

Imaging in ankylosing spondylitis



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'The advent of magnetic resonance imaging has proven to be a milestone in the field.'

Clinicians and researchers have turned to imaging to address several major challenges in the clinical evaluation and treatment of ankylosing spondylitis (AS). The advent of more effective therapies targeting the pro-inflammatory cytokine tumor necrosis factor (TNF)- α has provided a more justifiable need to establish a diagnosis early in the disease course, particularly if it can be shown that such therapies have disease-modifying potential. Unfortunately, symptom duration prior to diagnosis of AS remains stubbornly at 8–9 years in most advanced countries [1]. This reflects the low discriminant value of the history in distinguishing between inflammatory and mechanical causes of back pain [2], the lack of physical signs related to spinal and sacroiliac joint inflammation in early disease, and the low sensitivity and specificity of laboratory abnormalities that are confined to acute-phase reactants [3]. The same limitations preclude objective evaluation of disease activity in patients with established disease. The advent of magnetic resonance imaging (MRI) has proven to be a milestone in the field, through its ability to permit direct visualization of inflammatory lesions in the spine and sacroiliac joints. Scoring systems that permit quantification of the degree of inflammation on MRI scans have also been developed, which now allow the objective analysis of disease severity in longitudinal studies and in clinical trials evaluating the efficacy of new anti-inflammatory agents. Advances in the use of other imaging modalities have been more limited and primarily confined to the development of a scoring tool to quantify structural damage on plain radiography of the spine. This tool is now being used to assess the disease-modifying potential of standard therapies, such as nonsteroidal anti-inflammatory agents, as well as anti-TNF- α therapies. Although it is now undeniable that advances in imaging have enhanced their value to both the clinician and the researcher, there has been insufficient awareness of the pitfalls inherent to the use of these imaging modalities in the setting of AS.

The primary advantage of MRI is its ability to visualize lesions within soft tissues and bone in 3D. T1-weighted sequences primarily detect the signal from fat, and the contrast with bone, which is dark, enhances anatomical delineation of joint structures. T2-weighted sequences suppress the signal from fat that is present in bone marrow, allowing visualization of an underlying water signal that may be related to inflammation, cyst, tumor and other pathologies associated with increased vascular permeability. The two images should be analyzed simultaneously as they provide complementary information. For example, loss of the fat signal in subchondral bone marrow on the T1 image of the sacroiliac joint, accompanied by a corresponding water signal on the T2 image, typically denotes inflammation.

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The presence of subchondral bone marrow edema in the postero-inferior region of the synovial portion of the joint is one of the earliest features of sacroiliitis [4]. By contrast, loss of the fat signal on the T1 image in subchondral bone marrow without the corresponding presence of a water signal on the T2 image suggests an alternative explanation for the fat replacement, such as bone sclerosis, fibrosis or chronic erosion. Consequently, both the loss of the fat signal on T1 images and the presence of a water signal on T2 images represent nonspecific findings. In scanning the spine and sacroiliac joints of patients with AS, the specificity of MRI lesions is determined to a great extent by the anatomical localization of these lesions and the very low probability of alternative pathologies at these sites. The finding of increased water signal on T2 images of the sacroiliac joints in an individual 20–40 years of age is very unlikely to reflect underlying tumor or infection. Degenerative changes and anatomical variation may also be

associated with MRI findings in the sacroiliac joints resembling those seen in sacroiliitis, although the former are uncommon in the age group typically developing sacroiliitis [5]. Systematic evaluation of sensitivity and specificity of MRI features of inflammation in the sacroiliac joint has been limited, although it suggests that the presence of an increased water signal on T2 images in subchondral bone marrow has high specificity for AS when compared with patients with nonspecific causes of lower back pain [6].

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There are two more pressing questions related to the use of MRI as a diagnostic tool in the evaluation of sacroiliitis. Does MRI possess enhanced sensitivity over plain imaging in the early detection of sacroiliitis and what is the prognostic significance of the inflammatory lesions observed on MRI? Are they merely evanescent phenomena or do they reflect more permanent lesions that, if left untreated, lead to structural damage? These two questions ought to be examined concurrently in longitudinal studies, since the current gold standard for sacroiliitis is the presence of abnormalities on x-rays of the sacroiliac joints. At present, sensitivity has been examined in limited cross-sectional studies at single sites. One group used contrast-enhanced MRI and dynamic imaging to compare patients with inflammatory back pain ($n = 36$) according to the European Spondyloarthropathy Study Group (ESSG) criteria, but with normal pelvic x-rays, and patients with established AS ($n = 36$) according to the modified New York criteria, with those who had mechanical causes for lower back pain ($n = 53$) [7]. A positive MRI for sacroiliitis was defined on the basis of maximal enhancement after administration of a contrast agent. On this basis, MRI was almost 100% sensitive and specific for clinically defined inflammatory back pain. In a second study that examined 48 patients with equivocal changes on plain x-ray and clinical features of AS with a mean duration of inflammatory back pain (IBP) of 0.8 years, MRI evidence of inflammation using contrast enhancement was evident in 76% of patients; however, specificity was not addressed [4]. In a third study that described a cohort of 68 patients with IBP (57 and 14 fulfilled ESSG and modified New York criteria, respectively) of less than 2-years duration, inflammation in the sacroiliac joints could be

detected using MRI in only approximately a third (22/68) of the patients [8]. Ten patients also showed no abnormalities on plain radiography of the sacroiliac joints, while virtually all patients with abnormal pelvic x-ray also had abnormalities on MRI. MRI was less sensitive in the detection of structural changes. Another important finding in this study was that it is probably sufficient to look for subchondral bone marrow edema as a sign of inflammation. The contribution of other sites of the joint to a diagnosis of sacroiliitis was only marginal. Only one patient had inflammation that was restricted to joint capsule and ligaments.

A significant limitation of these studies is that it is not clear how many and which specific patients with IBP will ever develop sacroiliitis evident on plain radiography. Several surveys have shown that inflammatory back pain is very common in patients with mechanical causes of back pain [9,10]. On the other hand, patients with MRI abnormalities are much more likely to be human leukocyte antigen (HLA) B27-positive and to demonstrate a good symptomatic response to nonsteroidal anti-inflammatory agents [11]. Longitudinal studies are limited in both number of patients studied and duration of follow-up. One study evaluated 17 patients with IBP of 3–14 months duration, but with normal pelvic x-ray, who were followed for 1.5–2.5 years [12]. Virtually all patients had abnormalities on baseline MRI that persisted on follow-up MRI 2–30 months later, and 11 developed plain radiographic features of sacroiliitis on follow-up, suggesting that inflammation observed on MRI is of prognostic significance. Direct computed-tomography-guided biopsy of the sacroiliac joints has also demonstrated significant correlations between the degree of contrast enhancement on MRI of the sacroiliac joints and the histopathological grade of inflammation [13]. The balance of the data indicates that MRI of the sacroiliac joints is most diagnostically useful in those patients with a clinical suspicion of IBP who are HLA B27-positive and have a normal pelvic x-ray.

Systematic evaluation of MRI abnormalities in the spine of patients with AS has been confined to descriptive studies. These have demonstrated that inflammatory lesions are most commonly observed in the thoracic spine, especially the costo-vertebral joints, in patients with established disease [14,15]. Systematic comparison with plain radiography has shown no advantage for MRI in the assessment of structural changes in

the spine [16]. No studies have evaluated the sensitivity and specificity of MRI features of inflammation observed in AS and it is likely that commonly seen abnormalities, such as spondylodiscitis, may be indistinguishable from a herniated disc and other abnormalities commonly observed in patients with mechanical back pain [17]. Other abnormalities, such as bone edema at the vertebral corners that represent the MRI counterpart of the Romanus lesion, may be more specific. Similarly, there have been no longitudinal studies that have addressed one of the most sought-after questions in the field, namely, does inflammation lead to erosion and then ankylosis? This assumption has bordered on dogma, despite its lack of support by any experimental data until recently. Effective suppression of inflammation in the ankylosing enthesitis model of AS in DBA/1 mice did not affect the development of ankylosis [18]. This has major implications for the treatment of AS, because if the process of inflammation and ankylosis are not coupled then it cannot be assumed that the amelioration of inflammation observed on MRI following the institution of anti-TNF- α therapies portends a disease-modifying effect. At this time therefore, MRI cannot be used as a surrogate for structural damage end points until systematic longitudinal studies have been performed.

Considerable energy and debate has recently focused on the preferred scoring approach for quantification of inflammatory lesions observed on MRI in the spine and sacroiliac joints for the purposes of clinical trials research and observational studies. Two principle methods have been reported for scoring inflammatory lesions in the spine. Both rely on the assessment of the signal on fat-suppressed images (STIR and T2 fat-sat) in the anterior segment of the spine (vertebral body) and do not score lesions in the posterior elements of the spine. Both methods assess MRI sagittal slices of the spine divided into two halves, a cervico-thoracic and a thoraco-lumbar portion, and also use the disco-vertebral unit (DVU) as the primary anatomical region for scoring inflammation. This is defined as the region between two imaginary lines drawn through the middle of adjacent vertebrae and including adjacent vertebral end-plates with the intervening disc. The SPondyloArthritis Research Consortium of Canada (SPARCC) MRI spinal inflammation index takes advantage of the ability of MRI to visualize lesions in all three dimensions [19]. In particular, each DVU is divided into quadrants and the presence/absence of bone edema in each quadrant

scored dichotomously in three consecutive sagittal slices so that the magnitude of the lesion can be assessed in the sagittal, antero-posterior and coronal planes. The developers of this method have proposed that scoring be limited to a maximum of six of the most severely affected levels on the basis that the mean number of affected DVU per patient in a prior study was 3.2. The second approach has been developed by investigators in Berlin and scores inflammatory lesions in all 23 DVU adjacent to opposing vertebral end-plates, each DVU being scored on a single sagittal slice of the spine [16,20]. Scores are based on an estimate of the area of the DVU involved in inflammation. Since inflammatory lesions observed on MRI are often asymmetrical, they are, therefore, more precisely quantified with a method that systematically assesses lesions in several dimensions. In addition, evaluation of abnormalities in all 23 vertebral segments necessitates the scoring of regions subject to artefact and/or limited anatomical resolution. This may limit responsiveness [21]. A recent validation exercise has been conducted under the auspices of the Outcomes MEasures in Rheumatoid Clinical Trials (OMERACT) organization, using multiple readers to determine which method performs best with respect to feasibility, reliability and ability to discriminate between active and control therapies [22]. Both scoring methods demonstrate high responsiveness after administration of anti-TNF- α therapies, although the SPARCC method is consistently more reproducible, particularly when evaluated by neutral observers with limited experience in either method. In addition, the SPARCC method uses a greater part of the scoring range. This may be an advantage in the evaluation of therapies that are less potent anti-inflammatory agents than anti-TNF- α therapies.

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Several approaches to the scoring of disease activity in the sacroiliac joints have been proposed that can be generally categorized as being primarily based on either a global scheme that focuses on the single most severely affected semicoronal image, or on a more detailed method that scores several consecutive semicoronal images that depict the synovial portion of the sacroiliac joint (the SPARCC scoring method) [23,24]. In the latter method, each sacroiliac joint is divided into

quadrants and the presence of marrow edema in each quadrant is scored on a dichotomous basis. Scoring lesions in consecutive semicoronal slices again permits assessment of individual lesions in 3D [24]. A multireader exercise conducted under the auspices of OMERACT showed that agreement between readers and sensitivity to change was somewhat better for the more detailed SPARCC scoring method [25]. The high discriminatory capacity of this method was recently confirmed in a randomized, placebo-controlled trial of adalimumab in AS, where a significant effect of active treatment on sacroiliac joint inflammation visible on MRI was first demonstrated, despite the presence of frequent chronic changes in patients with long-standing disease [26].

As already alluded to, MRI has not proven to be superior to plain imaging in the assessment of structural changes in the spine and sacroiliac joints. The primary advance in plain imaging has been the development of a scoring tool to quantify structural damage in the spine. The modified Stoke AS Spinal Score (mSASSS) rates sclerosis, squaring, erosions, syndesmophytes and ankylosis in the anterior vertebral corners of the cervical and lumbar spine [27]. In a longitudinal study of 20 patients examined over four time points in known chronological order, it was shown that structural damage progression could be reliably assessed only from 2 years onwards, and that almost 50% of patients demonstrated radiographic progression that was greater than 0, although median progression after 2 years was only 1.5 mSASSS units, barely equivalent to a single syndesmophyte [28]. Although this scoring method has now been adopted by OMERACT [29] and used in clinical trials [30], it has several limitations of both a conceptual and metrological nature. It combines damage (erosions) and reparation (sclerosis, syndesmophytes and

ankylosis) concepts, even though the two may be unrelated. This may be of relevance to the assessment of therapeutics that have a primary impact on only one of the two processes. The inherently slow rate of progression results in a low signal-to-noise ratio and this compromises clinical trial evaluation necessitating a minimum 2-year period of study [31]. Although it has been suggested that 2 years may be sufficient to assess structural damage progression, change in progression is less evident when films are read blinded to chronology, so that longer periods of evaluation are desirable [32]. Furthermore, the reliability of assessment of progression scores has yet to be assessed when films are read blinded to chronology. Assessment of disease modification will therefore continue to be a formidable challenge in the field and reappraisal of approaches to assessment of structural damage is warranted.

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It is now undeniable that MRI constitutes a major advance in the diagnostic evaluation of patients with AS and in the assessment of novel therapeutics. Key questions remain for clinician and researchers and will be primarily addressed in systematic longitudinal studies. In particular, what is the diagnostic sensitivity and prognostic significance of lesions observed in the spine and sacroiliac joints? This will determine if MRI can be used as a surrogate for structural damage outcomes. Nevertheless, MRI should now, at the very least, be part of the diagnostic toolkit and it behoves the clinician to become familiar with the approach to evaluation and common features observed in AS.

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