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What Constitutes a Positive MRI for Clinical Trial Recruitment of Psoriatic Arthritis Patients With Axial Involvement?

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ABSTRACT. There has been a resurgence of interest in defining the axial inflammation component of psoriatic arthritis (PsA) since recent randomized controlled trials (RCTs) raised the possibility that this entity may respond differentially to therapeutics compared to patients with axial spondyloarthritis. A workshop was conducted during the 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis annual meeting to review the literature on diagnosing PsA and to determine which criteria might be most appropriate. There was quite strong agreement that magnetic resonance imaging (MRI) had an important role to play in helping to define axial inflammation in PsA and that a data-driven methodology for generating optimal MRI quantitative cut-offs for lesions in the sacroiliac joints and/or spine that reflect imaging typical of axial inflammation in PsA would be most desirable.

Key Indexing Terms: GRAPPA, inflammation, MRI, psoriasis, psoriatic arthritis, spine

Introduction

There has been an increasing interest in defining the axial inflammation component of psoriatic arthritis (PsA) since recent randomized controlled trials (RCTs) found that patients with PsA responded differently to therapeutics compared to patients with axial spondyloarthritis (axSpA).[1,2,3] However, significant doubts remain because axial PsA (axPsA) continues to be largely defined by the finding of sacroiliitis on conventional radiography, and to date there has been no attempt aimed at defining this entity using more advanced imaging modalities, especially magnetic resonance imaging (MRI). As it has been repeatedly shown, detection of radiographic sacroiliitis is unreliable, even in expert hands or after substantial calibration, and is especially challenging during early disease.[4,5,6] Consequently, clinical trials in axSpA, which have relied on the detection of radiographic sacroiliitis, have typically ended up recruiting patients with long-standing disease > 10 years in duration when radiographic changes are obvious.[7,8] This has precluded access to new therapies used in earlier forms of axSpA in many countries and may become a significant concern for axPsA if RCTs adopt a similar study design for recruiting patients.

Diagnosis of axSpA

It was the recognition of this major challenge that led the Assessment of SpondyloArthritis international Society (ASAS) to develop new classification criteria for early axSpA, incorporating MRI detection of sacroiliitis as an alternative to radiographic sacroiliitis.[9] Moreover, a positive MRI has been defined as the presence of subchondral bone marrow edema (BME) in a typical location in the sacroiliac joints (SIJs) that is "highly suggestive" of axSpA. Quantitative minimal requirement for the extent of BME was also defined as the presence in ≥ 2 locations on a single semicoronal slice through the SIJs, or in ≥ 2 consecutive slices if only 1 BME lesion is present.[10,11] In contrast to the emphasis on the qualitative aspect by ASAS, several published reports primarily target the application of the quantitative component. If this quantitative approach is used, the diagnosis of BME can be found in up to 40% of control groups, which included patients with nonspecific back disorders and healthy individuals such as athletes, military recruits, and postpartum women.[12,13,14,15] Nevertheless, since interpretation of what is highly suggestive of sacroiliitis may vary widely according to reader expertise, it is still important to attempt to generate a standardized definition that quantifies the element of severity. This will ensure that it can be widely understood and applied in a reliable manner and that it will also be capable of distinguishing, with high specificity, axial inflammation from nonspecific back disorders that may clinically mimic axSpA.

A recent ASAS initiative conducted by the ASAS MRI working group (ASAS-MRI WG) aimed to reassess quantitative

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MRI definitions for active and structural lesions that would best reflect an appearance considered highly suggestive of axSpA on an MRI scan.[16] The methodology and results of this working group are highly relevant to future GRAPPA initiatives aimed at defining what constitutes a "positive" MRI typical for axial inflammation in PsA and was therefore discussed at the GRAPPA 2021 annual meeting MRI workshop.

In the ASAS initiative, 7 expert readers from the ASAS-MRI WG evaluated 160 MRI scans from patients recruited to the ASAS classification cohort study (ASAS-CC). The ASAS-CC is an inception cohort of patients with undiagnosed back pain of ≥ 3 months duration and with an onset < 45 years of age referred to a rheumatologist with suspicion of axSpA.[9] Central reader MRI evaluations were conducted in 2 stages after diagnosis had been ascertained by local rheumatologists, both at baseline and after an average of 4.4 years of follow-up of this cohort. In the first step, central readers provided a yes/no response and degree of confidence rating (–4 [definitely absent] to +4 [definitely present]) to 2 global evaluation questions: (1) "Are there typical acute/active inflammatory lesions compatible with axial SpA present in the SIJ or at entheseal sites outside the SIJ," and (2) "Are typical chronic inflammatory lesions present in or around the SIJ?" In the second step, granular evaluations were conducted in all consecutive semicoronal slices through the SIJs using Spondyloarthritis Research Consortium of Canada methodology.[17,18] BME was recorded for SIJ quadrants and structural lesions were recorded for either SIJ quadrants (erosion, fat lesions, sclerosis) or upper and lower SIJ halves (fat metaplasia in an erosion cavity, ankylosis). The sensitivity and specificity for the numbers of SIJ quadrants and consecutive slices with BME, erosion, sclerosis, and fat lesions where a majority of readers (≥ 4/7) agreed as to the presence of a definite lesion typical of axSpA (high confidence ≥ +3/4) were calculated.

The optimal MRI cut-offs for an active lesion were either ≥ 4 SIJ quadrants with BME at any location, or in the same quadrant in ≥ 3 consecutive slices. These are substantially more stringent than the quantitative part of the previous ASAS definition[9] and consistent with cut-offs generated in prior cross-sectional studies that included healthy controls, patients with nonspecific back pain, and those with diffuse idiopathic skeletal hyperostosis.[15,19,20] For definite structural lesions, the optimal cut-offs were any one of (1) ≥ 3 SIJ quadrants with erosion or ≥ 5 with fat lesions, (2) erosion at the same location for ≥ 2 consecutive slices, (3) fat lesions at the same location for ≥ 3 consecutive slices, or (4) presence of a deep (ie, > 1-cm depth) fat lesion. These cut-offs are also consistent with prior data from cross-sectional studies.[20,21] Similar methodology has recently been used to demonstrate that an MRI cut-off for BME of ≥ 4 vertebral corners achieved specificity of ≥ 95% for a positive MRI of the spine indicative of axSpA, according to global evaluation, and also had ≥ 95% positive predictive value for diagnosis of axSpA after 4.4 years of follow-up.[22]

Several considerations suggest that optimal cut-offs for a positive MRI may differ in patients with PsA and axial inflammation. First, patients with PsA tend to be older and have a greater BMI than axSpA patients without psoriatic disease (PsD). There is therefore a greater likelihood of degenerative lesions, such as BME, in the SIJs and spine that may resemble the appearance of axSpA lesions. Second, the phenotype of PsA affecting the SIJs and spine may be more variable. Radiography is more likely to demonstrate asymmetrical sacroiliitis and syndesmophytes, as well as spinal changes without abnormalities in the SIJs, as compared to what is seen in ankylosing spondylitis.[23,24] Third, there are no prospective data addressing the evolution of active and structural changes on MRI.

Workshop Discussion Polling

There was consensus at the 2021 GRAPPA annual meeting that data-driven definitions for a positive MRI indicative of axial inflammation should be determined independently in PsA. In particular, 68.4% of participants answered no to the question, "Is there an international consensus of axial involvement in PsA and if so, which?" Some participants considered MRI inflammation in ≥ 2 locations in the SIJs or spine (10.5%) or a positive MRI according to the ASAS definition (21.1%) as appropriate answers.

For the question, "If an international consensus definition was made, do you think MRI should be part of it?" 91.6% answered yes based on the findings in the SIJs and/or spine. A small number could either not provide an answer (4.2%) or considered MRI findings in the SIJs alone as sufficient (4.2%).

The question, "What should be the approach to radiography?" elicited diverse responses as follows: (1) apply the modified New York (mNY) criteria[25] (12.5%); (2) apply the mNY criteria plus add grade 2 unilateral sacroiliitis (0%); (3) apply the mNY criteria but use only ≥ grade 3 (18.8%); (4) apply radiography of the SIJs or spine (eg, using the Bath Ankylosing Spondylitis Radiological Index[26] (12.5%); or (5) do not apply radiography and apply only MRI (56.3%).

For the question, "What should be the approach to MRI evaluation?" a definite consensus response was evident as follows: (1) define optimal MRI cut-offs per SIJ quadrants and/or vertebral corners in a data-driven exercise (17.7%); (2) define a positive MRI by expert group consensus (5.9%); (3) combination of A and B (76.4%); or (4) an alternative approach.

There was no consensus in the responses to the question, "What should be the external reference for defining positive imaging?" with responses as follows: (1) group expert consensus (23.1%); (2) expert reader independent assessment (majority consensus; 30.8%); (3) expert clinician diagnostic ascertainment (7.7%); or (4) all-inclusive external standards (38.4%).

Conclusion

Although clear consensus was not evident for responses to all questions, there was nevertheless strong agreement that MRI was important in helping to define axial inflammation in axSpA and that a data-driven methodology for generating optimal MRI quantitative cut-offs for lesions in the SIJs and/or spine that reflect imaging typical of axial inflammation in PsA would be ideal. The design of the Axial Involvement in Psoriatic Arthritis (AXIS) study, which aims to define classification criteria for axial PsA, will permit the generation of data-driven MRI cut-offs that optimally

reflect majority consensus of expert readers regarding the presence of positive imaging for axial disease in PsA. This will be a major step forward toward defining the concept of axial PsA.

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