

Newer Imaging Technology for the Diagnosis of Early RA and Monitoring of Inflammation and Joint Damage

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I saw my first patient with rheumatoid arthritis (RA) when I was 12 years old. My father, Nathan Troum, was also a rheumatologist, and I would join him when he saw patients in his office. At that time, in 1964, the typical treatments available for patients with RA were intramuscular gold, high-dose aspirin, and corticosteroids—indomethacin was just introduced.

In the 1980s, methotrexate was approved for RA and, in more recent years, biologic response-modifying agents have added significantly to our armamentarium. It was then that rheumatologists realized that we needed better tools to help detect early damage. Such tools would enable us to use more effective medications in an attempt to prevent damage early. That was the pretext for my getting involved with office-based magnetic resonance imaging (MRI).

MRI for Early Detection of RA

It has been well known for many years that MRI is at least twice as sensitive for the detection of erosions as compared with plain radiographs. However, patients are reluctant to have a standard MRI, which necessitates being enclosed in a large tubular MRI machine for 45 minutes simply to image their hands and wrists. Thus, many rheumatologists have not used MRI for this purpose. Now, with the availability of extremity MRI, rheumatologists and musculoskeletal radiologists can partner to interpret these images and follow the structural changes over time, which offers better technology for detecting early inflammation and for monitoring inflammation and structural damage in RA.

As rheumatologists, we try to alter the natural course of RA. Without treating RA, the natural course of the disease often leads to disability, as evidenced by poorer health assessment questionnaire (HAQ) scores, increased number of tender/swollen joint counts, and progression of Sharp or modified Sharp/van der Heijde scores. Traditional disease modifiers usually only slow or retard the disease process, but with the new biologic response-modifying agents and methotrexate, we can prevent progression. I consider RA to be in

its early stage if it is less than 3 months, but the definition of early RA is evolving. Based on clinical studies, the definition ranges from less than 6 months, even as soon as 6 weeks, to less than 5 years from the onset of symptoms. Microscopic changes are already occurring early in the disease course, including osteoclastogenesis. In fact, within the first 2 years of disease onset, 50% to 70% of patients already have radiologic damage,^{1,2} indicating that early detection and prevention are of paramount importance.

A study a few years ago showed that 75% of the progression of the median radiographic progression rate occurs within the first 5 years.³ Other studies suggest that progression happens more quickly, and it has been demonstrated that even a brief delay of therapy can affect the progression of structural damage.⁴ The relationship between long-term disability and structural damage was examined by Maillefert et al.⁵ Their prospective study of 135 patients with disease duration of less than a year showed a significant correlation between the HAQ score at year 5 and changes observed in the radiologic total damage during the first year. A change of at least 2 points of the total damage X-ray score (van der Heijde's modified Sharp score) during the first year of follow-up was the best predictor of subsequent disability at year 5.

Importance of Sensitive Joint Imaging for Early Diagnosis

Previous demand for joint imaging was modest. We've all used X-rays at the initial visit and hopefully annually thereafter to follow structural damage. However, with effective structure-modifying therapy, that is, biologics, imaging for early detection of pre-erosive and early erosive damage can become an important component of initiating or changing therapy. This leads us to consider the pros and cons of various imaging techniques including MRI, ultrasound, computer tomography scan, and X-ray.

Structure-modifying therapies raise the bar, shifting therapeutic strategy from controlling pain and limiting toxicity to actually minimizing joint destruction. Our focus should be on early intensive treatment before there is irreversible damage. Thus, there is a demand now for better methods of identifying patients who warrant intensive therapy, ultimately hoping to control costs, limit toxicities, and to monitor treatment effectiveness.

When assessing a patient with RA, I perform an MRI at baseline and depending on the aggressiveness of the patient's

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disease, possibly another at 6 months, or certainly by 1 year. I will also use MRI to assess progression of structural damage if I'm considering changing therapy. Information from an MRI should not be used solely to make a diagnosis or treatment decision but in concert with taking a patient history and performing a physical examination, including a total tender/swollen joint count; laboratory tests including inflammatory markers; and HAQ, Disease Activity Score (DAS), or other score. Some type of measurement over time needs to be documented to assess the true status of your patient.

Although monitoring inflammation may be one way of assessing patient status, Kirwan showed that in RA, inflammation may remain elevated in the first 2 years but then later dissipate over a 30-year period.⁶ Moreover, although erosive damage continues, disability mirrors the extent of erosions over that same time period. Additionally, stable clinical symptoms don't always tell you how your patient is doing. Drossaers-Bakker et al. showed radiographic progression over 12 years despite stable clinical symptoms in 112 female patients.⁷ When the Sharp score was 0, the HAQ score was 0.63 and the DAS score 2.9. Over the next 6 and 12 years, the HAQ score increased somewhat, whereas the DAS score decreased. The Sharp scores dramatically increased over this time frame. So the expectation would be that disability would ultimately follow.

The 2002 American College of Rheumatology guidelines for treating rheumatoid arthritis state that successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease-modifying agents. The ultimate goals of managing RA are to prevent or control joint damage, prevent loss of function, and decrease pain, with the primary goal of arresting and preventing structural damage.⁸ This is the rationale I give for wanting to obtain advanced imaging when it is perceived as costly by many payors. Thirty percent or more of RA patients may not show erosions or progression of erosions. Because I treat RA aggressively, it's possible that more of my patients could receive biologic response-modifying therapies than actually need to be on that type of therapy. So I need a better predictor

of early disease aggressiveness and progression to know who may or may not need these advanced therapies.

Limitations of Radiography

There is demand for better early predictors of progression and more sensitive erosion detection. Paulus and colleagues showed that a negative X-ray predicts nonprogression only if a patient has had RA for over 19 months, and that X-ray is only 41% accurate if RA is less than 6 months.⁹ McQueen et al. showed that less than 20% of patients had X-rays showing erosions within 6 months or less of having symptoms.^{10,11} Thus, the shift to a more proactive approach from diagnosing bone erosions to identifying pre-erosive features is important and is not detectable by X-ray.

There are also technical limitations of radiography. First, it is insensitive for bone erosions as X-ray lucency reflects primarily cortical bone loss, and projectional superimposition obscures nontangential erosions. Second, X-ray cannot accurately assess cartilage loss as joint space narrowing is an indirect measure of cartilage loss. Third, it has low sensitivity to change over time. And finally, but importantly, you cannot visualize cartilage, synovium, bone marrow, or tendons, which are all an integral part of the affected structure, and some (synovitis and bone marrow edema-osteitis) are predictive of erosions in patients with RA.

Several studies, published as early as the early 1990s to more recently in 2006, show that MRI is at least twice as sensitive as X-ray for detecting erosions.¹²⁻¹⁶ Most recently, this has been shown in an article published by our group in a 2-year prospective study of 405 patients being aggressively treated for RA and being followed at 8-month intervals with MRI.¹⁶ Lindegaard et al. also demonstrated this in a prospective 1-year follow-up study of patients being aggressively treated for RA.¹⁵ Figures 1 and 2 illustrate how erosions can be observed with MRI but not with X-ray.

Some have questioned whether erosions seen with MRI are real. Studies show that erosions found with MRI correlate with erosions identified with arthroscopy of the metacarpophalangeal (MCP) joint, computer tomography scans, and



FIGURE 1. High quality X-ray image (A) and low-field MRI (B) of the same metacarpophalangeal region. Arrow indicates location of erosion on the MRI.

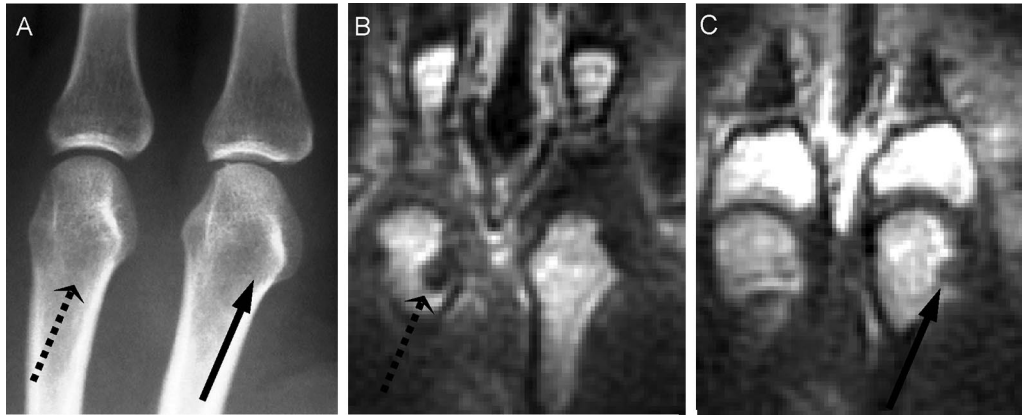


FIGURE 2. X-ray image (A) and MRI (B) of the same metacarpophalangeal region. Corresponding erosion locations shown by X-ray and MRI are indicated by the solid and dashed arrows.

ultrasound. Their appearance is also identical to other holes in the bone as you might expect to see with a tumor, ganglia, screw hole, or postoperative defect. In addition, there are a multiplicity of anatomic distributions and clinical context that give specificity to the diagnosis of MRI erosions. Also important to remember is that in the MCP joints, erosions are very rare in the normal metacarpal head, occurring only 0.2% to 0.4% of the time.

In 42 patients with early RA (defined as less than 6 months), McQueen and colleagues found 45% with erosions by MRI at baseline, whereas only 15% showed erosions at baseline with X-ray.¹⁷ In 2004, Ostendorf et al. published a study with 25 patients with early RA (<1 year) in which 60% of patients with a negative X-ray had an abnormal MRI; 36% showed erosions; 24% showed pre-erosive features, synovitis, and edema (osteitis).¹⁸

Baseline erosion scores with MRI have been shown to be predictive of 2-year X-ray erosions. Only 18% of patients without MRI erosions at baseline showed X-ray erosions at 2 years; however, 61% with MRI erosions at baseline showed X-ray erosions at 2 years.¹¹ This is where advanced imaging, whether it be MRI or ultrasound, can be very important and helpful.

Types of MRI Machines

There are several different types of MRI systems available: conventional whole-body MRIs with 1.5 T, a whole-body MRI with 0.2 T, and a 3.0 T machine, which is restricted to use by radiologists. There are 3 0.2 T in-office MRI machines or extremity MRI systems currently available, the E-Scan XQ (Esaote SpA, Genova, Italy) and C-Scan (Hologic, Inc, Bedford, MA) and the portable MV-R by MagneVu (Carlsbad, CA; 0.2 T), in addition to a 1.0 T machine, OrthOne (ONI Medical Systems, Wilmington, MA) (Fig. 3). These scanners provide a comfortable, open setting for the patient. There are differences between these extremity scanners ranging from the extent of the field of view able to be scanned (smallest field—MV-R by MagneVu) to the joints able to be visualized and whether special shielding is needed for the examination room (OrthOne).

The question may arise: Do you need a large machine to detect erosions? Taouli et al. found that you do not need a stronger magnet to detect early RA.¹⁹ In our 2004 publication, we used a portable MRI machine¹⁴ that had a focused field of view. We examined the MCP joints and were also able to image the wrist. In this study of 227 wrists and second and third metacarpal joints of 132 consecutive patients with RA, the largest study looking at RA comparison of X-ray versus MRI, patients had RA for a median of 8 years.¹⁴ We found that 95% of the patients had evidence of erosion by MRI but only 59% by X-ray in these different locations, as read by 2 musculoskeletal radiologists.

We later examined 405 RA patients in a prospective study, mostly receiving tumor necrosis factor- α inhibitors, with a baseline office MRI using the MV-R machine by MagneVu.¹⁶ For 156 patients who had 246 follow-up examinations, an average of 8 months, ranging from 1 to 19 months, a change in erosions or erosion diameter was considered significant when there was at least a 20% change. Some patients had X-rays for comparison, so we were able to see that MRI picked up changes in erosion size, whereas X-ray was not sensitive enough to detect the same changes.¹⁶ Smaller MRI machines have the advantages of lower cost, greater convenience, greater comfort, less claustrophobia, and being an in-office procedure. However, the same restrictions apply to the use of these in-office MRI devices as with the whole body machines (i.e., no pacemakers, metallic implants, etc).

The technical performance requirement of an imaging machine depends on whether the machines are being used in clinical trials, academic research, or clinical practice. Rheumatologists' needs are also different than radiologists' needs. Radiologists need to image other areas; the head, spine, abdomen, not just the extremities. So they need a large-bore, whole-body magnet. Radiologists also cater to other specialists, including neurologists, oncologists, and surgeons, and need sophisticated pulse sequences, stronger gradients, and specialized coils. As rheumatologists, we need to detect pre-erosive bone lesions, erosions, tendonitis, and tenosynov-

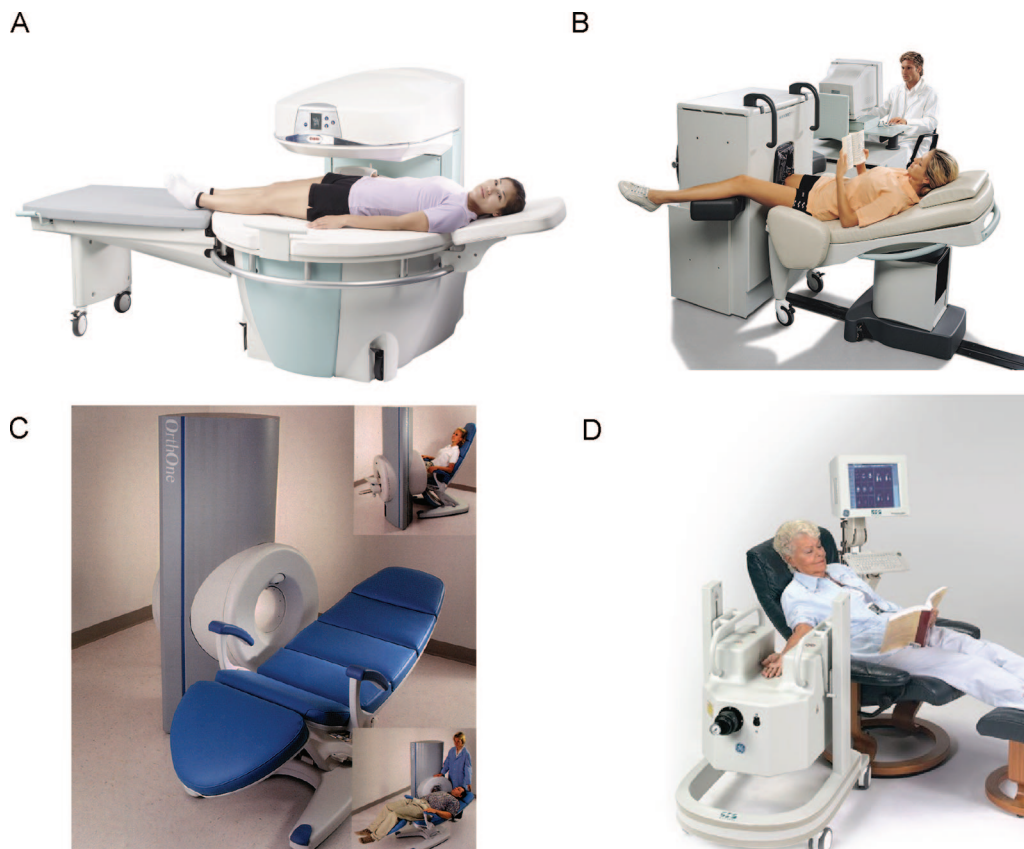


FIGURE 3. Four types of MRI machines are available for in-office use. The MRI systems shown here are printed with permission from the manufacturer: smaller MRI systems, (A) E-Scan XQ (Esote SpA, Genova, Italy; 0.2 T), (B) C-Scan (Hologic, Inc, Bedford, MA; 0.2 T), and (C) OrthOne (ONI Medical Systems, Wilmington, MA; 1.0 T); and a portable MRI, (D) MV-R (MagneVu, Carlsbad, CA; 0.2 T).

vititis, so the small low-field extremity MRI is really sufficient for our goals.

Ultrasound is another imaging option for the rheumatologist. You can detect surface erosions with high-resolution ultrasound, and it is more sensitive than X-ray but less sensitive than MRI. Some of the advantages of ultrasound are that it is relatively inexpensive, portable, real time, and is better than X-ray for measuring soft tissue changes including synovitis. It is also helpful for joint aspiration and injection techniques because of joint space localization. Bone shadowing is one of the disadvantages, which can obscure the medial and lateral aspects of the metacarpal and carpal bones. It is also difficult to standardize its use in clinical trials as the results vary depending on the operator. Ultrasound also takes extra time during an office visit that may not be available.

In summary, the trend to early intensive treatment gives us greater need for more sensitive indicators, a shift in emphasis to pre-erosive features. So the demand for these better or more advanced imaging techniques will increase. I think imaging should become an essential component of evaluation for appropriate therapy and monitoring of therapeutic response. MRI may be the best option, but when it is not available, ultrasound would be next best alternative. Current obstacles for the use of office MRI systems include

the cost, training to interpret the results for the nonradiologist, and reimbursement issues. MRI is also clearly advantageous for use in clinical trials and may help in the early diagnosis of an aggressive RA phenotype so that these patients can be treated earlier with aggressive therapies. Specialized MRI systems, or office MRIs, are proposed to offer a cost-effective clinical solution for assessing structural changes in patients with inflammatory arthritis that can be incorporated into use in clinical practice.

REFERENCES

1. van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol.* 1995;34(suppl 2):74–78.
2. Sundry JS St. Clair EW. Early DMARD therapy for RA: primary care physicians play a major role in diagnosis and follow-up. *J Musculoskel Med.* 2002;19:395–403.
3. Lindqvist E, Jonsson K, Saxne T, et al. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. *Ann Rheum Dis.* 2003;62:611–616.
4. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med.* 2001;111:446–451.
5. Maillefert JF, Combe B, Goupille P, et al. The 5-yr HAQ-disability is related to the first year's changes in the narrowing, rather than erosion score in patients with recent-onset rheumatoid arthritis. *Rheumatology.* 2004;43:79–84.

6. Kirwan JR. Conceptual issues in scoring radiographic progression in rheumatoid arthritis. *J Rheumatol*. 1999;26:720–725.
7. Drossaers-Bakker KW, de BM, van ZD, et al. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum*. 1999;42:1854–1860.
8. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum*. 2002;46:328–346.
9. Paulus HE, Oh M, Sharp JT, et al. Correlation of single time-point damage scores with observed progression of radiographic damage during the first 6 years of rheumatoid arthritis. *J Rheumatol*. 2003;30:705–713.
10. McQueen FM, Stewart N, Crabbe J, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. *Ann Rheum Dis*. 1999;58:156–163.
11. McQueen FM, Benton N, Crabbe J, et al. What is the fate of erosions in early rheumatoid arthritis? Tracking individual lesions using x rays and magnetic resonance imaging over the first two years of disease. *Ann Rheum Dis*. 2001;60:859–868.
12. Foley-Nolan D, Stack JP, Ryan M, et al. Magnetic resonance imaging in the assessment of rheumatoid arthritis—a comparison with plain film radiographs. *Br J Rheumatol*. 1991;30:101–106.
13. Jorgensen C, Cyteval C, Anaya JM, et al. Sensitivity of magnetic resonance imaging of the wrist in very early rheumatoid arthritis. *Clin Exp Rheumatol*. 1993;11:163–168.
14. Crues JV, Shellock FG, Dardashti S, et al. Identification of wrist and metacarpophalangeal joint erosions using a portable magnetic resonance imaging system compared to conventional radiographs. *J Rheumatol*. 2004;31:676–685.
15. Lindegaard HM, Vallo J, Horslev-Petersen K, et al. Low-cost, low-field dedicated extremity magnetic resonance imaging in early rheumatoid arthritis: a 1-year follow-up study. *Ann Rheum Dis*. 2006;65:1208–1212.
16. Chen TS, Crues JV III, Ali M, et al. Magnetic resonance imaging is more sensitive than radiographs in detecting change in size of erosions in rheumatoid arthritis. *J Rheumatol*. 2006;33:1957–1967.
17. McQueen FM, 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;57:350–356.
18. Ostendorf B, Scherer A, Modder U, et al. Diagnostic value of magnetic resonance imaging of the forefeet in early rheumatoid arthritis when findings on imaging of the metacarpophalangeal joints of the hands remain normal. *Arthritis Rheum*. 2004;50:2094–2102.
19. Taouli B, Zaim S, Peterfy CG, et al. Rheumatoid arthritis of the hand and wrist: comparison of three imaging techniques. *Am J Roentgenol*. 2004;182:937–943.

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