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

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Chapter 10

Integrated longitudinal analysis does not compromise precision and reduces bias in the study of imaging outcomes: A comparative 5-year analysis in the DESIR cohort

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ABSTRACT

Objective: To assess if an integrated longitudinal analysis using all available imaging data affects the precision of estimates of change in patients with axial spondyloarthritis (axSpA), with completers analysis as reference standard.

Methods: Patients from the DESIR cohort fulfilling the ASAS axSpA criteria were included. Radiographs and MRIs of the sacroiliac joints and spine were obtained at baseline, 1, 2 and 5 years. Each image was scored by 2 or 3 readers in 3 'reading-waves' (or campaigns). Each outcome was analysed: i. According to a 'combination algorithm' (e.g. '2 out of 3' for binary scores); and ii. Per reader. Change over time was analysed with generalised estimating equations by 3 approaches: (a)'integrated-analysis' (all patients with ≥1 score from ≥1 reader from all waves); (b1)Completers-only analysis (patients with 5-year follow-up, using scores from individual readers); (b2)Completers analysis using a 'combination algorithm' (as (b1) but with combined scores). Approaches (b1) and (b2) were considered the 'reference'.

Results: In total, 413 patients were included. The 'integrated analysis' was more inclusive with similar levels of precision of the change estimates as compared to both completers analyses. In fact, for low-incident outcomes (e.g. % mNY-positive over 5-years), an increased incidence was 'captured', with more precision, by the 'integrated analysis' compared to the completers analysis with combined scores (% change/year (95%CI): 1.1 (0.7; 1.5) vs 1.2 (0.5; 1.8), respectively).

Conclusion: An efficient and entirely assumption-free 'integrated analysis' does not jeopardise precision of the estimates of change in imaging parameters and may yield increased statistical power for detecting changes with low incidence.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton. Patients with axSpA show, in different degrees, inflammatory and structural (osteoproliferative and/or osteodestructive) changes in the sacroiliac joints (SIJs) and spine. However, the complex relationship between these abnormalities, including their sequence, frequency and rate of change over time, is not yet well known.[1]

Axial pathological lesions in axSpA can be detected and quantified by the available imaging techniques, including both inflammatory (magnetic resonance imaging; MRI) and structural changes (both radiographs and MRI), and several scores have been developed for this purpose.[2-5] The role of imaging to assess axial inflammatory activity and structural damage over time in axSpA has been assessed in previous studies, but these are few,[6-8] rendering the appropriate use of imaging in the monitoring of axSpA yet to be defined.[9]

To clarify this role, long-term data is needed. However, collection and analysis of such data pose some methodological challenges, including loss to follow-up that often jeopardises the interpretation of findings. The Interpretation may further be challenged by the fact that different readers may have contributed to obtaining scores, in multiple 'reading-waves'. A common approach is to choose a convenient read wave, to only evaluate patients with complete follow-up (completers analysis) and to aggregate scores of individual readers into some algorithm (e.g. agreement ≥ 2 out of 3 readers). Such approaches are not assumption-free, may cause non-random data loss (bias by study completion), and may as such yield biased estimates and loss of external validity.

An alternative method has been previously proposed to analyse long-term imaging data in patients with rheumatoid arthritis (RA) using all available information provided by all readers in different 'reading-waves' in an assumption-free manner (a so called 'integrated analysis').[10] Our aim was to investigate if the use of the 'integrated analysis' affects the precision of estimates for imaging outcomes in patients with axSpA, with a conventional completers analysis as reference standard.

METHODS

Patients and study design

Five-year follow-up data of patients with inflammatory back pain (≥ 3 months but <3 years), and with symptoms suggestive of axSpA according to the treating rheumatologist from the DEvenir des Spondylarthopathies Indifférenciées Récentes (DESIR) cohort (clinicaltrials.gov ID: NCT01648907) were used.[11] In addition, patients had to fulfil the Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria and to have at least one radiograph and/or MRI reading available during the 5-year follow-up. The database used for the current analysis was locked on 20th of June 2016.

The study was conducted according to Good-Clinical-Practice-guidelines and was approved by the appropriate local medical ethical committees. Written informed consent was obtained from participating patients before inclusion.

Imaging scoring procedures

Radiographs and MRIs of the SIJ (X-SIJ; MRI-SIJ) and spine (X-Spine; MRI-Spine) were obtained at baseline, 1, 2 and 5 years. Radiographs were performed in all centers (N=25) and in all time-points. MRIs were performed at baseline in all centers and, by protocol, follow-up MRIs were only performed in centers in Paris (N=9). Each image was independently scored, in 3 separate 'reading-waves' (or campaigns) by trained central readers, blinded to clinical data and to the results of other imaging modalities and without known chronology. In wave 1, baseline images were scored by 2 readers and 1 adjudicator (in case of disagreement). In wave 2, images from baseline, 1 and 2 years were also scored by 2 readers and one adjudicator. In wave 3, images from baseline, 2 and 5 years were scored by 3 central readers. The readers and adjudicators varied across modalities and waves (Online Supplementary Table S1).

SIJ imaging outcomes

Inflammation on MRI-SIJ was assessed according to the ASAS definition (positive/negative) and by the Spondyloarthritis Research Consortium of Canada (SPARCC) score (range: 0-72).[2, 3, 12] The adapted SPARCC MRI-SIJ Structural score by Webers *et al* was used to define individual structural lesions on MRI-SIJ (fatty lesions, erosions, sclerosis, partial ankylosis and total ankylosis).[13] In the absence of a formal definition of a positive structural MRI-SIJ, we considered three definitions that have been shown to be the most discriminatory in early axSpA: ≥5 fatty lesions and/or erosions; ≥3 erosions; and ≥3 fatty lesions.[14] Continuous structural lesions on MRI-SIJ were defined as number of fatty lesions and/or erosions (range: 0-80), number of erosions (range: 0-40), number of fatty lesions (range: 0-40) and total number of lesions (range: 0-144). Structural lesions on X-SIJ were assessed according to the mNY-grading method as a continuous variable (range: 0-8) and as mNY positive/negative.[15] Two binary definitions of X-SIJ structural damage were also assessed: worsening of ≥ 1 grade in ≥ 1 SIJ (yes/no); and worsening of ≥ 1 grade in ≥1 SIJ, with grade ≥ 2 in the worsened joint at 5 years (yes/no).[16]

Spine imaging outcomes

Bone marrow edema (BME) on MRI-Spine was defined according to the ASAS definition (≥3 corner lesions; yes/no).[17] In addition, a cut-off of 5 lesions was also assessed, as it has been shown to be highly specific of axSpA.[14] The spine SPARCC score (range: 0-414) and spine Berlin score (range: 0-69) were used as continuous inflammatory outcomes.[4, 18] Structural lesions on MRI-Spine were scored according to the Canada–Denmark (CANDEN) method.[5] As for MRI-SIJ, in the absence of a formal definition, we defined structural damage as ≥5 fatty lesions, since this cut-off has been shown to be highly specific for axSpA.[14] The total number of structural lesions (fatty lesions, erosions, bone spurs, ankylosis; range: 0-322) was also assessed. Structural lesions on X-Spine were assessed as the presence of ≥1 syndesmophyte (yes/no) and by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[19]

Statistical analysis

Each outcome was analysed by generalised estimating equations (GEE) models with an exchangeable 'working' correlation structure, taking into account the repeated scores over time. The parameter estimate for 'time', as the main variable of interest in the models, can be interpreted as the absolute change of the score per year for continuous outcomes; and as the change per year in the percentage of positive cases for binary outcomes. Each outcome was analysed per patient and per time-point in two ways: i. according to a 'combination algorithm'; and ii. per individual reader. For the algorithm, the combined score for binary (yes/no) outcomes in waves 1 and 2 resulted from the agreement of 2 readers and, in case of disagreement, involves the adjudicator score. Binary outcomes in wave 3 were scored by the agreement of ≥ 2 out of 3 readers. The combined scores for continuous outcomes were defined as the mean of the available scores.

The change per year was estimated with three analytical-methods: (a) 'integrated-analysis', including all patients with ≥1 available score from ≥1 reader from all 'reading-waves' (reader and the wave added to the models to adjust for higher levels of correlation); (b1) completers only analysis, including only patients with complete 5-year follow-up, using scores from individual readers from wave 3 (adjusted for reader); and (b2) aggregated completers analysis, using a combination algorithm (as (b1) but with combined scores, thus without reader adjustment). Both completers analysis (b1 and b2) were used as the 'reference' against which the 'integrated analysis' was compared.

Goodness-of-fit statistics (quasi-likelihood under the independence model criterion; QIC), were used to get an impression on how much of the outcome variability is explained by each model. Different transformations of time were tested to assess which yielded the lowest QIC (better fit). A non-linear model was chosen if best fitting the data, and if the non-linear factor (e.g. quadratic term) added to the model was statistically significant ($p<0.05$).

RESULTS

Change of inflammatory and structural lesions over time

In total, 413 patients were included and 366 completed the 5-year follow-up. The mean (SD) symptom duration was 1.6 (0.9) years; 52% were males and 89% HLA-B27% positive (Online Supplementary Table S2).

The estimated change over time of the SIJ imaging outcomes, with the 'integrated analysis' is shown in Fig. 1 (spine outcomes: Online Supplementary Fig. S1). Inflammation on MRI-SIJ was detected in a large proportion of patients at baseline [estimated % (95%CI): 43 (38; 47)] and significantly decreased over time, especially during the first 2 years, i.e. following a quadratic distribution (QIC linear model: 8726; QIC quadratic model: 8710; quadratic term p-value: 0.028). On the contrary, structural damage on MRI-SIJ and X-SIJ significantly increased over time. For instance, we found an increase of 1.1% per year in the percentage of patients being mNY-positive over a time span of 5 years. In general, spine abnormalities were scarce at baseline and remained low over time.

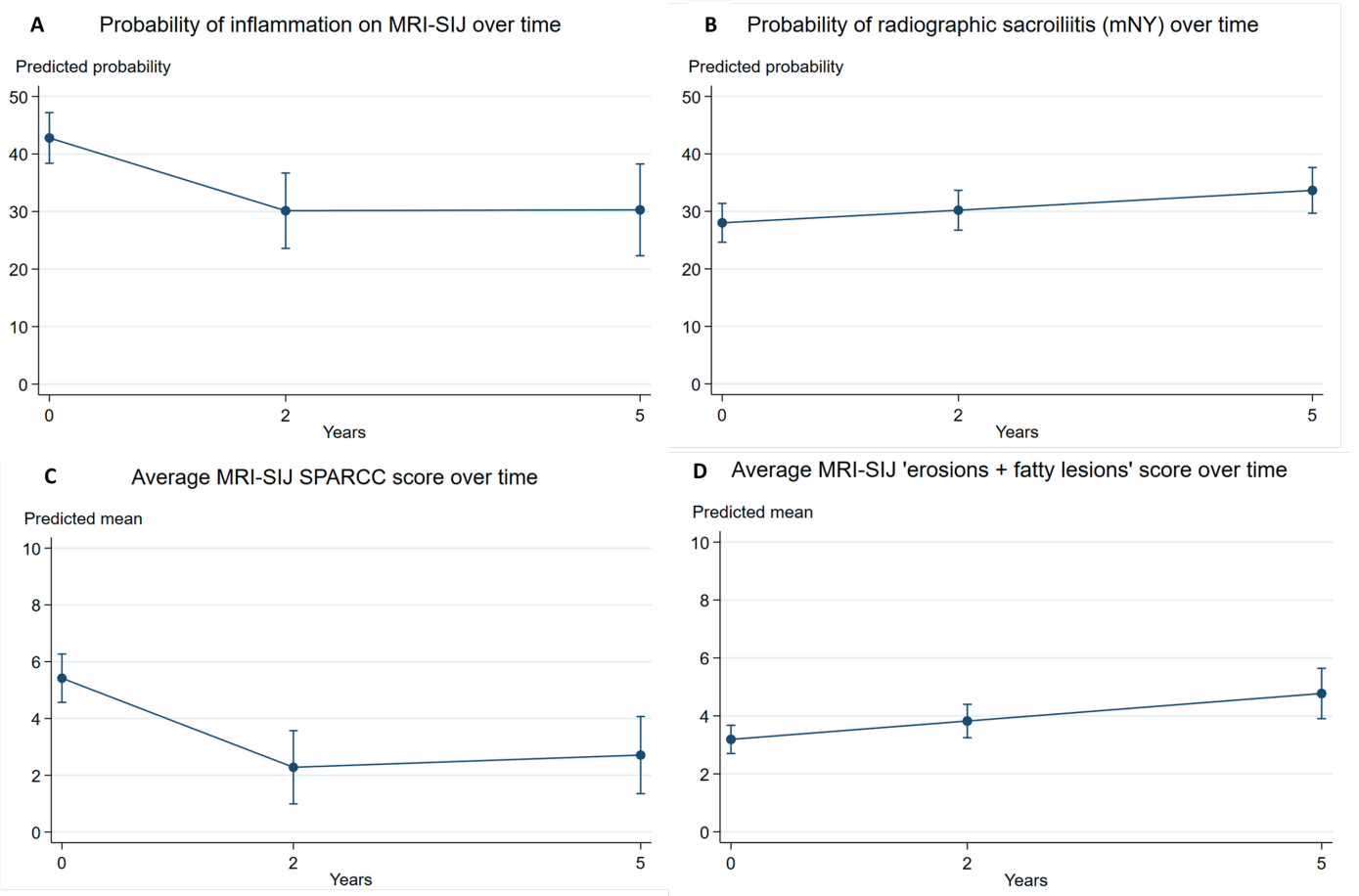

Figure 1. Estimated change of sacroiliac joints outcomes over 5 years ('Integrated analysis'). Point estimates: probability of each binary outcome or mean of each continuous outcome in each time point. Error bars: 95% confidence intervals. **Panel A**: There is an average yearly 7.4% (95% CI: -11.7; -3.1) reduction in the probability of having BME on MRI-SIJ (ASAS definition), following a quadratic distribution (quadratic term: OR=1.06 (95% CI 1.01; 1.11); p-value=0.028), which means that every year there is a decrease of 0.06 odds in the rate of decrease of BME positivity. **Panel B:** There is an average yearly 1.1% (95% CI: 0.7; 1.5) increase in the probability of radiographic sacroiliitis (mNY definition), following a linear distribution (quadratic term not significant). **Panel C:** there is an average yearly decrease of 1.7 (95% CI: -2.6; -0.9) units in the SPARCC score over 5 years, following a quadratic distribution (quadratic term: β=0.34 (95% CI 0.14; 0.55); p-value=0.001), which means that every year the rate of decrease reduces by 0.34 units. **Panel D:** There is an average yearly 0.32 (95% CI: 0.2; 0.5) units increase in the total number of erosions and fatty lesions over time, following a linear distribution (quadratic term not significant). MRI, magnetic resonance imaging; SIJ, sacroiliac joints; BME, bone marrow edema; mNY, modified New York criteria; SPARCC, spondyloarthritis research consortium of Canada; CI, confidence interval.

Comparison of different analytical methods to capture change

The estimated change over time for binary and continuous imaging outcomes by the three analytical approaches is shown in Tables 1 and 2, respectively. The 'integrated analysis' (method a) was more inclusive compared to the completers analysis with individual readers' scores (method b1) and completers analysis with combined scores (method b2), both for binary ((a): N=360-411 vs (b1 and b2): N=313-364) and continuous outcomes ((a): N=399-411 vs (b1): 342-364 and (b2): 338-364).

The decrease of MRI-SIJ detected inflammation was captured by all analytical methods with similar precision both for the binary ASAS definition of a positive MRI-SIJ and the continuous SPARCC score (negative coefficients with similar 95%CI excluding zero). Similar findings were also seen for MRI-SIJ structural changes, but in the opposite direction (positive coefficients with similar 95%CI excluding zero). Of note, the subtle increase in binary X-SIJ structural lesions was detected with more precision by the 'integrated analysis' as compared to both completers analysis [e.g. worsening of ≥ 1 grade in ≥1 SIJ with a grade ≥2 in the worsened joint at 5 years: (a): 1.76 (1.06; 2.46) vs (b1): 1.55 (0.78; 2.32) and (b2): 2.05 (0.81; 3.28), respectively].

All analytical methods were unable to detect a significant change for both inflammatory and structural lesions in the spine, except for the formation of new syndesmophytes, captured with similar precision by the three approaches (% change/year (95% CI): (a): 0.84 (0.46; 1.22) vs (b1): 0.48 (0.16; 0.80) vs (b2): 0.50 (0.10; 0.91)).

DISCUSSION

In this 5-year longitudinal study in patients with early axSpA, we tested a new approach to analyse imaging outcomes over time as compared to the 'traditional' completers analysis. We have shown that, by applying the 'integrated analysis', we can efficiently use all available data in an entirely assumption-free manner without compromising precision, and it may even yield increased statistical power for detecting low incident abnormalities. In addition, the 'integrated analysis' may, to some extent, protect against attrition bias and avoid bias by 'convenient choices'.

A previous post-hoc analysis of two randomised trials in patients with RA has also shown the robustness of the 'integrated analysis' as compared to a completers analysis.[10] Here we report, for the first time, the application of this innovative analytical method to observational data and in patients with early axSpA. We 'challenged' this technique with several imaging scores and have shown that the precision of the estimates of change was similar to the one obtained by the completers analysis, or even better: in case of outcomes with a low incidence.

Table 1. Change per year in the percentage of positive cases for binary imaging outcomes over 5-years of follow-up, according to 3 different analytical methods, in early axSpA patients fulfilling the ASAS axSpA criteria

	Integrated analysis (a)*	**Completers analysis with individual readers scores** (b1)†	**Completers analysis with combined scores for readers** (b2)‡
Imaging outcomes	**% change per year (95% CI) (N=360-411)**	**% change per year (95% CI) (N=313-364)**	**% change per year (95% CI) (N=313-364)**
SACROILIAC JOINTS			
Inflammatory lesions (MRI-SIJ)			
Sacroiliitis (ASAS criteria)[2]	**-7.35 (-11.65; -3.05)£**	**-5.40 (-8.87; -1.92)£**	**-3.13 (-5.09; -1.18)**
Structural lesions (MRI-SIJ)[13]			
≥ 5 fatty lesion and / or erosions	**4.41 (2.30; 6.53)£**	**3.17 (1.49; 4.85)£**	**2.12 (0.97; 3.27)**
≥ 3 erosions	0.25 (-0.67; 1.17)	0.28 (-0.58; 1.13)	0.10 (-1.30; 1.49)
≥ 3 fatty lesions	**4.68 (2.68; 6.67)£**	**3.30 (1.73; 4.86)£**	**2.03 (1.02; 3.04)**
Structural lesions (X-SIJ)			
mNY dichotomous	**1.10 (0.67; 1.53)**	**0.87 (0.48; 1.26)**	**1.18 (0.54; 1.81)**
mNY 1-grade change[16]	**2.18 (1.40; 2.96)**	**2.03 (1.16; 2.89)**	**2.30 (0.88; 3.71)**
mNY 1-grade change and value ≥ 2[16]	**1.76 (1.06; 2.46)**	**1.55 (0.78; 2.32)**	**2.05 (0.81; 3.28)**
SPINE			
Inflammatory lesions (MRI-Spine)			
BME: ≥ 3 lesions (ASAS criteria)[17]	-0.82 (-2.31; 0.67)	-0.44 (-1.39; 0.51)	0.14 (-0.88; 1.17)
BME: ≥ 5 lesions (ASAS criteria)[14]	-0.72 (-2.20; 0.76)	-0.30 (-1.26; 0.65)	-0.33 (-1.41; 0.76)
Structural lesions (MRI-Spine)			
≥ 5 fatty lesions[14]	-0.22 (-0.85; 0.41)	-0.12 (-0.45; 0.20)	¥
Structural lesions (X-Spine)			
≥ 1 syndesmophyte	**0.84 (0.46; 1.22)**	**0.48 (0.16; 0.80)**	**0.50 (0.10; 0.91)**

*Analysis taking into account the 3 different reading campaigns, i.e. waves, and the different readers from all waves; 3-level generalised estimating equations (GEE) models, taking into account the within-patient correlation for the repeated measures and adjusting for the reader and wave; † Data from one reading wave only (wave 3) and taking the different readers (n=3 per modality) into account; 2-level GEE, taking into account the within-patient correlation for the repeated measures and adjusting for the reader; ‡ Data from one reading wave only (wave 3) and using combined scores calculated from the individual readers (n=3) scores; 1-level GEE, taking into account the within-patient correlation for the repeated measures of the combined scores (i.e. '2 out of 3'); £Quadratic transformation; ¥ No convergence achieved: only 5 events during follow-up.

axSpA, axial spondyloarthritis; MRI-SIJ, magnetic resonance imaging of the sacroiliac joints; X-SIJ, radiograph of the sacroiliac joints; ASAS, Assessment of SpondyloArthritis international Society; mNY, radiographic sacroiliitis according to the modified New York criteria; MRI-spine, MRI of the spine; X-spine, radiograph of the spine; SPARCC, Spondyloarthritis Research Consortium of Canada score; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; GEE: generalised estimating equations.

Table 2. Yearly progression rate of continuous imaging outcomes over 5-years of follow-up, according to 3 different analytical methods, in early axSpA patients from the DESIR-cohort who fulfil the ASAS axSpA classification criteria

	Integrated analysis (a)*	**Completers analysis with individual readers scores**(b1)	**Completers analysis with combined scores for readers** (b2)
Imaging outcomes	**units change per year (95% CI) (N=399-411)**	**units change per year (95% CI) (N=342-364)**	**units change per year (95% CI) (N=338-364)**
SACROILIAC JOINTS			
Inflammatory lesions (MRI-SIJ)			
SPARCC SIJ score (0-72)[3]	**-1.74 (-2.57; -0.90)£**	**-1.02 (-1.57; -0.46) £**	**-1.03 (-1.60; -0.47) £**
Structural lesions (MRI-SIJ)[13]			
Number of fatty lesions /erosions (0-80)	**0.32 (0.18; 0.45)**	**0.51 (0.28; 0.74) £**	**0.28 (0.16; 0.40)**
Number of erosions (0-40)	0.05 (-0.03; 0.12)	0.04 (-0.02; 0.10)	0.03 (-0.03; 0.10)
Number of fatty lesions (0-40)	**0.27 (0.16; 0.38)**	**0.45 (0.25; 0.65) £**	**0.25 (0.15; 0.35)**
Total structural lesions†† (0-144)	**0.39 (0.24; 0.54)**	**0.37 (0.23; 0.50)**	**0.37 (0.23; 0.50)**
Structural lesions (X-SIJ)			
mNY continuous grade (0-8)	**0.05 (0.03; 0.07)**	**0.04 (0.03; 0.06)**	**0.04 (0.03; 0.06)**
SPINE			
Inflammatory lesions (MRI-Spine)			
SPARCC Spine score (0-414)[4]	-0.21 (-0.54; 0.12)	-0.14 (-0.37; 0.10)	-0.15 (-0.39; 0.10)
Berlin Spine score (0-69)[18]	-0.11 (-0.25; 0.02)	-0.05 (-0.13; 0.03)	-0.05 (-0.14; 0.03)
Structural lesions (MRI-Spine)			
Total structural lesions** (0-322)[20]	0.02 (-0.01; 0.05)	0.03 (-0.0003; 0.06)	0.03 (-0.01; 0.06)
Structural lesions (X-Spine)			
mSASSS score (0-72)	**0.09 (0.04; 0.14)**	**0.07 (0.03; 0.11)**	**0.06 (0.02; 0.10)**

*Analysis taking into account the 3 different reading campaigns, i.e. waves, and the different readers from all waves; 3-level generalised estimating equations (GEE) models, taking into account the within-patient correlation for the repeated measures and adjusting for the reader and wave; † Data from one reading wave only (wave 3) and taking the different readers (n=3 per modality) into account; 2-level GEE, taking into account the within-patient correlation for the repeated measures and adjusting for the reader; ‡ Data from one reading wave only (wave 3) and using combined scores calculated from the individual readers (n=3) scores; 1-level GEE, taking into account the within-patient correlation for the repeated measures of the combined scores (i.e. Mean of 3 readers); £ Quadratic transformation; †† fatty lesions, erosions, sclerosis, partial ankylosis, total ankylosis; ** fatty lesions, erosions, bone spurs, ankylosis;

axSpA, axial spondyloarthritis; MRI-SIJ, magnetic resonance imaging of the sacroiliac joints; X-SIJ, radiograph of the sacroiliac joints; ASAS, Assessment of SpondyloArthritis international Society; mNY, radiographic sacroiliitis according to the modified New York criteria; MRI-spine, MRI of the spine; X-spine, radiograph of the spine; SPARCC, Spondyloarthritis Research Consortium of Canada score; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; CD score, Canada-Denmark score; GEE: generalised estimating equations.

The largely overlapping precision suggests that both analytical approaches can be applied when analyzing change over time in imaging outcomes. However, our results argue in favour of using the 'integrated analysis' for several reasons. First, with this method, we included all patients with at least one score in at least one time point who would, otherwise, be excluded from a completers analysis. Thus, to some extent, it may deal better with possible bias by attrition – a common problem of long-term cohorts. Second, this technique directly handles data from

different readers and 'reading-waves', with no need for 'combined scores' (e.g. 2 out of 3), which are not without assumptions and prone to bias. The 'trade off' is adding some variability ('noise') to the estimates, which may lead to a lower precision (i.e. wider 95% CI). But that is not what we have found. Arguably, by including all scoring data without 'hidden' assumptions, we may better approximate the 'true' point-estimates (the 'signal'). In fact, despite similar levels of precision, differences in the point-estimates were found between methods. Third, integrated analysis increases statistical power to detect subtle changes, which is of particular interest when assessing structural damage in patients with early disease as shown here. Taken all together, the 'integrated analysis' increases external validity without compromising (or even improving) internal validity.

In addition, the integrated analysis 'increases the sample size without increasing the number of patients. This means: the number of available scores for analysis is not only determined by the number of patients but also by the number visits, the number of readers and the number of 'reading-waves'. Obviously, these multiple observations per patient cannot be interpreted as independent observations. Each time point is clustered within patient, each patient is clustered within reader, and each reader is clustered within the 'reading-wave'. Ignoring the lack of independency between observations would result in an artificially narrow 95% CI. This is why we have applied GEE models, which appropriately deals with correlated data.[21, 22]

In summary, here we describe the 'integrated analysis', a novel and sophisticated analytical method that may be used in future studies focusing on imaging, including those dealing with the assessment of treatment effects on imaging outcomes. This approach may be of special interest in studies with long-term follow-up, and/or when the outcomes are expected to occur infrequently over time.

SUPPLEMENTARY DATA

Supplementary data are published online on the website of Seminars in Arthritis and Rheumatism

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