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Magnetic resonance imaging in rheumatoid arthritis: current status and future directions.

C G Peterfy

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Magnetic Resonance Imaging in Rheumatoid Arthritis: Current Status and Future Directions

CHARLES G. PETERFY

ABSTRACT. The performance of alternative imaging endpoints in clinical trials can be compared in terms of validity, rate of change, measurement precision, and convenience and cost. With respect to technical performance, magnetic resonance imaging (MRI) appears to show greater sensitivity than radiography for detecting bone abnormalities in rheumatoid arthritis (RA). In addition to monitoring changes in the bones, cartilage, and synovium, MRI can directly visualize the full spectrum of tendon pathology, and has been shown to identify tendonitis and tendon rupture with greater accuracy than clinical examination. MRI is currently regarded to be the most sensitive imaging technique for identifying trauma, infection, ischemia, and primary and secondary neoplasia of bone. Several studies have also shown MRI to be highly sensitive for detecting what appear to be bone erosions in the hands and wrists of patients with RA. MRI shows remarkable promise as a tool for identifying and monitoring structural damage in the joints of patients with RA. MRI appears to be able to identify bone erosions with greater sensitivity than radiography, and to disclose edema-like changes in the marrow, which may precede actual erosion formation. As new therapies with structure modifying capabilities enter the clinic, the ability to identify patients appropriate for those therapies and then to monitor the effectiveness and safety of treatment become increasingly important. (J Rheumatol 2001;28:1134–42)

THE INNOVATOR'S DILEMMA

While the roles played by imaging in clinical trials are essentially the same as those in clinical practice, i.e., diagnosing disease, assessing its severity and prognosis, monitoring disease progression and treatment response, and evaluating complications associated with the disease or its therapy, the priorities differ slightly between these 2 contexts, and it is in the former that the demand for imaging endpoints as surrogate outcomes first arises. Indeed, in the absence of structure modifying therapies, clinical practice has little need for tools to identify patients who would benefit from such therapy or to monitor whether the therapy is working. However, validated and precise methods for these tasks are essential to establishing the efficacy and safety of putative new therapies. This is the fundamental "catch-22" that drug development currently operates under. And so, it is during clinical testing of new therapies that imaging tools that ultimately will be used in clinical practice first get developed, and therefore the priorities of clinical trials that shape the early evolution of these tools.

PERFORMANCE METRICS ALIGNED WITH THE PRIORITIES OF CLINICAL TRIALS

The performance of alternative imaging endpoints in clinical trials can be compared in terms of validity, rate of change, measurement precision, and convenience and cost[1]. Validity must be considered in both biological and technical terms. Not only must the morphological, compositional, or physiological feature being used as a surrogate endpoint be pathophysiologically linked to the true clinical outcome of interest, but the technique used to measure the feature must be accurate and precise. The relative importance of each criterion depends on the objectives of the study. Pivotal phase III studies upon which a labeling claim may be based are held to a higher validity standard than phase II proof-of-concept or dose selection studies aimed at prioritizing candidate compounds or determining the conditions for subsequent phase III studies.

The rate of change of the imaging feature and the precision with which that change can be measured determines the minimum number of subjects and study duration[2,3]. Subject number and study duration have an enormous impact on the direct costs of clinical testing, as well as the revenue potential of a new drug over the finite lifespan of its patent. Measurement precision is maximized by centralized analysis in which standardized conditions, highly trained readers, and specialized computer programs can be combined. Central analysis is therefore the preferred approach in clinical trials in which image data can be read in batches at fixed points during the study. Clinical practice, on the other hand, demands rapid turnaround and is geared towards individual patients rather than a study population.

Convenience and cost are always important considerations, but they differ substantially between single-site studies and large, multisite clinical trials, which place greater emphasis on availability of imaging technology, simplicity and stability of the imaging protocol, ease of data transfers, and patient tolerance.

C.G. Peterfy, MD, PhD, Chief Medical Officer, Synarc, Inc.
Address reprint requests to Dr. C. Peterfy, Synarc, Inc., Suite 1850, 455 Market Street, San Francisco, CA 94105.
E-mail: charles.peterfy@synarc.com

FUNDAMENTAL ADVANTAGES OF MRI OVER RADIOGRAPHY

Up to the present day, radiography has been the mainstay of imaging evaluation of rheumatoid arthritis (RA). The validity of radiography, however, is limited to bone erosion, cartilage loss (indirectly through joint space narrowing), and joint malalignment, since radiography cannot visualize synovium, joint effusion, articular cartilage, bone marrow, or ligaments and tendons directly. Moreover, radiographic delineation of bone erosions, trabecular patterns, and joint spaces is confounded by projectional superimposition, which can obscure overlapping structures. Nevertheless, with carefully standardized image acquisition and centralized analysis by trained, validated readers and specialized digital display and analysis workstations (Figure 1) radiography can discriminate progression within 6 to 12 months, depending on the study population, the number of subjects examined, and whether the study is placebo or comparitor controlled. Radiography is widely available, easy to perform, well tolerated, and inexpensive. However, the films are difficult to store and distribute. Digitization and digital acquisition technology offers a solution to these problems, and is currently the trend in clinical radiology departments around the world.

MRI offers a number of advantages over conventional radiography for evaluating structural damage to the joints in RA[4-6]. These include tomographic viewing perspective, broad tissue contrast, and digital format. Tomography provides cross sectional images in contrast to 2 dimensional projections of the anatomy and therefore obviates the problem of superimposition. The ability to visualize bone marrow, synovium, articular cartilage, ligaments, and tendons extends the scope of structural evaluations and allows the joint to be examined as a whole organ. Digital image format enables web based data transfers, improves image archival recovery and display, and facilitates computer aided analysis. The question is: how does one leverage these attributes to improve patient selection and to monitor disease progression and therapeutic response in clinical trials along the performance criteria discussed above?

SPECIALIZED MRI SYSTEMS

A number of new MRI systems have recently been developed that differ radically from the traditional whole-body design of conventional MRI, and that offer intriguing alternatives for imaging patients with arthritis[7]. These systems come in various sizes and field strengths (Figure 2), and offer a variety of potential advantages over conventional MRI, including significantly lower cost (potentially less than one-quarter that of conventional MRI); greater patient comfort and safety, including fewer biohazards associated with aneurysm clips, pacemakers, etc.; and greater convenience and versatility, including the possibility of office based imaging. While the demand for such technology in clinical practice is currently low, this may increase as new structure modifying therapies enter the market.

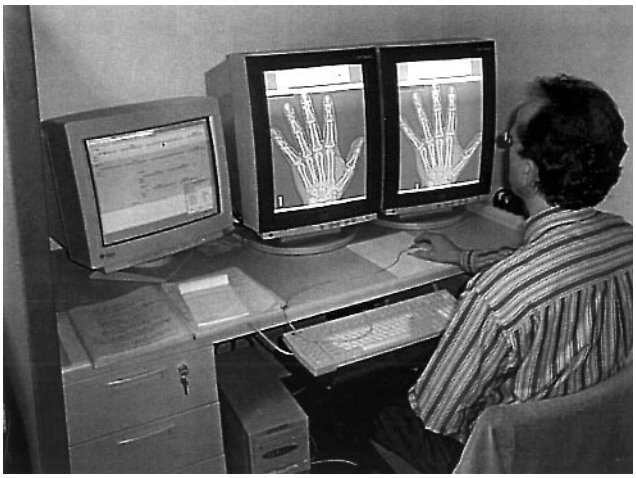

Figure 1. Digital radiographic reading station. Serially acquired digitized radiographs are viewed side by side following edge enhancement and magnification. Reading results are registered on an electronic score sheet (left screen) and automatically stored in a database.

PROMISING MRI ENDPOINTS

Of the numerous possible MRI endpoints (Table 1), several show promise for clinical trials. The following discussion reviews the current status of these endpoints and indicates where future advances may be expected.

Bone erosions and edema-like lesions. MRI is currently regarded to be the most sensitive imaging technique for identifying trauma, infection, ischemia, and primary and secondary neoplasia of bone. Several studies have also shown MRI to be highly sensitive for detecting what appear to be bone erosions in the hands and wrists of patients with RA[8-16] (Figure 3). The key question is, are bone defects and erosions seen with MRI the same as those seen with radiography? While direct pathological verification of this is currently lacking, there is considerable face and construct validity to this assertion. Although direct experience with MRI in RA is somewhat limited, experience with MRI in other musculoskeletal conditions is extensive and attests that the appearance of defects in bone is highly conserved[17]. Erosions in metacarpophalangeal and proximal interphalangeal joints look and behave the same as those in carpal bones. There is less experience with other joints, but erosions in the shoulder appear the same as those in the hands[18]. Without direct pathological correlations, the true discriminative power, i.e., sensitivity and specificity, of MRI for bone erosions is not known. Surprisingly, this has never been established for radiography either. This limitation notwithstanding, the main differential considerations on MRI are intraosseous ganglia and edema-like changes in the bone marrow (Figure 3). Intraosseous ganglia and cysts can

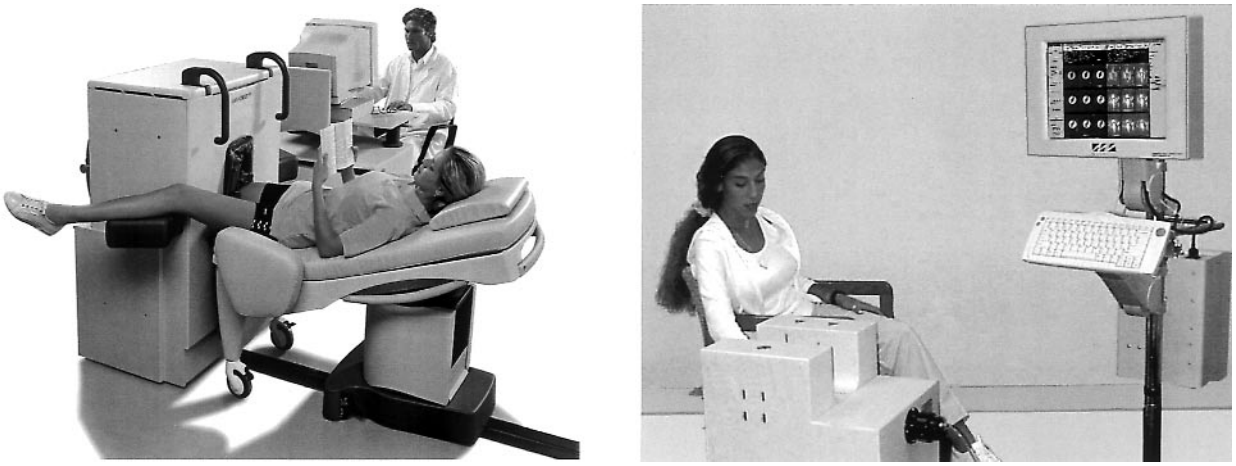

Figure 2. Small MRI systems. Low field strength closed (left: Artoscan, Esaote, Genoa, Italy) and open (MagneVu, San Diego, CA, USA) scanners are small, convenient, and inexpensive.

Table 1. Different MRI endpoints.

Joint Component	Endpoint		
	Morphological	Compositional	Physiological
Bone	Erosion number Erosion score Erosion volume Marrow edema-lesion number Marrow edema-lesion score Marrow edema-lesion volume	Marrow water/fat spectral ratio	Marrow inflammation (Gd-enhancement parameters)
Cartilage	Joint-space width Cartilage score Cartilage volume/thickness	Collagen (T2, magnetization transfer) Proteoglycan ($GdDTPA^{2-}$, Na-MRI) Water (proton density)	Water diffusion coefficient
Synovium/ Tenosynovium/ Effusion	Volume score Volume quantity	Fibrosis (T2) Hemosiderosis (T2*)	Inflammation (Gd-enhancement parameters)
Ligament	Integrity score	Collagen (T2)	Inflammation (Gd-enhancement parameters)
Tendon	Integrity score	Collagen (T2)	Inflammation (Gd-enhancement parameters)

mimic bone erosions seen in RA, but rarely present in numbers greater than one or 2 per wrist[19]. Marrow edema-like lesions, on the other hand, can be quite numerous in RA, but are distinguishable from bone erosions by the appearance of their margins and their internal signal behavior. Erosions typically show well defined, rounded margins and contain only synovial fluid or synovial tissue. They contain no marrow fat or trabecular bone. In contrast, marrow edema-like lesions have the appearance of free water in the medullary cavity, with ill defined margins, and often show evidence of interspersed marrow fat and trabecular bone. These residual marrow constituents generate T1 and T2* effects that can be seen with conventional spin-echo and gradient-echo techniques.

As is the case for bone erosions, the exact pathological identity of edema-like lesions in RA has never been directly verified, and is only surmised from the MRI appearance of other conditions similarly associated with free water in the marrow, such as acute trauma, osteomyelitis, and osteonecrosis[17]. Accordingly, the true sensitivity and specificity

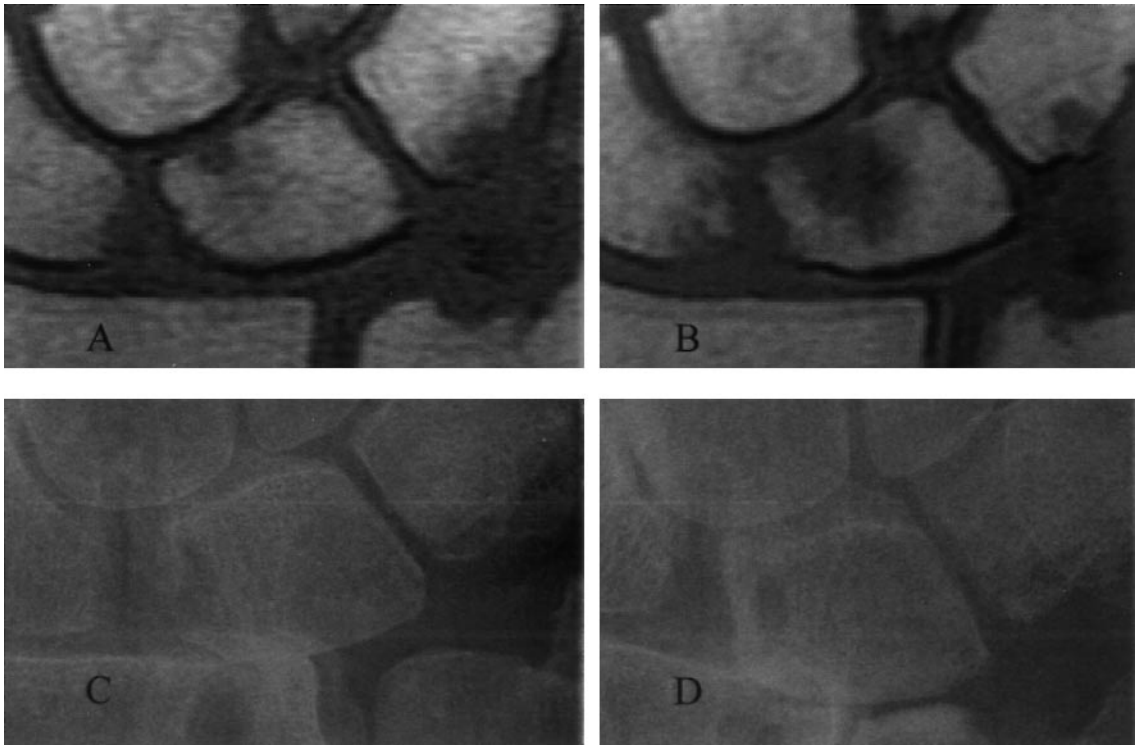

Figure 3. Bone erosion and marrow edema-like changes in RA. T1 weighted spin-echo MRI (A, B) and radiograph (C, D) images at baseline (A, C) and 18 months (B, D). Baseline MRI (A) shows a small, well circumscribed erosion in the lunate along its capitate articular surface. At 18 months (B), the lesion is larger and shows ill defined, feathery margins consistent with peripheral edema or inflammation. Although radiographs show erosion of the lunate along its scaphoid articular surface, which was visible on a different section of the MRI, the radiographs do not depict the erosion of the capitate articular surface of the lunate at baseline or the edema-like changes in the lunate at 18 months.

of MRI for discriminating edema-like changes from bone erosions is not known. Edema-like lesions are found in the same subarticular locations as erosions and often present as a peripheral corona along the perimeter of these erosions. It is speculated that these edema-like changes mark sites of active bone destruction and are precursors of frank erosions[14,20]. In a recent study, McQueen, *et al*[21] found that the presence of marrow edema-like changes at a particular site on baseline MRI carried a 6.5-fold risk of erosion at the same site within one year. It is also speculated but not verified that marrow edema-like changes may be reversible, whereas bone erosions constitute permanent structural damage, with limited capacity for complete repair. Other questions about the natural history of bone abnormalities in RA include whether erosions can arise endosteally or whether they always form by erosion of the cortex.

With respect to technical performance, MRI appears to show greater sensitivity than radiography for detecting bone abnormalities in RA[18]. Marrow edema-like changes are unique to MRI and cannot be seen with radiography. Bone erosions and defects are visible with both techniques, but most studies have reported 2 to 4-fold greater sensitivity with MRI[8-16]. This advantage of MRI is largely attributable to its tomographic viewing perspective, as projectional superimposition on conventional radiography would be expected to obscure small erosions and defects viewed *en face* and those in certain locations, such as the trapezoid, triquetrum, and pisiform bones (Figure 4). Diagnostic accuracy is also affected by MRI field strength, coil performance, and other imaging variables (plane of section, 2D versus 3D acquisition, flip-angle, TR, TE, echo-spacing, phase-encoding direction, spectral suppression, voxel size and orientation, number of sections, number of signal averages, etc.). However, systematic, comprehensive examination of all combinations of these factors would be extremely challenging, and only crude comparisons have been done so far. This extraordinary range of technical influences on image contrast and spatial resolution is the basis for MRI's unparalleled ability to discriminate tissues and delineate anatomy[4,5,22]. However, it also makes it difficult to generalize MRI protocols across even a single disease, such as RA. Which MRI technique is most appropriate for a particular research or clinical question depends as much on circumstances and budget as it does on the objectives of the investigation. This is less a problem with radiography, which is technically more straightforward, and therefore easier to standardize.

The rate of change of bone abnormalities in RA relates to

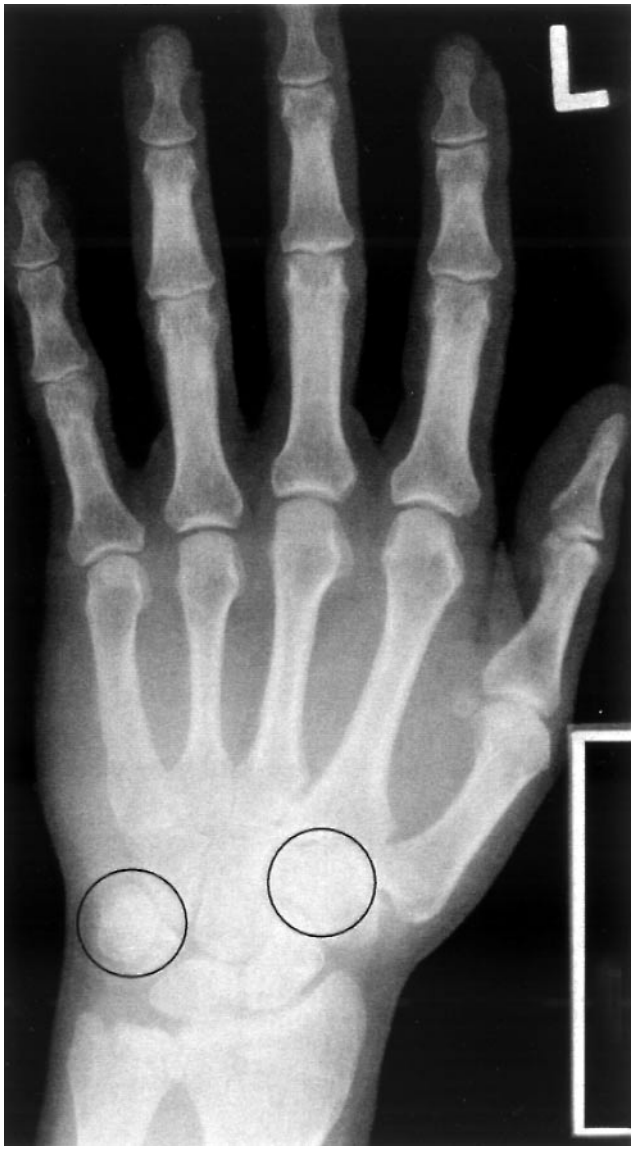

Figure 4. Radiograph of the hand and wrist. Because of the projectional viewing perspective of conventional radiography, overlapping structures are superimposed. This may obscure findings, particularly in regions such as the trapezium and trapezoid, and the triquetrum and pisiform bones (circles).

pathophysiology rather than imaging technology. MRI does not accelerate bone erosion. However, by resolving smaller magnitudes of change, MRI may be able to discriminate smaller differences in progression rates between 2 groups. Accordingly, factors that affect measurement precision are important in clinical trials. These include heterogeneity of the study population, variability associated with image acquisition, and variability attributable to the way the images are analyzed. Variability associated with image acquisition is minimized by doing all the imaging at a single center. In such cases, cutting-edge technologies and highly sophisticated and demanding protocols can sometimes be accommodated. However, in multicenter clinical trials, the imaging protocol used must be applicable to widely available technology. It must also be meticulously standardized, show stable performance across different sites and over time, be easy to perform, and be well tolerated by patients.

Variation associated with image analysis is similarly minimized by centralized reading, in which conditions can be maximally standardized, and specially trained readers combined with sophisticated image analysis software and workstations (Figure 5) to achieve the best results. Centralized reading can therefore support more complex and demanding scoring methods and quantitative analyses than are feasible in clinical practice, which typically demands rapid turnaround and therefore on-site readings or teleradiology services. Readings for clinical trials, in contrast, are usually not needed until all the patients have completed the study, and therefore readings can be done in batches by a remote central facility.

Very few longitudinal studies of bone erosion in RA with MRI have been reported[11,21,23-26]. Most have simply counted the number of erosions or eroded bones in the hands and wrists. A few studies[10,15,27,28] have used scoring methods that take into account the size and distribution of erosions, similar to the methods developed by Sharp[29] and Larsen[30], but no accepted standard method currently exists.

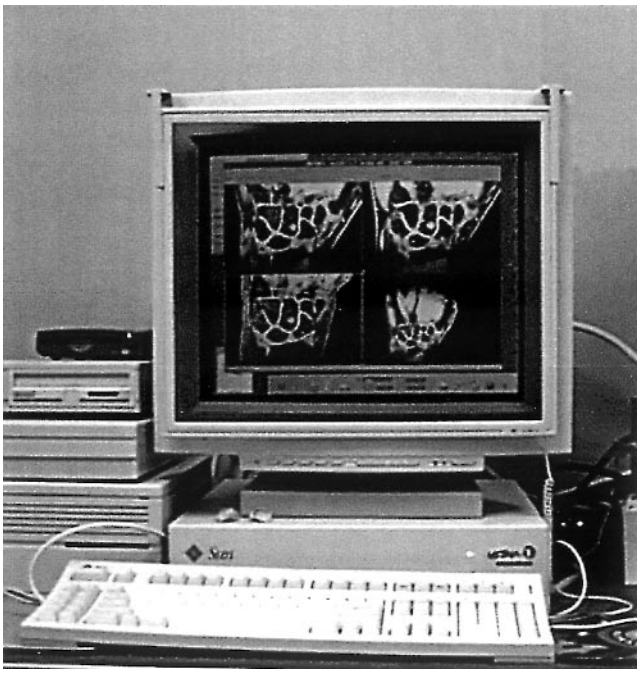

Figure 5. Specialized MRI workstation for serial image reading. Four windows are shown. The 2 top windows and the bottom left window each contain stacked coronal MRI images of the same wrist from one of 3 time points in a study. Images from all 3 time points are viewed together to improve the reader's ability to detect small changes. The images in these windows are magnified to facilitate reading. The bottom right window contains a nonmagnified image from one of the 3 data sets for anatomic reference.

Synovitis and joint effusion. Even more intriguing than its ability to delineate bone abnormalities in RA is MRI's unique capacity to directly visualize pre-erosive synovial changes. These include not only synovial hyperplasia and joint effusion but increased blood flow associated with inflammation. In the absence of fatty infiltration (lipoma arborescens)[31], fibrosis, or iron accumulation (hemosiderosis), thickened synovial tissue can be difficult to differentiate from adjacent synovial fluid using conventional MRI pulse sequences[32]. However, injection of Gd-DTPA, a paramagnetic MRI contrast agent that increases T1 relaxation and therefore signal intensity on T1 weighted images, enhances the hypervascular synovium and allows it to be distinguished from adjacent noninflamed tissues[11,32-39] (Figure 6). Using established image processing techniques, the volume of this enhancing, inflammatory compartment in the wrist or fingers can be quantified[40,41]. However, rapid diffusion of Gd-DTPA from inflamed synovium into adjacent joint fluid quickly blurs the distinction between these 2 compartments, and confounds attempts to accurately quantify one or the other[32-34]. This equilibration of signal intensity between synovium and effusion can be extremely rapid, requiring less than 5 minutes in highly inflamed small joints[33]. Accordingly, accurate quantification of synovial volume may be possible in some cases only within the first few seconds of Gd-DTPA injection, making it difficult to thoroughly cover the joint in one examination. New macromolecular Gd-containing contrast media with lower vascular leak rate may[42] allow better delineation of synovium in the future[43], but with conventional Gd-DTPA this remains a challenge. Since both effusion and synovial hyperplasia are expressions of the same process in RA, however, there may still be value in quantifying the volume of the entire Gd-DTPA-enhancing compartment within a joint on delayed postinjection images once sufficient equilibration has occurred.

A number of studies have found "synovial" volume to correlate with joint swelling and tenderness[11,24,40,41,44], and to be predictive of bone erosion on followup images[11,12,26]. In one study[21], the presence of synovitis at a carpal site on baseline MRI carried a 2.14 odds ratio ($p = 0.003$) for finding erosion in an adjacent bone within one year.

In addition to volume, the rate and magnitude of synovial enhancement on sequential MR images following bolus intravenous injection of Gd-containing contrast material has been shown to correlate with the histological severity of inflammation in the synovium[45-47] and with clinical markers of disease activity[26]. Enhancement of synovium can be accurately quantified by dynamic MRI of single sections through the wrist[48]. However, debated issues remain: where in the joint to image, what plane of section to use, how to deal with the intrinsic heterogeneity of inflammation in the synovial compartment, and which variable of enhancement (enhancement rate, enhancement maximum, relative enhancement over baseline) should be used[26].

Semiquantitative scoring methods have also been developed to grade the severity of synovitis in patients with RA[11,21,26]. These ordinal endpoints are cruder, but technically easier to perform, and they allow examination of the entire joint rather than a single section. Synovial enhancement rate, volume, and semiquantitative score have all been shown to predict bone erosion on followup imaging. Of these variables, however, static synovial score was found to be the most predictive [chi-square = 9.2 (1 df), $p = 0.03$][26].

The rate at which synovial markers change with disease and therapy is not precisely known. However, since Gd-

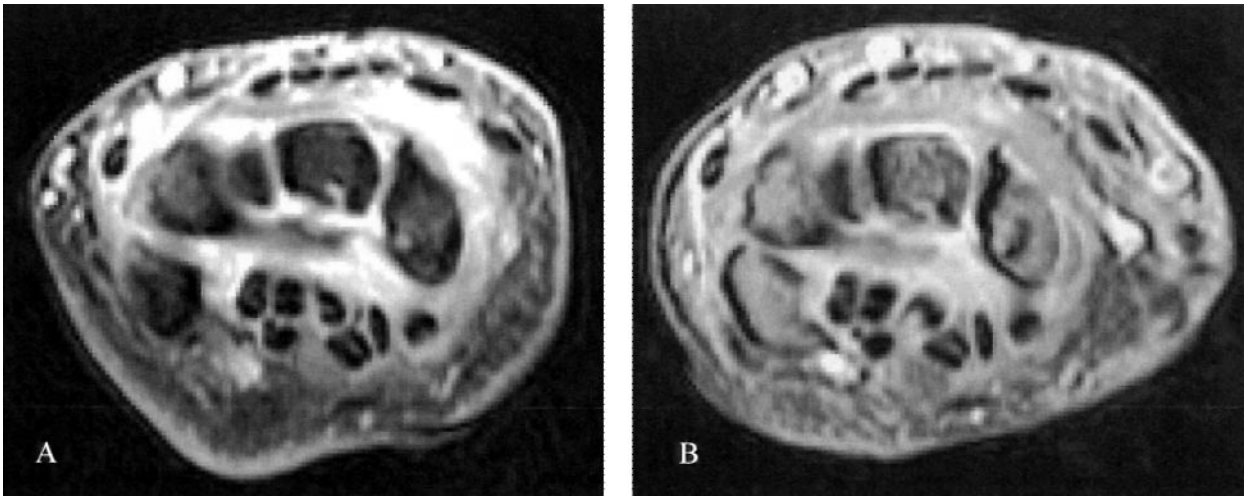

Figure 6. Synovial enhancement with Gd-DTPA. A. Axial 3D gradient echo image of a wrist following iv Gd-DTPA shows extensive enhancing synovitis and distention of the synovial cavity. B. Repeat MRI with Gd-DTPA after 3 months of DMARD therapy shows marked reduction in the amount of enhancing tissue but similar distention of the synovial cavity (note the dorsally displaced extensor tendons).

DTPA enhancement reflects blood flow and tissue perfusion, the responsiveness of these disease process markers is potentially dramatic (Figure 7). In one study[44] synovial volume decreased within only 2 weeks of treatment with low dose methotrexate. Several other studies[11,23-26,49,50] have also shown that synovial volume and synovial enhancement decrease with therapy, but the followup interval in many of these was 6 months or longer.

Articular cartilage. Another unique strength of MRI is its ability to directly visualize the articular cartilage[1,51-53]. Direct imaging of this tissue is more specific than radiographic joint space width, and tomography provides greater anatomical coverage of the joint surface than does projection. A number of morphological and compositional MRI markers of cartilage integrity have been developed[1,54-56], but most of this work derives from the knee. Because articular cartilage in the hand and wrist is extremely thin, high resolution techniques are required to image it. These can be achieved with pulse sequences available on conventional, clinical MRI systems, e.g., fat suppressed, T1 weighted, thin partition 3D gradient-echo[57]. However, this technique does not delineate bone abnormalities and synovial changes as well; additional pulse sequences must therefore be included in the imaging protocol if a complete assessment is desired. These extra sequences add imaging time; consequently cost and patient tolerance often become limiting. As a result, studies that have focused on bone erosion and synovial changes in RA have not included optimal cartilage imaging techniques. In one study[10], MRI did not show a significant advantage over radiography for monitoring joint space narrowing in patients with RA. However, it is not known whether MRI optimized for articular cartilage would have performed better. Articular cartilage is easier to image in large joints, such as the knee, but to date, most studies that have examined the knees of patients with RA using MRI have focused on synovial changes rather than the cartilage. More work is needed in this area.

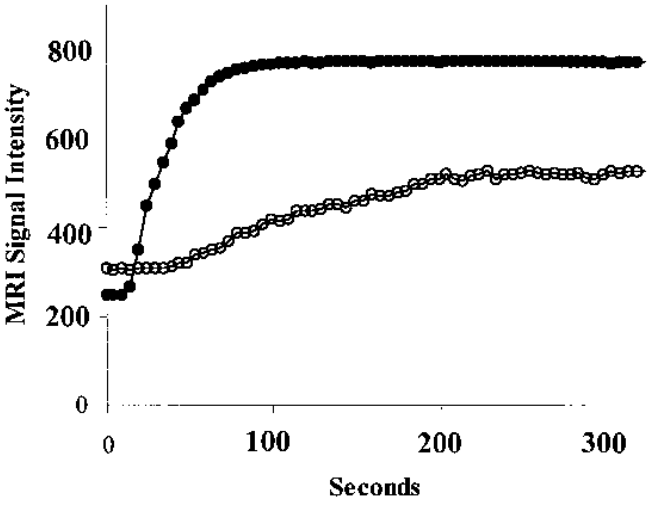

Figure 7. Imaging synovial enhancement rate. The graph depicts the rate of change in MR signal in a region of interest in synovial tissue in a patient with RA immediately prior to (●) and 5 weeks after (○) initiation of treatment with methotrexate. Note the reduction in both the rate of enhancement and maximum degree of enhancement after treatment.

Tendons and ligaments. In addition to monitoring changes in the bones, cartilage, and synovium, MRI can directly visualize the full spectrum of tendon pathology, and has been shown to identify tendonitis and tendon rupture with greater accuracy than clinical examination[58]. Tendon rupture may result from mechanical fraying of tendons passing over jagged erosions or from direct tenosynovial invasion[59,60]. Normal tendons show smooth margins and homogeneously low signal intensity on T2 weighted MR images. In tenosynovitis, fluid can be seen within the tendon sheath, but the tendon itself appears normal. Tendonitis usually results in enlargement and irregularity of the tendon, but the most reliable sign is increased signal intensity within the tendon itself on T2 weighted images. Tendon rupture can be partial or complete, and is depicted by varying degrees of tendon discontinuity.

McQueen, *et al*[21] combined tendonitis with bone erosion, marrow edema, and synovitis to form a composite MRI score for RA. They found that this composite score was more predictive of future bone erosion than any component of the score independently. Based on ROC (receiver operator characteristic) analysis, they found the optimal composite score to predict new erosions at one year with 93% sensitivity and 82% specificity. Ligaments can also be examined with MRI. However, to date, very little attention has been given to assessing ligament integrity in RA with MRI.

In conclusion, MRI shows remarkable promise as a tool for identifying and monitoring structural damage in the joints of patients with RA. Not only does MRI appear to identify bone erosions with greater sensitivity than radiography, but MRI discloses edema-like changes in the marrow that may precede actual erosion formation. Moreover, MRI can identify and measure synovitis and its response to therapy before bone edema or erosions have developed. As new therapies with structure modifying capabilities enter the clinic, the ability to identify patients appropriate for those therapies and then to monitor the effectiveness and safety of treatment become increasingly important.

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