The use of MRI in early RA

Introduction

MRI is becoming an integral part of the rheumatologist’s toolkit, both for assisting in the diagnosis of RA and for monitoring disease progression and the response to therapy. However, as the case for all imaging and indeed investigations in general, it has its limitations and there are pitfalls for the unwary. While many rheumatologists are happy to liaise with radiologists and seek their advice for the interpretation of scan results, there is now much information regarding the clinical significance of MRI findings that is primarily in the rheumatology literature (with which many radiologists are unfamiliar), making it increasingly important for clinicians to have at least a summary knowledge of these advances. New developments in imaging have entered the clinical arena at just the same time as advances in therapeutics and the strategy for effectively managing RA is changing rapidly, with the emphasis now on the very early use of disease-suppressing therapy with agents including biological DMARDs (bDMARDs), aiming to completely suppress erosions and joint damage. The expense and occasional risk associated with this strategy means that diagnostic accuracy is even more important than previously, as is tailoring high-cost therapies to those most at risk for aggressive disease. MRI can be most helpful as an addition to conventional radiography, to assist the clinician in achieving optimal management for the individual patient.

What are the changes seen within the rheumatoid joint on MRI?

MRI scanning generates an image of the joint by detecting protons that have been exposed to an extremely powerful magnetic field, applied in pulses. This affects their spin in certain ways that are recorded as variations in signal on different MR sequences [1]. Spatial information is obtained using this signal and transformed by computing software into a 3D image. The great advantage of MRI over conventional radiography is that it allows depiction of inflammation as well as structural damage. Inflamed tissue, including synovium and tenosynovium, contains an infiltrate of cells as well as newly formed blood vessels. There are more mobile H⁺ ions (in the form of H₂O) in these cells and vessels than in normal tissues, influencing the MRI signal. For example, synovitis appears on T₁-weighted (T₁w) images as thickened membrane (showing its anatomical features), which is high signal on T₂-weighted images (T₂w), indicating its high H⁺ content, and enhances on T₁w post-contrast images, revealing the fact that it is highly vascularized. Similar changes can be seen in the tenosynovium and signal changes within the substance of tendons can indicate whether they are normal, swollen and inflamed, or split and attenuated, which may herald rupture [2].

Bone pathology is also extremely well seen using MRI. An erosion appears as a break in cortical bone, with an underlying region where inflammatory tissue replaces the normal fat-containing trabecular bone (intermediate ‘grey’ signal replacing the normal ‘white’ high signal of fat on T₁w images). If erosions contain inflamed synovial membrane, they will enhance post-contrast. Bone marrow oedema is a feature that was unrecognized prior to the development of MRI and can only be seen using this modality. It is characterized by increased signal on fat-suppressed T₁w images indicating the abnormal presence of H⁺ ions (as H₂O) within trabecular bone. Lastly, cartilage can be imaged using MRI and thinning can be detected at the large joints, as well as changes in water content, indicating pathological change [1].

MRI scanning to make a diagnosis of RA

There are two main ways in which MRI can assist the clinician in this respect. First, the presence of subclinical synovitis can be confirmed, allowing for example, the patient with non-specific hand and/or wrist pain to be differentiated from the patient with true inflammatory synovitis. The literature is fairly sparse regarding this application, but Brown et al. [3] have recently shown that MRI synovitis can be detected in almost a third of RA patients who are in apparent clinical remission with no swollen or tender joints. Studies comparing normal individuals with RA patients have shown that while minor synovial enhancement may be seen in normal wrists, significant thickening and inflammation of the synovial membrane is confined to those with inflammatory arthritis [4]. Where there is a clinical diagnosis of RA, >90% have MRI evidence of synovitis and 70–80% have tenosynovitis [5].

The second way by which MRI can assist in making a diagnosis of RA is by revealing erosions that comprise one of the seven ACR 1987 diagnostic criteria [6]. There is overwhelming evidence that MRI scanning can detect erosions long before plain radiography [7]. In one study, they were demonstrated at the wrist in 45% of the patients at the time of diagnosis, compared with X-ray erosions that were present in only 25% [5]. They occur even earlier at the feet and have been detected 9 weeks from symptom onset [8]. The superiority of MRI over radiography in this instance is primarily due to its being a 3D imaging modality. Many X-ray erosions are missed simply because they are not profiled. An early concern that MRI erosions were ‘not real’ has now largely been debunked by comparisons with the 3D radiographic technique of CT scanning. Almost 90% of the lesions at the wrist and the MCP joints can be confirmed by both modalities [9, 10]. Having said this, it must be acknowledged that false positives can occur as many early MRI erosions are small and occur in regions where there may be irregular bony contours or deceptive ligamentous attachments. There are also pitfalls due to imaging artefacts, such as the phenomenon of ‘partial voluming’ that occurs when two tissues of very different signal characteristics (such as inflamed synovial membrane and bone) abut one another [11]. Therefore, making a diagnosis of RA on the basis of one or two MRI erosions is risky but can be ‘firmed up’ (i) if erosions are clearly seen in two planes and (ii) if they occur with active synovitis and/or bone oedema.

It has been suggested that MRI erosions should be added to the diagnostic criteria for RA [12]. In a recent study, a cohort of Scandinavian patients with unclassified polyarthritis were reclassified as RA or non-RA on the basis of findings from MRI scans of the hands and whole-body scintigraphy [13]. This classification was found to be correct 2 yrs later in 39 of 41 individuals when criteria were reapplied. Despite these encouraging results, it is true that there are no disease-specific MRI features of RA as synovitis, tenosynovitis, bone oedema and bone erosion have all been described in seronegative SpAs as well as SLE [13].
Can MRI scans help identify the RA patient at risk for aggressive disease?

There is now good evidence that MRI scans of the wrist can be used to help identify those patients at high risk for aggressive, erosive disease. First, the finding of MRI erosions indicates that joint damage has already begun, and serial scans can reveal the rate of erosive progression [14]. Second, bone oedema is a key predictor of erosive joint damage and functional outcome [14, 15]. Studies of bone histology from joint replacement specimens, matched with pre-surgical MRI scans, have revealed that regions of MRI bone oedema contain an inflammatory cellular infiltrate [16, 17]. These cells are in close apposition to activated osteoclasts sitting in resorption lacunae on trabecular bone (Dalbeth et al., submitted), implying cross-talk and a possible mechanism to explain the development of erosions. This is consistent with MRI evidence indicating that bone oedema is a pre-erosive change, increasing the risk of bone erosion more than 6-fold after 6 yrs according to one study [14]. A recent Norwegian study of 84 early RA patients, scanned prior to initiating therapy, revealed MRI bone oedema to be the strongest predictor of erosion progression over 1 yr [18]. The largest and most recent data set comes from the CIMESTRA study [19], which that incorporated baseline MRI scans into the protocol. This showed that bone oedema at the hand and wrist was the strongest independent predictor of radiographic progression at the hands and feet after 2 yrs, explaining 41% of the variation in progression of the total Sharp score.

To the rheumatologist, synovitis may appear to be the most important indicator of aggressive disease. In fact, the MRI evidence disputes this and data from the CIMESTRA study failed to show MRI synovitis to be an independent predictor of erosions at all. However, a number of groups have shown that a high score for all MRI disease activity and damage features combined (including synovitis, bone oedema, tenosynovitis and erosions) is the best indicator of poor prognosis [7, 20]. From the opposite perspective, a low combined score has been shown to be highly predictive of a good outcome [20]. Figure 1 shows an MRI scan of the wrist from a 33-yr-old woman with a 2-month history of wrist pain. At the time of the scan she was seronegative for RF but subsequently developed aggressive RA. The MRI scan showed widespread bone oedema plus synovitis, tenosynovitis and very early erosions.

Can MRI scans be used to monitor response to therapy?

A number of groups have investigated MRI features as ‘imaging biomarkers’ for measuring therapeutic responses. Changes in MRI synovitis were first assessed at the knee by Østergaard et al. [21] who demonstrated a 50% reduction in synovial membrane and effusion volumes during the week after IA steroid injection. When studies of bDMARDs are considered, MRI outcomes that can detect change over a short period of time are particularly attractive. Most of the data remain preliminary, and results of large clinical trials using MRI outcomes are awaited. Zikou et al. [22] evaluated the volume of synovial pannus in 13 patients pre- and post-adalimumab and found this to fall by 86% after 1 yr, correlating with other inflammatory markers. However, an investigator-initiated study of anakinra in RA failed to show concordance between clinical and MRI measures of synovitis, with persistence of MRI features despite improvements in tender and swollen joint counts [23]. Haavardsholm et al. [24] recently showed a combined MRI inflammation score incorporating...
synovitis, tenosynovitis and bone oedema to be the most sensitive measure of response to anti-TNF agents.

Two major issues have caused reluctance on the part of pharmaceutical companies to use MRI outcome measures in large clinical trials. The first is cost and the second has been establishing reproducibility for scoring MRI change. The development of the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) system and its accompanying reference atlas [25] has helped deal with the latter obstacle and most studies now show good to excellent interobserver reliability for MRI parameters, at levels equivalent to radiographic damage scores [18]. For the clinician, the cost of MRI scans remains a barrier but when extremely high-cost therapies are contemplated, the $500–600 required for a scan of the dominant wrist pales in comparison. Extremity MRI may be an answer as far as reducing cost is concerned but it is only approximately half as sensitive as high-field (1.5 T) MRI for detecting bone oedema [26] and therefore may not be so useful for prognostication. Advances are continuing at the high-field end and 3 T MRI is now coming into clinical practice. This may allow imaging of cartilage at the small joints of the hands and could provide additional power for detecting and monitoring very early joint damage.

Summary

To conclude, MRI scanning offers the rheumatologist a chance to visualize joint inflammation as well as damage. This information can be used for diagnosis, prognostication and monitoring responses to therapy. The presence of MRI erosions and in particular bone oedema should be regarded as red flags for potential bone damage in the future. Active intervention with conventional DMARDs and particularly bDMARDs, with their potential bone damage in the future. Active intervention with conventional DMARDs and particularly bDMARDs, with their potential bone oedema should be regarded as red flags for detection and monitoring very early joint damage.

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