Sengupta, R., Marzo-Ortega, H., McGonagle, D., Wadeley, A. and Bennett, A. (2018) 'Short-term repeat magnetic resonance imaging scans in suspected early axial spondyloarthritis are clinically relevant only in HLA-B27-positive male subjects', *Journal of Rheumatology*, 45 (2), pp. 202-205.

Short term repeat MRI Scanning in Suspected Early axSpA is only clinically relevant in HLA-B27 positive male subjects.

Raj Sengupta[1,6], Helena Marzo Ortega[2, 3], Dennis McGonagle[2,3], Alison Wadeley[4] and Alexander. N. Bennett[3,5]

(1) Royal National Hospital for Rheumatic Diseases, Bath, UK. rajsen99@gmail.com

(2) NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK. H.Marzo-Ortega@leeds.ac.uk

(3) Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK. D.G.McGonagle@leeds.ac.uk

(4) Culture and Environment College of Liberal Arts, Bath Spa University, Bath, UK. a.wadeley@bathspa.ac.uk

(5) Academic Department of Military Rehabilitation, Defence Medical Rehabilitation Centre, Headley Court, Epsom, UK.

alexander.n.bennett@btinternet.com

(6) University of Bath, Bath, UK

On behalf of British Society for Spondyloarthritis (BRITSpA)

Corresponding author: Dr Alexander Bennett, Defence Medical Rehabilitation Centre, Headley Court, Epsom, KT186JW, UK. alexander.n.bennett@btinternet.com

Abstract

Background: This study investigated the natural history of MRI determined bone marrow oedema (BMO) over a 12-week period in individuals with suspected axSpA.

Methods: 109 MRI scans were performed on 30 patients fulfilling ASAS Inflammatory Back Pain criteria at baseline, 4,8 and 12 weeks.

Results: 29-patients completed the study. Only 4(14%) patients changed from MRI "negative" to "positive" (all HLA-B27+ve (OR 2.74). Three of 7 (43%) male HLA-B27+ve patients, 1 of 8 (12.5%) HLA-B27+ve female patients and no HLA-B27-ve patients changed from MRI "negative" to "positive".

Conclusion: Repeat MRI scans within a 12-week period should be considered in HLA-B27+ve males.

Keywords: MRI, diagnosis, axial spondyloarthritis

Background

Sacroiliac joint (SIJ) involvement is a unifying feature in spondyloarthritis (SpA) and radiographic sacroiliitis is a pre-requisite for the diagnosis of Ankylosing spondylitis (AS). However, x-ray changes may be delayed contributing to substantial delays in diagnosis of up to a decade. (1,2). Recently the International Society for Assessment of Spondyloarthritis (ASAS) have re-classified SpA into axial (axSpA) and peripheral (pSpA). The ability of MRI to demonstrate objective evidence of potentially diagnostic inflammatory lesions early in the course of the disease renders it especially useful for the diagnosis of axSpA, particularly when conventional SIJ radiographs are normal or show equivocal changes.(3,4). Furthermore, a "positive" baseline MRI scan is of prognostic value(4,5) and may predict response to biologic therapy(6).

However, the sensitivity of MRI is limited as up to 65% of subjects with inflammatory back pain (IBP) suspected of axSpA have a negative SIJ MRI at baseline(7) and up to 38% of active AS/axSpA patients have no inflammatory lesions of the SIJ(6,8). AxSpA follows a fluctuating course in early disease and this has been shown both clinically and on MRI(9,10). Further, the optimal timing of MRI scanning of IBP cases with normal x-rays is poorly defined. One previous study showed that 27% of HLA-B27+ve patients had a "positive" repeat MRI scan after 2-years(7) but clinically, such long waits in symptomatic cases are difficult to justify. This study evaluates clinically suspected axSpA cases with MRI at four time-points over a 12-week period.

Methods

Participants were recruited from the DMRC, Headley Court, Epsom and the RNHRD, Bath. Local ethical approval was obtained for the study from the Cornwall and Plymouth Research Ethics Committee (Reference number 11/SW/0038) and all patients provided informed written consent. Inclusion criteria were IBP as defined by the ASAS criteria(11) and normal SIJ on AP pelvis

radiographs (scored centrally). As it is unclear whether NSAIDs might affect MRI BMO, participants were asked to either discontinue all NSAID use or remain on a regular dose throughout the study duration to ensure consistency between scans of each participant**.** Additional simple analgesia was permitted if required. Recruited subjects had a total of 4 MRI scans using a pre-defined protocol at baseline, 4, 8 and 12-weeks. The protocol included sagittal T1 and STIR of the cervicothoracic spine, thoracolumbar spine and coronal oblique of the SIJs. At each visit, patient reported outcome measures (Bath indices), medication history and CRP were recorded.

MRI scans

MRI scans were scored according to the Leeds Scoring system(8,10). In addition, all images were assessed for ASAS definitions of a positive scan of the SIJs(12) and Spine (13), thereafter referred to as "positive" or "negative" depending on whether definitions were fulfilled or not respectively. In the SIJs, although the readers focus was on BMO lesions, if BMO lesions were equivocal and not necessarily "highly suggestive of axSpA", additional presence of structural lesions (erosion, sclerosis, fatty deposition or fusion) could be used to influence the decision as per the updated ASAS definition(14). Experienced readers (HM-O and DMcG) scored the scans and radiographs and were blinded for any clinical data and time points. Any disagreement between the 2 readers was settled by consensus. Radiographs were scored according to the modified New York Criteria(1). Intra-reader reliability for ASAS MRI positive definitions at the SIJs and spine were "excellent" with a Kappa(15)(SE) = .80 (.19) $p = 0.01$ and 1.00 (.00) $p < .0001$ respectively. Reliability for mNYC classification of x-rays had 100% agreement (SE) = 1.00 (.00) $p < .0001$ (absolute agreement).

Results

Thirty participants were recruited (Table 1), of whom 29 completed the study, 25 (86%) attended all 4 visits, 2 patients attended 3 visits and 1 patient attended 2 visits. A total of 109 MRI scans were performed. As well as meeting the inclusion criteria, all patients had a least one clinical SpA feature (Table 2) and 25 (86%) had 2 or more. Thirteen patients (45%) took regular NSAIDs throughout the study. All patients were assessed by ANB and RS. nr-axSpA was diagnosed in 79% of the patients. On application of ASAS classification, 26% met the imaging arm, 39% clinical arm and 35% met both arms.

ASAS status

Seventeen participants (59%) met the ASAS clinical criteria for axSpA prior to any imaging. Eleven (38%) met ASAS imaging arm classification criteria during the study and a further 3 (10%) had a positive MRI of the spine but normal SIJs (plus HLA-B27+ve and $\geq$ 1 clinical feature).

Fifteen (52%) participants were ASAS MRI negative (spine and SIJ) at baseline and remained so during the entire study and 10 (34%) patients were either spine and/or SIJ positive for the duration of the study. A total of 4 (14%) patients changed from ASAS axSpA MRI negative to positive (spine (n=3) or SIJ (n=1)) during the study. All these patients met ASAS clinical arm classification criteria at baseline.

CRP status and change

Of the 28 patients who had blood test results available, CRP levels were normal in 25 subjects (89%) at baseline - 20 remained normal throughout and 5 patients' CRP became elevated above the upper limit of normal during the study. Three subjects had a raised CRP at baseline - 1 remained raised throughout study and 2 normalized. There was no relationship between CRP changing and MRI scans becoming positive at any time point during the study

HLA-B27 status and Sex

All 4 patients whose MRI changed from negative to positive were HLA-B27+ve. Comparing patients who were HLA-B27+ve to HLA-B27-ve, the odds ratio (OR) for their ASAS MRI status changing from negative to positive was 2.74.

Three of the 4 patients (75%) whose MRI changed from negative to positive were male. Ten patients' MRI scans were positive throughout - 9 were male (90%). Four of 15 (27%) HLA-B27+ve patients with negative baseline scan developed "positive" scans during the 12-week study period. Three of seven (43%) HLA-B27+ve male patients, compared to one out of eight (12.5%) HLA-B27 +ve female patients and no HLA-B27-ve patients changed from ASAS MRI definition negative to positive during the study.

Discussion

A positive MRI aids diagnosis in clinically suspected axSpA, however MRI may be negative or inconclusive in a significant proportion of these patients(7). This study tested the hypothesis that repeat MRI scanning in suspected but undiagnosed axSpA over 12-weeks may increase the diagnostic yield. In the studied cohort of IBP patients with typical axSpA features (HLA-B27+ve =72%, two or more SpA features = 86%) only 14% of patients changed their ASAS MRI definition from negative to positive over the 12-week period. Whilst the yield of repeating an MRI scan in patients with IBP and a normal baseline scan is low, there may be a place in repeating the scan within 12-weeks, especially in HLA-B27+ve males as 43% of these patients changed from negative MRI to positive during the study period. Neither baseline CRP or presence of other SpA features (dactylitis, arthritis, enthesitis) predicted change in MRI status.

The majority of our cohort (59%) met ASAS clinical criteria at baseline. Fifty-two percent were ASAS imaging negative at baseline and remained so throughout the study. Overall in this study of 12-week duration, there was little change in MRI inflammatory lesions.

The natural variation of inflammatory MRI lesions of BMO in axSpA remains poorly defined. From a SIJ perspective, one study showed that 73.5% of patients, who had BMO at the SIJs at baseline, had persistent lesions one year later (16), even in the absence of clinical symptoms. In the spine, 31% of vertebral corners showed persistence of inflammatory lesions at a 2 year time point(17) . These observations together with the findings from our study, suggest that once an inflammatory lesion develops, there is likely to be little change in the spine and SIJ lesions within the first year unless biologic therapies are introduced. However, our study supports the findings of van Onna, that if the baseline scan is negative, then the proportion changing to positive scan at follow up is higher in HLA-B27+ve patients (27%) compared to patients who are HLA-B27-ve (0%)

Strengths of our study include the realistic clinical time frames for potential follow up scans and the fact that the study was specifically designed to investigate the utility of repeat scans within a 12-week window, which has not previously been performed. Other strong aspects include the minimal absence of follow up MRI scans in the cohort and data on NSAID use was collected on all patients throughout the study. The main limitations of our study are the lack of asymptomatic and/or mechanical back pain control arms.

To conclude, this study evaluated the natural history of axSpA related inflammatory lesions on MRI and the role of repeat MRI scanning within a 12-week period in clinically suspected early axSpA.

In a symptomatic patient with suspected axSpA, where baseline MRI scanning is normal, a repeat MRI scan may be of diagnostic utility in HLA-B27+ve males but not in females or HLA-B27-ve subjects. These results are highly relevant to aid clinical decision making and add to the body of evidence on the utility of MRI in the diagnosis of axSpA.

References

1. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.

2. Mau WZHMREA. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year follow-up. J Rheumatol 1988;15:1109-14.

3. Heuft-Dorenbosch L, Landewe R, Weijers R, Wanders A, Houben H, van der Linden S, et al. Combining information obtained from magnetic resonance imaging and conventional radiographs to detect sacroiliitis in patients with recent onset inflammatory back pain. Ann Rheum Dis 2006;65:804-8.

4. Bennett AN, McGonagle D, O'Connor P, Hensor EM, Sivera F, Coates LC, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. Arthritis Rheum 2008;58:3413-8.

5. Maksymowych WP, chiowchanwisawakit P, Clare T, Pedersen SJ, Ostergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93–102.

6. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 2008;67:1276-81.

7. van Onna M, Jurik AG, van der Heijde D, van Tubergen A, Heuft-Dorenbosch L, Landewe R. HLA-B27 and gender independently determine the likelihood of a positive MRI of the sacroiliac joints in patients with early inflammatory back pain: a 2-year MRI follow-up study. Ann Rheum Dis 2011;70:1981-5.

8. Bennett AN, Rehman A, Hensor EM, Marzo-Ortega H, Emery P, McGonagle D. Evaluation of the diagnostic utility of spinal magnetic resonance imaging in axial spondylarthritis. Arthritis Rheum 2009;60:1331-41.

9. Stone MA, Pomeroy E, Keat A, Sengupta R, Hickey S, Dieppe P, et al. Assessment of the

impact of flares in ankylosing spondylitis disease activity using the Flare Illustration. Rheumatology 2008;47:1213-8.

10. Marzo-Ortega H, McGonagle D, O'Connor P, Hensor EM, Bennett AN, Green MJ, et al. Baseline and 1-year magnetic resonance imaging of the sacroiliac joint and lumbar spine in very early inflammatory back pain. Relationship between symptoms, HLA-B27 and disease extent and persistence. Ann Rheum Dis 2009;68:1721-7.

11. Sieper J, van der Heijde D, Landewe R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009;68:784-8.

12. Rudwaleit M, Jurik AG, Hermann KG, Landewe R, van der Heijde D, Baraliakos X, 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.

13. Hermann K-GA, Baraliakos X, van der Heijde DM, Jurik AG, Landewé R, Marzo-Ortega H, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. Ann Rheum Dis 2012;71:1278-88.

14. Lambert RGW, Bakker PAC, van der Heijde D, Weber U, Rudwaleit M, Hermann KG, 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.

15. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 1968;70:213-20.

16. Marzo-Ortega H, McGonagle D, O'Connor P, Hensor EM, Bennett AN, Green MJ, et al. Baseline and 1-year magnetic resonance imaging of the sacroiliac joint and lumbar spine in very early inflammatory back pain. Relationship between symptoms, HLA-B27 and disease extent and persistence. Ann Rheum Dis 2009;68:1721-7.

17. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Therapy 2008;10:R104.