be demonstrated in this setting.

Furthermore, our analysis only focused on SIJ, and only scarce data are available on the functional impact of radiographic damage at the SIJ.[5] Syndesmophyte development at the spine level might be more relevant in terms of functional impact; nevertheless, it has been shown that it is unlikely to find extensive structural damage in the spine in the absence of radiographic sacroiliitis.[4 25]

Finally, our results on radiographic progression reflecting the long-term structural outcome of these patients at the sacroiliac level are reassuring and provide valuable data for clinicians to use to inform their patients. Our cohort confirms the role of local (ie, BME on MRI-SIJ) and systemic (ie, disease activity, ASDAS) inflammation as predisposing factors for developing radiographic sacroiliitis over 10 years, especially in the presence of HLA-B27; we have also found no mediation role of BME on the HLA-B27 effect on mNY, despite the limitation of a reduced sample size used for this specific analysis. In any case, the interaction was significant. These findings suggest that both a genetic predisposition (ie, HLA-B27) and another factor (eg, mechanical stress as it has been suggested[26]) that will cause inflammation at the SIJ, are needed for structural changes (ie, radiographic axSpA) to occur, reinforcing HLA-B27 as a critical factor for the severity of axSpA.

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