Central reader evaluation of MRI scans of the sacroiliac joints from the ASAS classification cohort: discrepancies with local readers and impact on the performance of the ASAS criteria

Maksymowych, W.P.; Pedersen, S.J.; Weber, U.; Baraliakos, X.; Machado, P.M.; Eshed, I.; ... ; Lambert, R.G.W.

CLINICAL SCIENCE

Central reader evaluation of MRI scans of the sacroiliac joints from the ASAS classification cohort: discrepancies with local readers and impact on the performance of the ASAS criteria

Walter P Maksymowych ,[1] Susanne Juhl Pedersen,[2] Ulrich Weber ,[3,4] Xenofon Baraliakos ,[5] Pedro M Machado ,[6,7] Iris Eshed,[8] Manouk de Hooge ,[9] Joachim Sieper,[10] Stephanie Wichuk,[11] Martin Rudwaleit ,[12] Désirée van der Heijde ,[13,14] Robert B M Landewé,[15,16] Denis Poddubnyy ,[17] Mikkel Ostergaard,[18] Robert G W Lambert[19]

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-217232).

For numbered affiliations see end of article.

Correspondence to
Dr Walter P Maksymowych, Medicine, University of Alberta Faculty of Medicine and Dentistry, Edmonton, AB T6R 2G8, Canada; walter.maksymowych@ualberta.ca

Received 25 February 2020
Revised 19 April 2020
Accepted 21 April 2020
Published Online First 5 May 2020

ABSTRACT

Objectives The Assessment of SpondyloArthritis international Society (ASAS) MRI working group conducted a multireader exercise on MRI scans from the ASAS classification cohort to assess the spectrum and evolution of lesions in the sacroiliac joint and impact of discrepancies with local readers on numbers of patients classified as axial spondyloarthritis (axSpA).

Methods Seven readers assessed baseline scans from 278 cases and 8 readers assessed baseline and follow-up scans from 107 cases. Agreement for detection of MRI lesions between central and local readers was assessed descriptively and by the kappa statistic. We calculated the number of patients classified as axSpA by the ASAS criteria after replacing local detection of active lesions by central readers and replacing local reader radiographic sacroiliitis by central reader structural lesions on MRI.

Results Structural lesions, especially erosions, were as frequent as active lesions (≈40%), the majority of patients having both types of lesions. The ASAS definitions for active MRI lesion typical of axSpA and erosion were comparatively discriminatory between axSpA and non-axSpA. Local reader overcall for active MRI lesions was about 30% but this had a minor impact on the number of patients (6.4%) classified as axSpA. Substitution of radiography with MRI structural lesions also had little impact on classification status (1.4%).

Conclusion Despite substantial discrepancy between central and local readers in interpretation of both types of MRI lesion, this had a minor impact on the numbers of patients classified as axSpA supporting the robustness of the ASAS criteria for differences in assessment of imaging.

Key messages

What is already known about this subject?

- MRI of the sacroiliac joints is a crucially important evaluation tool for patients presenting with undiagnosed back pain and suspicion of axial spondyloarthritis (axSPA) although there is limited expertise in image interpretation which may compromise accurate diagnosis and classification of this disease.

What does this study add?

- The Assessments in SpondyloArthritis international Society MRI working group reports an expert reader assessment of MRI scans from patients presenting to rheumatologists with undiagnosed back pain and characterises MRI lesions that are highly specific for a diagnosis of axSpA.
- This central reader assessment demonstrates substantial differences in imaging interpretation with local readers. However, this does not affect the number of patients classified as having this disease because the clinical arm of the criteria compensates for differences in disease assignment by the imaging arm.

How might this impact on clinical practice or future developments?

- This report demonstrates the importance of both active and structural MRI lesions in diagnostic decision making and the importance of educational initiatives aimed at enhancing interpretation of these lesions. These data also provide reassurance that the Assessment of SpondyloArthritis international Society classification criteria have performance characteristics that may circumvent the limitations posed by the widespread lack of reader expertise in the interpretation of MRI scans.

INTRODUCTION

The Assessment of SpondyloArthritis international Society classification cohort study (ASAS-CC) recruited patients referred to a rheumatologist with undiagnosed back pain. It led to the ASAS classification criteria in which patients diagnosed with axial spondyloarthritis (axSpA) could be classified as having axSpA by either an imaging or clinical arm.[1] Imaging criteria for sacroiliitis could be either radiographic or the presence of bone marrow oedema (BME) as elaborated in the ASAS consensus definition.[2 3] The sensitivity and specificity of the

To cite: Maksymowych WP, Pedersen SJ, Weber U, *et al*. *Ann Rheum Dis* 2020;**79**:935–942.

criteria were 83% and 84%, respectively, and follow-up after 4.4 years indicated a high positive predictive value for a rheumatologist's diagnosis of axSpA.[4]

The assessment of MRI scans from the ASAS-CC by local readers was limited to determination whether the baseline scan demonstrated active and/or structural lesions typical of axSpA.[1] In the decade since this study our understanding of MRI lesions in the sacroiliac joint (SIJ) has increased substantially[5] but longitudinal data have been obtained from cohorts of patients with symptoms restricted to 2–3 years and not the typical patient referred to a rheumatologist where symptom duration averages 8–9 years.[6 7] Moreover, it has been recognised that BME can be observed in the SIJ in other disorders and even in 20%–40% of healthy individuals.[8–10] This has led to concerns focused on the accuracy of local reader interpretations of imaging findings on MRI in the ASAS-CC and whether discrepancies found between local and central readers might alter which patients are classified as having axSpA according to the ASAS criteria. Moreover, diagnosis of axSpA was changed by the local rheumatologist in only 11.2% of patients who were available at follow-up after 4.4 years in the ASAS-CC which has also raised concerns regarding diagnostic ascertainment bias.[4] Evaluation of follow-up MRI scans from this cohort to determine whether evolution of MRI findings supports these diagnostic conclusions has not been reported.

These considerations led to the decision by ASAS to convene the ASAS-MRI working group to conduct a multireader exercise to examine both the baseline and follow-up MRI scans from the ASAS-CC. We aimed to address the following questions: (A) What was the relative frequency of MRI lesions in the SIJ at baseline and follow-up according to the recently updated ASAS definitions[11] and expert rheumatologist diagnosis of axSpA? (B) What was the discrepancy between local and central readers in the detection of active and structural MRI lesions in the SIJ and how did this impact which patients were classified as having axSpA? (C) Did replacement of local reader assignment of radiographic sacroiliitis by central reader assignment of MRI structural lesions impact which patients were classified as having axSpA? (D) What was the evolution of MRI features of axSpA from baseline to follow-up and to what degree did this reflect diagnostic assignment by the local rheumatologist?

METHODS

The study cohort, local rheumatologist assessments, imaging assessments and follow-up of the ASAS-CC have been reported previously.[1 4 11 12]

ASAS eCRF for evaluation of MRI lesions in the SIJ

The online-available[12] electronic case report form (eCRF) comprised two sections: (A) A global scoring page where readers recorded the presence/absence of each type of MRI lesion according to published ASAS definitions.[11] Central readers provided a yes/no response to two primary MRI questions that local readers also addressed in the original baseline ASAS-CC CRF[1]: MRI Q1. 'Are there typical acute/active inflammatory lesions compatible with axial SpA present in SI joints or at entheseal sites outside the SI joint?' MRI Q2. 'Are typical chronic inflammatory (structural) lesions present in or around SI joints?' (B) A granular scoring web-based interface where inflammatory and structural lesions were recorded according to established rules.[12–14]

ASAS-CC MRI resource

Baseline and follow-up MRI scans of the SIJ were available from 278 and 170 cases, respectively. Granular assessment for MRI lesions was conducted only in cases where a Digital Imaging and Communications in Medicine (DICOM) series was available in semicoronal orientation.

Reading exercises

Two multireader exercises were conducted. Validated calibration modules aimed at standardisation of slice selection and defining SIJ quadrants were provided online for review prior to the readings.[15 16] In the first (exercise A), seven central readers assessed baseline MRI scans from 275 cases. In the second exercise (exercise B), eight central readers assessed MRI scans blinded to time point from 108 cases who had MRI performed at baseline and at 4.4 years follow-up. The eCRF for this exercise included an additional question that asked the reader to indicate whether the MRI scan was indicative of the presence of axSpA (yes/no).

Statistics

Frequencies of each MRI lesion were assessed descriptively according to individual and majority reader data (≥4/7 and ≥5/8 readers for exercises A and B, respectively). Comparison of lesion frequencies according to the local rheumatologist final diagnostic ascertainment of axSpA was analysed using the unpaired t-test and X^2 test for continuous and categorical variables, respectively. Agreement for detection of MRI lesions between central and local readers was assessed descriptively and using the kappa statistic. We calculated the number of patients who were classified differently after central reader detection of active lesions on MRI replaced local readers and after central reader detection of structural lesions on MRI replaced local reader detection of radiographic sacroiliitis for overall fulfilment of the ASAS criteria and for the imaging arm of the criteria.

RESULTS

Spectrum of MRI lesions at baseline and follow up in the ASAS-CC

In exercise A, 199/275 (72.3%) were diagnosed as having axSpA and 131/170 (77.1%) were diagnosed with axSpA at follow-up. For MRI Q1, active lesions typical of axSpA were observed by a majority of readers in 43.2% and 44.3% of cases diagnosed with axSpA at baseline and follow-up, respectively, as compared with 3.9% and 5.1% diagnosed without axSpA (table 1). The most frequent lesion was subchondral inflammation, which was observed in 51.3% and 13.2% of cases diagnosed with and without axSpA, respectively. Inflammation at the site of erosion, enthesitis and joint space fluid were each observed in 5%–10% of cases diagnosed as axSpA. The first two lesions were also 100% specific for axSpA. For MRI Q2, structural lesions typical of axSpA were observed in 39.4% and 44.6% of cases diagnosed with axSpA at baseline and follow-up, respectively, as compared with 9.7% and 6.5% without axSpA (table 1). The most frequent lesion was erosion followed by fat lesion. The frequencies of MRI lesions were similar when individual reader observations were analysed (online supplementary table 1). Most patients with lesions typical of axSpA had a combination of acute and structural lesions with only 4.6% of cases having only acute lesions and 4.6% having only structural lesions typical of axSpA (online supplementary table 2). There were 13% of cases who had active or structural lesions typical of axSpA by the majority of

Table 1 Frequencies of active and structural lesions in the SIJ of baseline MRI scans at the level of the majority of readers (≥4/7 reader agreement for the same case) according to local rheumatologist diagnosis of AxSpA (present yes/no) at baseline and follow-up

	Local rheumatologist diagnosis					
	Baseline			Follow-up		
Baseline variables	Axial SpA=Yes (n=199)	Axial SpA=No (n=76)	P value	Axial SpA=Yes (n=131)	Axial SpA=No (n=39)	P value
Mean age	30.3 (9.4)	33.6 (10.2)	0.016	30.1 (9.8)	35.6 (8.4)	0.001
Mean symptom duration	5.0 (5.8)	6.1 (7.4)	0.25	5.3 (6.1)	6.6 (7.0)	0.34
Males, %	109 (54.8)	30 (39.5)	0.024	77 (58.8)	13 (33.3)	0.005
Mean no of SpA features	2.8 (1.3)	1.3 (1.1)	<0.0001	2.9 (1.4)	1.2 (0.9)	<0.0001
B27 positive, %	126 (63.3)	18 (23.7)	<0.0001	93 (71.0)	6 (15.4)	<0.0001
Elevated CRP, %	80 (40.2)	10 (13.2)	<0.0001	51 (38.9)	4 (10.3)	0.0008
Definite radiographic sacroiliitis, %	36 (18.4)	1 (1.4)	0.0003	22 (17.3)	1 (2.6)	0.02
Active MRI lesion variable, no (%) of cases						
Active lesions typical of axSpA (MRI Q1)	86 (43.2)	3 (3.9)	<0.001	58 (44.3)	2 (5.1)	<0.001
Active lesions typical of axSpA and meets ASAS definition for positive MRI	79 (39.7)	2 (2.6)	<0.001	52 (39.7)	2 (5.1)	<0.001
Subchondral inflammation (any)	102 (51.3)	10 (13.2)	<0.001	65 (49.6)	7 (17.9)	<0.001
Inflammation at the site of erosion	20 (7.2)	0 (0)	<0.001	12 (9.2)	0 (0)	0.07
Capsulitis	8 (2.9)	0 (0)	0.11	5 (3.8)	0 (0)	0.59
Joint space fluid	16 (8.0)	2 (2.6)	0.17	10 (7.6)	0 (0)	0.12
Enthesitis	14 (5.0)	0 (0)	0.013	9 (6.9)	0 (0)	0.12
BME score, mean (SD)*	6.3 (12.0)	0.4 (0.6)	<0.001	6.0 (12.5)	0.5 (0.8)	<0.001
MRI structural lesion variable, no (%) of cases						
	Axial SpA=yes (n=175)	Axial SpA=no (n=62)	P value	Axial SpA=yes (n=112)	Axial SpA=no (n=31)	P value
Structural lesions typical of axSpA (MRI Q2)	69 (39.4)	6 (9.7)	<0.001	50 (44.6)	2 (6.5)	<0.001
Subchondral sclerosis	32 (18.3)	8 (12.9)	0.43	20 (17.9)	5 (16.1)	1.000
Erosion	64 (36.6)	3 (4.8)	<0.001	45 (40.2)	2 (6.5)	<0.001
Fat lesion	44 (25.1)	3 (4.8)	<0.001	28 (25)	3 (9.9)	0.085
Bone bud	1 (0.6)	0 (0)	1.00	1 (0.9)	0 (0)	1.00
Fat metaplasia in an erosion cavity	16 (9.1)	2 (3.2)	0.17	14 (12.5)	1 (3.3)	0.19
Ankylosis	6 (3.4)	0 (0)	0.34	5 (4.5)	0 (0)	0.59
Erosion score, mean (SD)†	3.1 (5.0)	0.8 (2.5)	<0.001	3.6 (5.6)	0.6 (1.7)	<0.001
Fat lesion score, mean (SD)†	3.4 (6.4)	0.7 (4.0)	0.003	4.2 (7.6)	0.2 (0.6)	<0.001
Sclerosis score, mean (SD)†	2.0 (4.3)	1.9 (6.2)	0.95	1.9 (4.2)	3.3 (9.9)	0.61
Fat metaplasia in an erosion cavity†	0.7 (4.1)	0.0 (0.1)	0.11	1.0 (5.2)	0.0 (0.0)	0.12
Ankylosis score†	0.1 (0.2)	0.05 (0.2)	0.55	0.1 (0.2)	0.0 (0.0)	0.002

*Cases with detailed scoring per SIJ quadrant/halve (mean (SD)) available: axSpA at baseline yes, n=109 No, n=49; axSpA at follow-up yes, n=69 no, n=17.
†Cases with detailed scoring per SIJ quadrant/halve (mean (SD)) available: axSpA at baseline yes, n=102 no, n=44; axSpA at follow-up yes, n=63 no, n=16.
ASAS, Assessment of SpondyloArthritis international Society; axSPA, axial spondyloarthritis; BME, bone marrow oedema; CRP, C reactive protein; SIJ, sacroiliac joint.

readers but were diagnosed as not having axSpA at baseline and follow-up.

In exercise B, assessment of MRI scans blinded to baseline and follow-up time points demonstrated that central reader detection of active lesions typical of axSpA was 100% and 95.2% specific for rheumatologist diagnosis of axSpA, respectively (table 2). Sensitivity for diagnosis of axSpA was 41% at baseline and 28% at follow-up. There was a decrease of 9.3% in the proportion of cases from the entire cohort with active inflammatory lesions typical of axSpA (MRI Q1) from baseline to follow-up (p=0.05). Subchondral inflammation was observed in 49% of cases diagnosed as axSpA at baseline and 36% at follow-up but also in 4.2% and 14.3% of baseline and follow-up scans from cases without axSpA. There were 19 (17.8%) cases that were started on tumour necrosis factor inhibitor (TNF) therapy during the course of follow-up. Of these cases, 57.9% had a reduction in inflammatory lesions compared with 5.7% of cases not receiving anti-TNF therapy (p<0.001).

Structural lesions typical of axSpA (MRI Q2) were observed in 38.2% and 51.2% of baseline and follow-up scans of cases diagnosed with axSpA, respectively. For the entire cohort, there was a significant increase of 9.4% (p=0.02) in cases with structural lesions from baseline to follow-up, and this was composed of an increased proportion with a fat lesion and ankylosis (table 2). Erosion was the structural lesion observed most frequently in axSpA, was more highly discriminatory than any active lesion per follow-up diagnostic assessment and was highly specific, being present in only a single case diagnosed at baseline as non-axSpA, and in no cases diagnosed as non-axSpA at follow-up.

Table 2 Frequencies of active and structural lesions in the SIJ of baseline and follow-up MRI scans at the level of the majority of readers (≥5/8 reader agreement for the same case) according to local rheumatologist diagnosis of axSpA (present yes/no) at baseline and follow-up

	Local rheumatologist diagnosis							
	Baseline				Follow-up			
	All cases (n=108)	Axial SpA=Yes (n=86)	Axial SpA=No (n=22)	P value	All cases (n=108)	Axial SpA=Yes (n=87)	Axial SpA=No (n=21)	P value
MRI indicative of axSpA according to central readers, (%)	44 (40.7)	43 (50.0)	1 (4.5)	<0.001	47 (43.9)	46 (52.9)	1 (4.8)	<0.001
Active MRI lesion variable, no (%) of cases								
Cases with global assessment of active lesions	**All Cases (n=107)**	**Axial SpA=Yes (n=85)**	**Axial SpA=No (n=22)**	**P-value**	**All Cases (n=107)**	**Axial SpA=Yes (n=86)**	**Axial SpA=No (n=21)**	**P-value**
Active lesions typical of axSpA	35 (32.7)	35 (41.2)	0 (0)	<0.001	25 (23.4)	24 (27.9)	1 (4.8)	0.023
Active lesions typical of axSpA and meets ASAS definition for positive MRI	35 (32.7)	35 (41.2)	0 (0)	<0.001	24 (22.4)	23 (26.7)	1 (4.8)	0.039
Subchondral inflammation	43 (40.2)	42 (49.4)	1 (4.5)	<0.001	34 (31.8)	31 (36.0)	3 (14.3)	0.056
Inflammation at the site of erosion	3 (2.8)	3 (3.5)	0 (0)	1.00	2 (1.9)	2 (2.3)	0 (0)	1.00
Capsulitis	3 (2.8)	3 (3.5)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	1.00
Joint space fluid	12 (11.2)	12 (14.1)	0 (0)	0.121	4 (3.7)	4 (4.7)	0 (0)	0.58
Enthesitis	2 (1.9)	2 (2.4)	0 (0)	1.00	2 (1.9)	2 (2.3)	0 (0)	1.00
Cases with Detailed Scoring of Active Lesions	**All cases (n=80)**	**Axial SpA=yes (n=64)**	**Axial SpA=no (n=16)**	**P value**	**All cases (n=66)**	**Axial SpA=yes (n=66)**	**Axial SpA=no (n=14)**	**P value**
BME score, mean (SD)	4.6 (8.8)	5.8 (9.5)	0.4 (0.5)	<0.001	3.4 (7.5)	4.0 (8.1)	0.8 (2.1)	0.007
Structural MRI lesion variable, no (%) of cases								
Cases with global assessment of structural lesions	**All n=85**	**Axial SpA=yes (n=68)**	**Axial SpA=no (n=17)**	**P value**	**All n=85**	**Axial SpA=yes (n=70)**	**Axial SpA=no (n=15)**	**P value**
Structural lesions typical of axSpA	28 (32.9)	26 (38.2)	2 (11.8)	0.039	36 (42.3)	36 (51.4)	0 (0)	<0.001
Subchondral sclerosis	8 (9.4)	6 (8.8)	2 (11.8)	0.66	5 (5.9)	5 (7.1)	0 (0)	0.58
Erosion	24 (28.2)	23 (33.8)	1 (5.9)	0.032	24 (28.2)	24 (34.3)	0 (0)	0.005
Fat lesion	21 (24.7)	18 (26.5)	3 (17.6)	0.55	23 (27.1)	22 (31.4)	1 (6.7)	0.059
Bone bud	1 (1.2)	1 (1.5)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	1.00
Fat metaplasia in an erosion cavity (FM-EC)	5 (5.9)	4 (5.9)	1 (5.9)	1.00	5 (5.9)	5 (7.1)	0 (0)	0.58
Ankylosis	3 (3.5)	3 (4.4)	0 (0)	1.00	5 (5.9)	5 (7.1)	0 (0)	0.58
Cases with Detailed Scoring of Structural Lesions	**All cases (n=49)**	**Axial SpA=yes (n=39)**	**Axial SpA=no (n=10)**	**P value**	**All cases (n=49)**	**Axial SpA=yes (n=41)**	**Axial SpA=no (n=8)**	**P value**
Erosion score, mean (SD)	2.3 (4.2)	2.6 (4.3)	1.2 (3.8)	0.37	2.3 (5.3)	2.8 (5.8)	0.1 (0.2)	0.004
Fat lesion score, mean (SD)	4.0 (7.7)	4.3 (7.5)	2.7 (8.6)	0.57	4.5 (7.8)	5.4 (8.3)	0.2 (0.3)	<0.001
Sclerosis score, mean (SD)	1.0 (2.9)	1.1 (3.2)	0.6 (1.3)	0.43	0.9 (2.8)	1.1 (3.0)	0.0 (0.0)	0.032
FM-EC	0.3 (0.8)	0.3 (0.9)	0.3 (0.8)	0.78	0.6 (1.5)	0.7 (1.6)	0.0 (0.0)	0.008
Ankylosis score	0.7 (4.5)	0.9 (5.1)	0.0 (0.1)	0.30	0.9 (4.5)	1.05 (4.89)	0.0 (0.0)	0.18

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; BME, bone marrow oedema; SIJ, sacroiliac joint.

In exercise B, MRI was considered indicative of axSpA in 44/108 (40.7%) of cases at baseline and in 43/86 (50.0%) diagnosed as axSpA by the rheumatologist. Change in MRI diagnosis from baseline to follow-up assessments was recorded in only 10/108 (9.3%) cases (four from axSpA to not axSpA and six from not axSpA to axSpA) according to agreement by ≥2 readers (table 3). Change in MRI diagnosis was recorded in only three cases according to a majority of readers (≥5/8). Change in rheumatologist diagnosis was recorded in 9/108 (8.3%) cases, two of which had a change in MRI diagnosis.

Local versus central reader detection of MRI lesions in the SIJ

The frequency of active lesions reported by local readers (61%) in cases diagnosed with axSpA was greater than for central readers (43.2% and 49.7% for majority (≥4/7) and ≥2 reader data, respectively) (table 4). This difference was similar for scans limited to cases that attended for follow-up evaluation and cases where only data from DICOM scans was analysed (online supplementary table 3).

Structural lesions typical of axSpA were reported by local readers in 44.4% of cases who were diagnosed with axSpA. This compares with 39.5% and 54.9% of cases when assessed by a majority and ≥2 central readers, respectively.

Discordance between central and local readers for detection of active lesions (MRI Q1) was recorded in 46 (17.8%) and 47 (18.2%) of cases according to ≥2 and majority (≥4/7) central reader data, respectively (kappa (95% CI) of 0.64 (0.54 to 0.73) and 0.62 (0.53 to 0.72)) (table 5). With central reading as external standard the false-positive rate for active lesions was 27.4% and 33.3% ('local overcall') for ≥2 and majority reader data, respectively. Reliability between the seven central readers was higher with a median kappa value of 0.74 and range of 0.63–0.83 for all possible reader pairs (online supplementary table 4). Discordance between central and local readers for detection of structural lesions (MRI Q2) was noted in 66 (30.0%) and 67 (30.5%) of cases according to ≥2 and majority (≥4/7) central reader data, respectively (kappa (95% CI) of 0.44 (0.32 to 0.55) and 0.38 (0.25 to 0.50)). Local versus central reader discrepancies were less evident when only data from DICOM scans was assessed (table 5).

Table 3 MRI considered indicative of axSpA at baseline and follow-up at the level of any two central readers or the majority of central readers (≥5/8 reader agreement for the same case) according to local rheumatologist diagnosis of axSpA (present yes/no) at baseline and follow-up

Rheumatologist's diagnosis	MRI indicative of axSpA (any two readers)			
	Yes at baseline and yes at follow-up (n=48), (%)	Yes at baseline and no at follow-up (n=4), (%)	No at baseline and yes at follow-up (n=6), (%)	no at baseline and No at follow-up (n=50), (%)
SpA yes at baseline and follow-up (n=82)	46 (56.1)	2 (2.4)	4 (4.9)	30 (36.6)
SpA no at baseline and yes at follow-up (n=5)	1 (20)	0 (0)	1 (20)	3 (60)
SpA yes at baseline and no at follow-up (n=4)	1 (25)	1 (25)	0 (0)	2 (50)
SpA no at baseline and no at follow-up (n=17)	0 (0)	1 (5.9)	1 (5.9)	15 (88.2)
Rheumatologist's diagnosis	**MRI indicative of axSpA (majority (≥5) of readers)**			
	Yes at baseline and yes at follow-up (n=43)	Yes at baseline and no at follow-up (n=1)	No at baseline and yes at follow-up (n=4)	No at baseline and no at follow-up (n=60)
SpA yes at baseline and follow-up (n=82)	42 (51.2)	1 (1.2)	2 (2.4)	37 (61.7)
SpA no at baseline and yes at follow-up (n=5)	1 (20)	0 (0)	1 (20)	3 (60)
SpA yes at baseline and no at follow-up (n=4)	0 (0)	0 (0)	0 (0)	4 (100)
SpA no at baseline and no at follow-up (n=17)	0 (0)	0 (0)	1 (5.9)	16 (94.1)

axSpA, axial spondyloarthritis.

Impact of central versus local reader discrepancies in detection of active lesions typical of axSpA (MRI Q1) on classification of axial SpA

There were 159 (63.1%) patients who fulfilled the ASAS axSpA criteria based on local-reading, and 148 (58.7%) and 143 (56.7%) patients based on ≥2 and majority central-reading, respectively (table 6). A total of 19 (7.5%) and 20 (7.9%) patients who were classified as axSpA after local reading were reclassified as not having axSpA after ≥2 and majority reader central evaluation. Conversely, eight (3.2%) and four (1.6%) cases who were classified as having axSpA after ≥2 and majority reader central evaluation, respectively, would have been reclassified as not having axSpA after local assessment. The numbers were similar when fulfilment of the imaging arm was the primary consideration (irrespective of the clinical arm).

Impact of replacing local reader detection of radiographic sacroiliitis by central reader detection of MRI structural lesions (MRI Q2) on classification of axSpA

In total, 120 (55.3%) cases fulfilled the axSpA criteria based on local reading of radiographic sacroiliitis and central reading of active inflammation on MRI. This changed to 125 (57.6%) and 117 (53.9%) of cases after replacement of radiographic sacroiliitis by ≥2 and majority central reader MRI structural lesions, respectively (table 6). A total of nine (4.1%) and four (1.8%) cases who were classified as not having axSpA were reclassified as having axSpA after replacing radiographic sacroiliitis with ≥2 and majority reader MRI structural lesions, respectively. Conversely, seven (3.2%) and eight (3.7%) cases were reclassified as not having axSpA after substitution by ≥2 and majority reader MRI structural lesions, respectively. The numbers were similar when fulfilment of the imaging arm was the primary consideration (irrespective of the clinical arm).

DISCUSSION

This first central reader evaluation of MRI scans from the ASAS-CC study applying consensus definitions for MRI lesions recently reported by ASAS[11] demonstrates several observations of major importance to the interpretation of MRI scans relevant to both diagnosis and classification of axSpA. First, structural lesions occur almost as frequently as active lesions in patients presenting with undiagnosed back pain to a rheumatologist. Second, subchondral bone marrow inflammation may occur in 10%–15% of cases diagnosed as non-axSpA while other active lesions such as inflammation in an erosion cavity, capsulitis, and enthesitis are highly specific for axSpA but each occur in only 5%–10% of cases. Third, central reader detection of active MRI lesions considered typical of axSpA and erosions was comparatively discriminatory between axSpA and non-axSpA. Fourth, there was relatively little change in the frequencies of active and structural lesions over a mean follow-up period of 4.4 years in this cohort of patients who received mainly conservative therapy. Fifth, although clear discrepancy between local and central readers in detection of MRI lesions was evident this had a minor impact on the total number of patients classified as axSpA using the ASAS criteria. Even substitution of radiography with structural lesions detected on T1W MRI by central readers did not materially impact the number of patients classified as having axSpA.

This is the first report that describes the frequencies of the broad spectrum of active and structural MRI lesions according to recently published ASAS definitions in patients presenting to the rheumatologist with undiagnosed back pain. Active or structural lesions typical of axSpA were observed by a majority of central readers in 55% of patients diagnosed by local rheumatologists with axSpA but also in 12.9% of non-axSpA cases suggesting that axSpA may have been under-recognised by local rheumatologists. Subchondral BME was observed in about 50% of cases diagnosed with axSpA although the definition of an ASAS positive MRI was met in only 40%. The corresponding frequencies in non-axSpA cases were 13.2% for subchondral BME and 2.6% for an ASAS positive MRI. This is much lower than the 20%–40% frequency often cited for an ASAS positive MRI in controls, both healthy and those diagnosed with non-specific back pain, in other cohorts.[8–10] This could be explained by central reader expertise in distinguishing BME lesions suggestive of axSpA versus non-specific findings and also the concomitant presence of structural lesions. It reinforces the importance of contextual interpretation of T1W and fat-suppressed scans for diagnostic interpretation of MRI scans previously emphasised in an ASAS consensus exercise.[3]

The revised ASAS definition of erosion was highly discriminatory and was detected in fewer than 10% of non-axSpA cases in both reading exercises although sensitivity of 30%–40% was lower than the 50%–60% reported in some previous studies of

Table 4 Central and local MRI reader assessment of active and structural MRI lesions in the SIJ according to diagnostic ascertainment by the local physician at baseline and follow-up in the ASAS classification study

Reader	MRI lesion type	Local rheumatologist diagnosis at baseline		P value	Local rheumatologist diagnosis at follow-up		P value
		AxSpA (n=187)	Not AxSpA (n=70)		AxSpA (n=122)	Not AxSpA (n=35)	
Active lesions							
Local	Active lesions typical of axSpA	114 (61.0%)	3 (4.3%)	<0.001	75 (61.5%)	5 (14.3%)	<0.001
Central (≥4/7 reader agreement)	Active lesions typical of axSpA	83 (43.2%)	3 (4.3%)	<0.001	56 (45.9%)	2 (5.7%)	<0.001
Central (≥4/7 reader agreement)	ASAS MRI positive	76 (40.6%)	2 (2.9%)	<0.001	50 (41%)	2 (5.7%)	<0.001
Central (any 2 readers)	Active lesions typical of axSpA	93 (49.7%)	6 (8.6%)	<0.001	60 (49.2%)	5 (14.3%)	<0.001
Central (any 2 readers)	ASAS MRI positive	89 (47.6%)	5 (7.1%)	<0.001	57 (46.7%)	4 (11.4%)	<0.001
Structural lesions							
		AxSpA (n=162)	Not AxSpA (n=58)		AxSpA (n=103)	Not AxSpA (n=28)	
Local	Structural lesions typical of axSpA	72 (44.4%)	3 (5.2%)	<0.001	44 (42.7%)	4 (14.3%)	0.007
Central (any 2 readers)	Structural lesions typical of axSpA	89 (54.9%)	10 (17.2%)	<0.001	56 (54.4%)	6 (21.4%)	0.003
Central (≥4/7 reader agreement)	Structural lesions typical of axSpA	64 (39.5%)	6 (10.3%)	<0.001	46 (44.7%)	2 (7.1%)	<0.001

ASAS, Assessment of SpondyloArthritis international Society; AxSpA, axial spondyloarthritis; SIJ, sacroiliac joint.

MRI in axSpA.[17 18] This may reflect differences in the definition of erosion. The first ASAS publication on MRI definitions in the SIJ cited only the requirement for a bony defect at the joint margin without specifying alteration in the signal from adjacent bone marrow.[2] The revised ASAS definition stipulates both a bony defect as well as loss of the adjacent bright marrow signal observed on a T1W sequence.[11] Fat lesion with the distinct features of axSpA, namely a sharp border and homogeneous increased T1W signal, was also discriminatory but sensitivity was less than for erosion at 25%–30% while specificity was 90%–95%, which was comparable to findings in other cohorts of early SpA that applied a similar definition.[18–20]

We observed local reader overcall in the range of 25%–35% when using the central reader assessment as external standard raising the possibility of diagnostic overcall. However, this had little impact on the number of patients classified with axSpA since patients could still be classified as axSpA by the clinical arm. Conversely, local readers detected fewer structural lesions than central readers. This could reflect the requirement for good quality T1W images so that the more complex structural lesions can be adequately visualised as the discrepancy was less evident when DICOM images were assessed. Nevertheless, substitution of radiographic sacroiliitis by structural lesions on MRI detected by central readers had a minor impact on the number of patients classified as axSpA. This may not be surprising as most patients with structural lesions also had active lesions typical of axSpA. Similar observations have been reported in two early axSpA cohorts.[21 22]

There are some limitations of our data. It has been over a decade since the local MRI reads were conducted and it is possible that discrepancy might be less evident if the study was a contemporary comparison. However, recent clinical trials of non-radiographic axSpA[23 24] have reported similar symptom duration prior to diagnosis as noted for the ASAS-CC suggesting that diagnostic delay has not changed a great deal over the past decade and that imaging findings may therefore not be different. Interpretation of local reader data is compromised by lack of data recorded in the ASAS-CC CRF as to which types of MRI lesion were observed. The assessment of structural lesions, especially erosion, is increasingly being performed using MRI sequences that can enhance the contrast between the joint space and bone.[25]

Table 5 Agreement between central and local readers for active (MRI Q1) and structural (MRI Q2) lesions typical for axSpA observed on all available MRI scans from patients in the ASAS classification cohort

Local reader		Central readers (all MRI scans)*				Central readers (DICOM MRI scans)†			
		Active lesion (≥2 readers)		Active lesion (≥4 readers)		Active lesion (≥2 readers)		Active lesion (≥4 readers)	
		Yes	No	Yes	No	Yes	No	Yes	No
Active lesion	Yes	85	32	78	39	42	17	37	22
	No	14	127	8	133	11	90	7	94
Kappa (95% CI)		0.64 (0.54 to 0.73)		0.62 (0.53 to 0.72)		0.62 (0.49 to 0.74)		0.59 (0.46 to 0.72)	
		Structural lesion (≥2 readers)		Structural lesion (≥4 readers)		Structural lesion (≥2 readers)		Structural lesion (≥4 readers)	
Structural lesion	Yes	58	25	43	40	29	9	21	17
	No	41	130	27	144	25	75	14	86
Kappa (95% CI)		0.44 (0.32 to 0.55)		0.38 (0.25 to 0.50)		0.62 (0.49 to 0.74)		0.59 (0.46 to 0.72)	

*Total with MRI data for assessment of active lesions=258, total with MRI data for assessment of structural lesions=220.
†Total with MRI data for assessment of active lesions=160, total with MRI data for assessment of structural lesions=138.
ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis.

Table 6 Impact of reader discrepancy (central vs local) for detection of active SIJ lesions on MRI and replacement of radiographs by MRI structural lesions on classification of axial SpA in the ASAS classification cohort

MRI assessment used	Overall SpA Classification=yes after MRI assessment N (%)	Overall SpA Classification=no after MRI assessment N (%)	Imaging Arm SpA Classification=yes after MRI assessment N (%)	Imaging Arm SpA Classification=no after MRI assessment N (%)
Impact of central versus local reader SIJ MRI inflammation assessment on SpA classification in cases with all clinical, radiographic, and central and local MRI inflammation data available (n=252)				
Local reader SIJ MRI Inflammation positive	159 (63.1)	93 (36.9)	126 (50)	126 (50)
≥2 central reader SIJ MRI inflammation assessment positive	148 (58.7)	104 (41.3)	111 (44.0)	141 (56.0)
Majority central reader (≥4/7) SIJ MRI inflammation assessment positive	143 (56.7)	109 (43.2)	102 (40.5)	150 (59.5)
Impact of replacement of radiographic sacroilitis by MRI structural lesions on SpA classification in cases with all clinical, radiographic, and central and local MRI inflammation data available (n=217)				
Central reader MRI Inflammation Positive*	120 (55.3)	97 (44.7)	83 (38.2)	134 (61.8)
Replace radiographic sacroiliitis with central reader (≥2) MRI structural positive†	125 (57.6)	92 (42.4)	100 (46.1)	117 (53.9)
Replace radiographic sacroiliitis with central reader (≥4/7) MRI structural positive†	117 (53.9)	100 (46.1)	85 (39.2)	132 (60.8)

*Positive imaging for classification is defined by either local reader positive for radiographic sacroiliitis or majority of central readers positive for MRI inflammation.
†Positive imaging for classification is defined by either central readers positive for MRI structural lesions or majority of central readers positive for MRI inflammation.
ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; SIJ, sacroiliac joint.

In conclusion, our analysis of MRI scans from patients referred to rheumatologists with undiagnosed back pain demonstrates the importance of both active and structural lesions in diagnostic decision making and the importance of educational initiatives aimed at enhancing interpretation of these lesions. These data also provide reassurance that the ASAS classification criteria have performance characteristics that may circumvent the limitations posed by the widespread lack of reader expertise in the interpretation of MRI scans. However, our study design was retrospective in nature and could not assess the impact of reader discrepancy on diagnostic ascertainment. Consequently, the performance of the ASAS criteria will require further testing in a study design where the impact of differences in interpretation of imaging on diagnostic ascertainment can be addressed.

Author affiliations
[1]Medicine, University of Alberta Faculty of Medicine and Dentistry, Edmonton, Alberta, Canada
[2]Department of Rheumatology, Copenhagen University Hospital Glostrup, Glostrup, Denmark
[3]Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, Sønderborg, Denmark
[4]Regional Health Research, University of Southern Denmark, Odense, Denmark
[5]Rheumazentrum Ruhrgebiet, Herne, Germany
[6]MRC Centre for Neuromuscular Diseases, University College London, London, UK
[7]Rheumatology, University College London Centre for Rheumatology, London, UK
[8]Radiology, Sheba Medical Center, Tel Hashomer, Israel
[9]VIB Center of Inflammation Research, Ghent University, Gent, Belgium
[10]Medical Department I, Rheumatology, University Clinic Benjamin Franklin, Berlin, Germany
[11]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[12]Internal Medicine and Rheumatology, Klinikum Bielefeld Rosenhöhe, Bielefeld, Germany
[13]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[14]Rheumatology, Diakonhjemmet Hospital, Norway
[15]Amsterdam Rheumatology Center, AMC, Amsterdam, The Netherlands
[16]Rheumatology, Zuyderland MC, Heerlen, The Netherlands
[17]Department of Rheumatology, Infectious Diseases and Rheumatology, Charité Universitätsmedizin Berlin, Berlin, Germany
[18]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup, Glostrup, Denmark
[19]Radiology and Diagnostic Imaging and Medical Imaging Consultants, University of Alberta, Edmonton, Alberta, Canada

Twitter Pedro M Machado @pedrommcmachado

Acknowledgements We thank Joel Paschke of CaRE Arthritis for development of the web-based ASAS MRI eCRF and scoring interface, for processing of MR images for reading online, and for image data cleaning and processing. We thank Matthew Maksymowych and Mikhail Protopopov for processing of MR images for reading online.

Contributors All authors contributed to the design of the study, review of study data, drafting of the final manuscript and agreed to the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement This consensus-based initiative was done without patient involvement. Patients were not invited to comment on the study design of the MRI reading exercise and were not consulted to interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The MRI scans and data from the readings reported in this study can be made available after submission of a study proposal to the ASAS MRI-WG.

ORCID iDs
Walter P Maksymowych http://orcid.org/0000-0002-1291-1755
Ulrich Weber http://orcid.org/0000-0001-6701-670X
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362
Pedro M Machado http://orcid.org/0000-0002-8411-7972
Manouk de Hooge http://orcid.org/0000-0002-0652-9808
Martin Rudwaleit http://orcid.org/0000-0001-5445-548X
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Denis Poddubnyy http://orcid.org/0000-0002-4537-6015

REFERENCES

1 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of assessment of spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
2 Rudwaleit M, Jurik AG, Hermann K-GA, *et al*. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520–7.
3 Lambert RGW, Bakker PAC, van der Heijde D, *et al*. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI Working group. *Ann Rheum Dis* 2016;75:1958–63.

4 Sepriano A, Landewé R, van der Heijde D, *et al*. Predictive validity of the ASAS classification criteria for axial and peripheral spondyloarthritis after follow-up in the ASAS cohort: a final analysis. *Ann Rheum Dis* 2016;75:1034–42.
5 Maksymowych WP. The role of imaging in the diagnosis and management of axial spondyloarthritis. *Nat Rev Rheumatol* 2019;15:657–72.
6 Dougados M, d'Agostino M-A, Benessiano J, *et al*. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598–603.
7 van den Berg R, de Hooge M, van Gaalen F, *et al*. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the spondyloarthritis caught early (space) cohort. *Rheumatology* 2013;52:1492–9.
8 Weber U, Jurik AG, Zejden A, *et al*. Frequency and Anatomic Distribution of Magnetic Resonance Imaging Features in the Sacroiliac Joints of Young Athletes: Exploring "Background Noise" Toward a Data-Driven Definition of Sacroiliitis in Early Spondyloarthritis. *Arthritis Rheumatol* 2018;70:736–45.
9 de Winter J, de Hooge M, van de Sande M, *et al*. Magnetic resonance imaging of the sacroiliac joints indicating sacroiliitis according to the assessment of spondyloarthritis International Society definition in healthy individuals, runners, and women with postpartum back pain. *Arthritis Rheumatol* 2018;70:1042–8.
10 Varkas G, de Hooge M, Renson T, *et al*. Effect of mechanical stress on magnetic resonance imaging of the sacroiliac joints: assessment of military recruits by magnetic resonance imaging study. *Rheumatology* 2018;57:508–13.
11 Maksymowych WP, Lambert RG, Østergaard M, *et al*. Mri lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI Working group. *Ann Rheum Dis* 2019;78:1550–8.
12 CARE Arthritis. ASAS MRImagine module. Available: https://www.carearthritis.com/mriportal/mrimagine/index/
13 Maksymowych WP, Dhillon SS, Chiowchanwisawakit P, *et al*. Development and validation of web-based training modules for systematic evaluation of active inflammatory lesions in the spine and sacroiliac joints in spondyloarthritis. *J Rheumatol Suppl* 2009;84:48–57.
14 Maksymowych WP, Wichuk S, Chiowchanwisawakit P, *et al*. Development and preliminary validation of the spondyloarthritis research Consortium of Canada magnetic resonance imaging sacroiliac joint structural score. *J Rheumatol* 2015;42:79–86.
15 Maksymowych M, Boutrup H, Cheah J, *et al*. Validation of online calibration modules for the spondyloarthritis research Consortium of Canada MRI scores based on real-time experiential learning. *Arthritis Rheumatol* 2017;69.
16 Care arthritis MRI scoring modules. Available: www.carearthritis.com/service/mri-scoring-modules/
17 Weber U, Lambert RGW, Østergaard M, *et al*. The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010;62:3048–58.
18 Weber U, Østergaard M, Lambert RGW, *et al*. Candidate lesion-based criteria for defining a positive sacroiliac joint MRI in two cohorts of patients with axial spondyloarthritis. *Ann Rheum Dis* 2015;74:1976–82.
19 Weber U, Pedersen SJ, Zubler V, *et al*. Fat infiltration on magnetic resonance imaging of the sacroiliac joints has limited diagnostic utility in nonradiographic axial spondyloarthritis. *J Rheumatol* 2014;41:75–83.
20 de Hooge M, van den Berg R, Navarro-Compán V, *et al*. Patients with chronic back pain of short duration from the space cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2016;75:1308–14.
21 van den Berg R, Lenczner G, Thévenin F, *et al*. Classification of axial spa based on positive imaging (radiographs and/or MRI of the sacroiliac joints) by local rheumatologists or radiologists versus central trained readers in the DESIR cohort. *Ann Rheum Dis* 2015;74:2016–21.
22 Ez-Zaitouni Z, van Lunteren M, Bakker PAC, *et al*. The influence of discrepant imaging judgements on the classification of axial spondyloarthritis is limited: a replication in the spondyloarthritis caught early (space) cohort. *Ann Rheum Dis* 2018;77:e1.
23 van der Heijde D, Cheng-Chung Wei J, Dougados M, *et al*. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018;392:2441–51.
24 van der Heijde D, Song I-H, Pangan AL, *et al*. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet* 2019;394:2108–17.
25 Diekhoff T, Greese J, Sieper J, *et al*. Improved detection of erosions in the sacroiliac joints on MRI with volumetric interpolated breath-hold examination (VibE): results from the SIMACT study. *Ann Rheum Dis* 2018;77:1585–9.