



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 non-cancerous tissues in rats¹. 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 1990s³. The concept was based on surrogate markers of synovial inflammation, e.g., measures of acute-phase response, predicting poor prognosis whatever the chosen outcome⁴. 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 findings⁵. More important clinically, however, gadolinium-enhanced MRI was found to be significantly more sensitive than clinical examination in detecting synovitis. This is apparent in early⁶ and established disease, even in patients with low disease activity states⁷. 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 remission⁸. 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 erode⁹. Moreover, the intensity of synovial inflammation correlates with the presence of bone edema⁹. Bone edema is the reversible MRI precursor of the bone erosion¹⁰.

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 RA¹¹, and on average, MRI lesions precede radiographic lesions by 2 years¹². 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 period¹³. 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 corticosteroids⁹, infliximab¹⁴, adalimumab¹⁵, and anakinra¹⁶. 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 synovium⁹, whereas infliximab demonstrated a significant influence on bone edema at only 4 weeks, but not on synovium until 12 weeks of therapy¹⁴. 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 therapy¹⁵. Anakinra given to patients with active RA despite methotrexate failed to significantly reduce MRI synovitis after 36 weeks of treatment¹⁶. 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 Quinn¹⁴ 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 ultrasound¹⁷. 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

REFERENCES

1. Damadian R. Tumor detection by nuclear magnetic resonance. *Science* 1971;171:1151-3.
2. Ostergaard M, Peterfy C, Conaghan P, et al. OMERACT rheumatoid arthritis magnetic resonance imaging studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT-RA-MRI scoring system. *J Rheumatol* 2003;30:64-71.
3. Emery P. The optimal management of early rheumatoid disease: the key to preventing disability. *Br J Rheumatol* 1994;33:765-8.
4. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? *Rheumatology Oxford* 2001;40:1211-20.
5. Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, et al. Quantification of synovitis by MRI: correlation between dynamic and static gadolinium-enhanced MRI and microscopic and macroscopic signs of synovial inflammation. *Magn Reson Imaging* 1998;16:743-54.
6. Huang J, Stewart N, Crabbe J, et al. A 1 year follow up study of

- dynamic magnetic resonance imaging in early rheumatoid arthritis reveals synovitis to be increased in shared epitope positive patients and predicts erosions at 1 year. *Rheumatology Oxford* 2000; 39:407-16.
7. Brown AK, Quinn MA, Karim Z, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: Evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006;54:3761-73.
 8. Molenaar ET, Voskuyl AE, Dinant HJ, et al. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004;50:36-42
 9. Conaghan PG, O'Connor P, McGonagle D, et al. Elucidation of the relationship between synovitis and bone damage: A randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. *Arthritis Rheum* 2003;48:64-71.
 10. McQueen F, Benton N, Perry D, et al. Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;48:1814-27.
 11. McQueen F, Stewart N, Crabbe J, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. *Ann Rheum Dis* 1998;57:350-6.
 12. Ostergaard M, Hansen M, Stoltenberg M, et al. New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. *Arthritis Rheum* 2003;48:2128-31.
 13. Lisbona MP, Maymo J, Perich J, Almirall M, Pérez-García C, Carbonell J. Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. *J Rheumatol* 2008;35:394-7.
 14. Quinn MA, Conaghan PG, Greenstein A, et al. Very early infliximab in addition to methotrexate in early poor prognosis rheumatoid arthritis reduces MRI synovitis and damage with sustained benefit after infliximab withdrawal; results from a double blind placebo-controlled trial. *Arthritis Rheum* 2005;52:27-35.
 15. Ostergaard M, Duer A, Nielsen H, et al. Magnetic resonance imaging for accelerated assessment of drug effect and prediction of subsequent radiographic progression in rheumatoid arthritis: a study of patients receiving combined anakinra and methotrexate treatment. *Ann Rheum Dis* 2005;64:1503-6.
 16. Zikou AK, Argyropoulou MI, Voulgari PV, et al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with adalimumab. *J Rheumatol* 2006;33:219-23.
 17. Wakefield RJ, Freeston JE, Hensor EM, et al. Delay in imaging versus clinical response: A rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. *Arthritis Rheum* 2007;57:1564-7.
 18. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2007;56:2129-34.
 19. Ejbjerg BJ, Narvestad E, Jacobsen S, et al. Optimised, low cost, low field dedicated extremity MRI is highly specific and sensitive for synovitis and bone erosions in rheumatoid arthritis wrist and finger joints: comparison with conventional high field MRI and radiography. *Ann Rheum Dis* 2005;64:1280-7.
 20. Schirmer C, Scheel AK, Althoff CE, et al. Diagnostic quality and scoring of synovitis, tenosynovitis and erosions in low-field MRI of patients with rheumatoid arthritis: a comparison with conventional MRI. *Ann Rheum Dis* 2007;66:522-9.