Editorial

Lessons from Magnetic Resonance Imaging Studies in Rheumatoid Arthritis

In 1969, Dr. Raymond Damadian recognized the potential of nuclear magnetic resonance (NMR) in medical research. NMR is the phenomenon of atomic nuclei emitting radio waves at predictable frequencies, when exposed to a powerful magnetic field. The technique had previously been used in the military to probe the composition of various substances. Damadian and colleagues invested much time and effort developing this technology. In 1972, he demonstrated the ability of NMR to differentiate cancerous and noncancerous tissues in rats[1]. Five further years of development led to the first human magnetic resonance image (MRI) scan on July 3, 1977. Thirty years hence, MRI has firmly established its place in modern medical practice. In rheumatology it has revolutionized practice in many disease areas, but what have we learned from MRI in rheumatoid arthritis (RA)? It is the only imaging tool that has the ability to assess simultaneously all relevant structures in inflammatory joint disease, i.e., the synovium, cartilage, bone, ligaments, tendons, and tendon sheaths and the presence or absence of synovial fluid. The 3 key lesions to rheumatologists studying RA are synovitis, bone edema, and erosion, which are now clearly defined by OMERACT (Outcome Measures in RA Clinical Trials)[2].

Table 1. OMERACT definitions of RA lesions detected by MRI.

Synovitis	An area in the synovial compartment that shows above-normal post-gadolinium enhancement of a thickness greater than the normal synovium
Bone edema	A lesion within the trabecular bone with ill-defined margins and signal characteristics consistent with increased water content
Erosions	A sharply marginated bone lesion, with correct juxtaarticular localization and typical signal characteristics, visible in 2 planes with a cortical break in at least 1 plane

It is the ability to accurately image the inflammatory lesions in RA that has generated the greatest sea change in rheumatology practice. Traditionally, damage assessed by plain radiographs determined therapy initiation and change. The concept of early intervention prior to damage by targeting inflammation was embraced in the early 1990s[3]. The concept was based on surrogate markers of synovial inflammation, e.g., measures of acute-phase response, predicting poor prognosis whatever the chosen outcome[4]. Although it was clearly accepted by most rheumatologists that systemic inflammation, measured by C-reactive protein or erythrocyte sedimentation rate, correlated with development of erosions in RA, little was really understood about the pathological process taking place at joint level.

MRI studies have added significantly to our understanding here. Early studies confirmed that imaging findings were genuine by demonstrating a good correlation of gadolinium-enhanced MRI-detected synovitis with macroscopic arthroscopy and histological findings[5]. More important clinically, however, gadolinium-enhanced MRI was found to be significantly more sensitive than clinical examination in detecting synovitis. This is apparent in early[6] and established disease, even in patients with low disease activity states[7]. This has raised the question as to the ability of clinicians to accurately detect synovial inflammation through clinical examination alone, and may explain the discordance found in some studies where damage has been observed to progress in patients in remission[8]. This observation is further supported when individual joints are studied over time; the severity of synovial inflammation correlates with subsequent local bone erosion, and where synovitis is not present, joints do not erode[9]. Moreover, the intensity of synovial inflammation correlates with the presence of bone edema[9]. Bone edema is the reversible MRI precursor of the bone erosion[10].

If we defer temporarily to previous damage-driven treatment strategies, MRI has demonstrated patient damage earlier and in greater numbers than previously thought. MRI detects significantly more bone erosions than conventional radiographs, e.g., 45% versus 15% in wrists of patients with early RA[11], and on average, MRI lesions precede radiographic lesions by 2 years[12]. Traditionally, therefore,

See Etanercept reduces synovitis as measured by MRI in active RA after 6 weeks, *page 394*

patients' accrued damage remained undetected and unknown to the clinician because the tool used to measure this was insufficiently sensitive. It would appear, therefore, that in RA, rheumatologists have an assessment tool that accurately assesses the primary site of inflammation. Studies would also support the direct relationship of synovial inflammation with joint damage.

In this issue of *The Journal*, Dr. Lisbona and colleagues report the effect of etanercept on MRI synovial and bone lesions in a study of 22 patients over a 6-week period[13]. A significant improvement in synovitis and a reduction in bone edema in the metacarpophalangeal joints are observed with etanercept therapy at the 6-week endpoint. The results concur with the early dramatic clinical improvement seen in some patients who start biologics. It is most likely that this degree of potency and ability to suppress synovitis so rapidly explains the radiographic outcomes observed in studies with etanercept and other anti-tumor necrosis factor-α (TNF-α) agents. This is not the first study to describe the effect of therapy on MRI outcomes in RA, but it adds to our knowledge base and further informs the research agenda. Other studies have looked at corticosteroids[9], infliximab[14], adalimumab[15], and anakinra[16]. Each study varies in design, particularly with regard to imaging intervals and disease duration, and thus not allowing direct comparison of results. Intraarticular corticosteroids appear to have a potent, if temporary, effect on the synovium[9], whereas infliximab demonstrated a significant influence on bone edema at only 4 weeks, but not on synovium until 12 weeks of therapy[14]. Moreover, the suppression of inflammation persisted for the duration of therapy and beyond. Adalimumab has been shown to reduce synovial inflammation in patients with refractory RA after 1 year of therapy[15]. Anakinra given to patients with active RA despite methotrexate failed to significantly reduce MRI synovitis after 36 weeks of treatment[16]. Whereas these observations help explain the efficacy of these agents, it is with interest we observe the structural changes in the joint in response to therapy and at different stages of disease. It is reasonable to expect the inflamed synovium, a physical structure in its own right, to take time to remodel and recover. Meanwhile, bone edema reflecting increased vascularity, cellular permeability, and cellularity may be more sensitive to early change. This in turn may be related to how long the patient has had inflammation, hence the difference observed between the Lisbona and Quinn[14] reports. The explanation may be found in the different anti-TNF-α agents used or in a relationship to the pharmacokinetics and pharmacodynamics. Wakefield, *et al* have sequentially followed synovial inflammation in patients with RA treated with infliximab using musculoskeletal ultrasound[17]. A significant time window may be required for synovial remodeling despite early volume reductions. The time to full synovial recovery or healing may indicate a timepoint at which therapy can be stepped back, as observed with prolonged clinical response following infliximab withdrawal[14,18]. Further therapeutic studies are required to elucidate the relationships between different biologic and nonbiologic treatments and MRI outcomes. Equally, there is a great deal more to learn about the natural history of joint lesions in RA and diseases such as osteoarthritis, psoriatic arthritis, and other arthritides.

The rheumatology community has benefited significantly from studies utilizing MRI outcomes in patients with RA. However, there are limitations, especially regarding day-to-day clinical practice. Whole-body MRI is expensive, and access is varied and limited to a single joint area; imaging is time-consuming and unsuitable for certain types of patients who may experience claustrophobia, or who have a pacemaker *in situ*, etc. That most studies to date have been performed by groups with a special interest and significant experience in this form of imaging is an additional issue. An answer to some problems with whole-body MRI is the proliferation of extremity MRI hardware. Validation and reliability studies are increasing in number[19,20], and longitudinal studies assessing sensitivity to change are continuing. This technology may increase the clinical utility and availability of MRI to rheumatologists and subsequently establish a place in daily practice. Needless to say, this technology may conceivably become available to all rheumatologists on a daily basis. However, MRI-based study findings can be embraced by all in their practice, with the emphasis on aggressive suppression of inflammation optimizing patient and bone outcomes.

MARK QUINN, MD, MRCP, MBChB,
Lead Clinician,
Consultant and Honorary Senior Lecturer in Rheumatology,
York Hospitals NHS Foundation Trust,
and Hull York Medical School,
Wigginton Road, York,
North Yorkshire, UK YO318HE

Address reprint requests to Dr. Quinn. E-mail: mark.quinn@york.nhs.uk

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