According to its definition based on clinical studies, early rheumatoid arthritis (RA) ranges from 6 weeks to less than 5 years from the onset of symptoms. Microscopic changes, including osteoclastogenesis, occur early in the course of the disease. Radiographic damage is seen in 50% to 70% of patients within the first 2 years of disease onset, indicating that early detection and prevention are of paramount importance. Lindqvist and colleagues reported that 75% of the median radiographic
progression in RA occurs within the first 5 years. Lard and colleagues\textsuperscript{4} suggested that structural damage progresses more quickly and that even a brief delay of therapy can affect the extent of damage that occurs.

More recently, attention has been focused on how early the active treatment of RA should be initiated. Finckh and colleagues\textsuperscript{5} demonstrated that a shorter disease duration is the strongest predictor of improvement in disease activity over 5 years, and delayed treatment led to further radiographic progression. Bathon and colleagues\textsuperscript{6} administered etanercept to patients within 1 year of onset of RA and reported that the bone erosion score showed a significantly slower rate of change in the etanercept group than in the methotrexate (MTX) group. Nell and colleagues\textsuperscript{7} prospectively investigated the changes of disease activity (Disease Activity Score [DAS] 28) in patients with early RA (<3 months). The group reported that DAS28 improved significantly after 3 months of disease-modifying antirheumatic drug (DMARD) therapy; this trend continued over the following 3 years. Others have placed increasing emphasis on assessing and diagnosing RA within the first 6 weeks of patient symptoms, initiating treatment using DMARD therapy in a similar time frame. This is reflected in both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) guidelines for patient care.\textsuperscript{8,9}

The availability of DMARDs, including biological therapy for early aggressive RA, generated the need for more sensitive imaging techniques. These give further insight into the underlying pathophysiology of RA and assist the clinician in predicting prognosis and monitoring long-term treatment. Thus, an accurate early diagnosis of RA assisted by detailed joint imaging may be especially beneficial in preventing disability.

**LIMITATIONS OF RADIOGRAPHY IN RA**

The first study comparing magnetic resonance imaging (MRI) and radiography of the wrist joint in patients with RA was published in 1988.\textsuperscript{10} There have been numerous subsequent publications using MRI in RA that have demonstrated the technique’s utility in detecting early arthritic changes.\textsuperscript{11} Many studies have compared the sensitivity of detecting bone erosions between MRI and conventional radiography. In addition, longitudinal studies have confirmed that many bone marrow lesions (osteitis) seen with MRI progress to radiographic erosions. Thus, in addition to lacking the capacity for multidimensional imaging (2-dimensional representation of 3-dimensional pathologic condition), radiographs do not detect early bone lesions because they are incapable of assessing osteitis (Figs. 1–3).

There is ongoing demand for better early predictors of progression and more sensitive erosion detection. Thus, the shift in approach from diagnosing bone erosions to identifying pre-erosive features is important but not possible with radiography. Technical limitations of radiography include lack of sensitivity for bone erosions because radiograph lucency primarily reflects cortical bone loss and projection superimposition obscures nontangential erosions. Radiography cannot accurately assess cartilage loss because joint space narrowing (JSN) only indirectly measures the magnitude of existing cartilage. In addition, radiography has a low sensitivity to change over time and, importantly, the cartilage, synovium, bone marrow, and tendons cannot be accurately visualized. Multiple studies have shown that MRI is at least twice as sensitive as radiography for detecting erosions.\textsuperscript{12–16}

**ADVANTAGES AND DISADVANTAGES OF MRI IN RA**

The main advantages of MRI are no exposure to x-ray radiation, tomographic/3-dimensional viewing, high resolution, good soft tissue contrast, and reproducibility.
This technique enables detailed visualization of bone marrow, synovium, cartilage, and tendons. Potential disadvantages of MRI are high cost and limited accessibility. In contrast-enhanced imaging protocols, there is a small risk of gadolinium toxicity, such as nephrogenic systemic fibrosis, especially in patients with renal impairment. Also, interpretation of magnetic resonance images is more complex and time consuming than radiographs, and they should be evaluated by an experienced musculoskeletal reader. High-quality images are assured only if patients remain immobile while the images are being obtained. In patients who are anxious, confused, or in severe pain, it is more challenging to obtain high-quality images. Claustrophobia also makes it difficult for some patients to cooperate with the study.

Contraindications to MRI also remain a problem in some patients. In addition, morbidly obese patients may not fit into a conventional MRI machine and patients with pacemakers, certain ferromagnetic appliances, and certain surgical clips and those with recent cardiac stent placement cannot be included in the study. Although there is no current evidence that MRI harms the fetus, pregnant women are usually advised not to undergo MRI examination unless medically necessary, but ultrasonography may be performed.

Ultrasonography is another viable imaging option for rheumatologists. Surface erosions can be detected with high-resolution ultrasonography because it is more sensitive than radiography, but less sensitive than MRI. Compared with MRI, ultrasonography is inexpensive, portable, and real time; it is also efficient than radiography for measuring soft tissue changes, including synovitis. The use of color Doppler and power Doppler aids in detecting the increased vascularity of synovitis, differentiating it from effusion. These are also useful for joint aspiration and injection techniques because they accurately identify the joint and periarticular structures. However, bone shadowing can obscure the medial and lateral aspects of the metacarpal and carpal bones. Standardization is difficult, limiting its use in clinical trials, because

Fig. 1. Imaging in a 56-year-old man with recent-onset RA. (A) Radiograph of the right hand shows no erosions. (B) Coronal T1-weighted image (0.2-T extremity MRI) shows moderate-size erosion in the third metacarpal head (arrow).
the findings vary depending on the operator and there has been no validated scoring system to date.

Compared with ultrasonography, MRI has a relatively low resolution, and, because contrast administration is required to reliably distinguish synovium from effusion, the imaging of multiple joints can be difficult. In addition to increased availability and fewer financial constraints relative to MRI, ultrasonography allows the clinician to assess the patient at the time of imaging and to examine the contralateral side or additional joints if necessary.

**TYPES OF MRI MACHINES**

There are several types of MRI machines available. In general, they are divided into conventional (whole body) and extremity MRI (eMRI) systems, in which only the extremity of interest is positioned into the magnet bore while the rest of the body remains outside. Both conventional and eMRI systems come in various field strengths,
ranging from a low 0.2 T to a high 1.5 T and more recently available 3.0-T magnets. Currently available eMRI systems include the 0.2-T C-Scan and E-Scan XQ (Opera), 0.25-T S-Scan, and 0.31-T O-Scan (Esaote SpA, Genoa, Italy), the portable 0.2-T MV-R by MagneVu (Carlsbad, CA, USA), and the high-field 1.0- and 1.5-T OrthOne (ONI Medical Systems, Wilmington, MA, USA). There are differences between these extremity scanners, ranging from the field of view available for scanning (smallest field: the MV-R) to the joints being visualized and whether special shielding is needed for the examination room.

**Low-Field MRI**

Detecting osteitis, synovitis, or erosions does not require a higher-Tesla magnet or whole-body machine. Taouli and colleagues\(^\text{17}\) found that a stronger magnet is not needed to detect early RA. Crues and colleagues\(^\text{14}\) compared radiography with MRI using a portable MRI machine with a focused field of view examining 227 wrists and the second and third metacarpal joints of 132 patients with RA with a median disease duration of 8 years. Erosions, as read by 2 musculoskeletal radiologists, were detected in 95% of patients by MRI and in only 59% by radiography in these different locations.

---

**Fig. 3.** Imaging in a 22-year-old woman with a 6-month history of severe seropositive, anti-CCP-positive RA. (A) Coronal short tau inversion recovery image of the right wrist shows synovitis (high-signal tissue in the synovial space) and bone marrow edema (increased signal within the bone marrow) in the carpal bones. (B) Postcontrast axial T1-weighted fat-saturated image confirming the previous findings. Tenosynovitis of extensor and flexor tendons is also seen (arrows). (C) Radiograph is incapable of visualizing synovitis, bone edema, or tendinitis.
In a prospective study of 405 patients, the majority with established RA and receiving tumor necrosis factor (TNF) α inhibitors were examined at baseline with eMRI. Of them, 156 patients had 246 follow-up examinations (average of 8 months) over a 2-year period. A change in erosions or erosion diameter was considered significant when there was at least a change of 20%. MRI detected new erosions or change in erosion size in 50% of patients, whereas radiography was not sensitive enough to detect these changes.

Since the introduction of extremity-dedicated low-field units (<1.0 T), there has been interest in comparing the diagnostic performance of low-field scanners with that of existing high-field (≥1.0 T) scanners.

Published data demonstrate excellent correlation between extremity units and whole-body systems. There are 6 published studies comparing eMRI with high-field conventional MRI evaluating small joints (Table 1). Overall, in diagnosing and scoring RA pathology, the agreement between the 2 field strengths was high (see Fig. 2).

With high-field MRI as the gold standard and using the Artoscan (0.2 T), Ejbjerg and colleagues found 93% sensitivity and 94% specificity for erosions and 90% sensitivity and 96% specificity for synovitis. However, the low-field unit displayed high specificity but only moderate sensitivity (39%) for detection of bone marrow edema. Bird and colleagues found high specificity but only moderate sensitivity on low-compared with high-field MRI in scoring synovitis and bone edema.

One study evaluated interreader reliability of the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) RA MRI score assessing change in disease activity and bone erosions using eMRI in comparison with high-field MRI. The intraclass correlation coefficients and smallest detectable difference results for the change in scores were good for erosions and synovitis but not acceptable for bone edema.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>103</td>
<td>18</td>
<td>65</td>
<td>17</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Unilateral wrist, MCP, PIP joints</td>
<td>Bilateral wrist, MCP joints</td>
<td>Unilateral wrist and MCP joints</td>
<td>Unilateral wrist, MCP, PIP joints</td>
<td>Dominant wrist and MCP joints</td>
<td>Bilateral wrist, MCP joints</td>
</tr>
<tr>
<td>eMRI Unit</td>
<td>0.2-T Artoscan</td>
<td>0.2-T Artoscan</td>
<td>0.2-T Artoscan</td>
<td>0.2-T C-Scan</td>
<td>0.2-T Artoscan</td>
<td>0.3-T CompacTscan</td>
</tr>
<tr>
<td>Synovitis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Osteitis</td>
<td>+</td>
<td>NA</td>
<td>±</td>
<td>NA</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Erosions</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>JSN</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Abbreviations: +, high agreement; ±, moderate or low agreement; JSN, joint space narrowing; MCP, metacarpophalangeal; NA, not assessed; PIP, proximal interphalangeal.*
Given these results, the optimal method for assessing bone edema may be high-field MRI. However, MRI systems, imaging protocols, and scoring methods differed amongst these studies.

Duer-Jensen and colleagues,\(^24\) using computed tomography (CT) as the reference, compared the ability of 2 different eMRI units (Artoscan and MagneVu) and conventional radiography to identify bone erosions in patients with RA of the metacarpophalangeal and wrist joints. The Artoscan showed higher sensitivity than the MagneVu and conventional radiography.

When assessing the practicality of obtaining an eMRI for the rheumatologist’s office or clinical setting, several issues must be addressed. It is now mandatory in the United States to get accreditation to perform MRI outside a radiology facility. Accreditation can be obtained through the American College of Radiology (ACR) or the Intersocietal Accreditation Commission.

In 2005, the International Society of Extremity MRI in Rheumatology (ISEMIR) was established with the purpose of bringing together rheumatologists, radiologists, and other specialties dedicated to MRI technology as applied to rheumatologic diseases.\(^25\) ISEMIR, renamed in 2011 as the International Society of Musculoskeletal Imaging in Rheumatology, now incorporates ultrasonography.

**MRI SCORING**

The RA MRI score (RAMRIS) was developed at OMERACT 6 in April 2002. The aim was to provide a well-defined reproducible measurement system appropriate for multicenter use. The consensus by the OMERACT 6 MRI committee was that cortical erosion, bone marrow edema, and synovial volume were the most reproducible measurements.\(^26\)

The RAMRIS system has limitations with significant variation in interreader correlation despite low intrareader variation.\(^27,28\) However, this validated scoring system has been applied for diagnosis, assessment of disease activity, prognosis, and monitoring response to treatment. Hirose and colleagues\(^29\) showed that RAMRIS is useful for assessing early response to TNF inhibitors.

RAMRIS is specific to the wrist and metacarpophalangeal joints but has been successfully modified to include the feet.\(^30\) Baan and colleagues\(^31\) demonstrated good to excellent interreader and intrareader reliability for MRI of the rheumatic foot using RAMRIS.

Other scoring methods have been developed. Crowley and colleagues\(^32\) investigated the reliability, feasibility, and validity of a computer-assisted manual segmentation (outlining) technique for measuring MRI bone erosion and edema at the wrist in RA. Segmentation measures the volume of MRI bone edema and erosion. When compared with RAMRIS, outlining was less reliable for bone edema but had similar reliability for quantifying erosions. Ostergaard and colleagues\(^33\) pioneered the segmentation technique in quantifying rheumatoid synovial membrane volume. Bird and colleagues\(^34\) subsequently applied it to measuring bone erosion volume. Chand and colleagues\(^35\) demonstrated excellent intraobserver and very good interobserver reliability, content validity (represented by strong correlation with RAMRIS synovitis), and moderate feasibility by measuring MRI synovitis using a computer-assisted manual segmentation method.

Cyteval and colleagues\(^36\) assessed a simplified scoring method (Simplified Rheumatoid Arthritis Magnetic Resonance Imaging Score [SAMIS]) developed to shorten interpretation time while retaining both correlation with RAMRIS and same or better intrareader and interreader reliability. The results from SAMIS closely correlated
with those of RAMRIS; however, the scoring time was dramatically reduced: 5 to 20 minutes for RAMRIS versus 2 to 7 minutes SAMIS.

**Dynamic Contrast-Enhanced MRI**

Rapid acquisition of sequential contrast-enhanced images following administration of contrast allows mapping of the time course of synovial enhancement. Resultant measures depend on both synovial perfusion and capillary permeability. A rapid bolus injection, followed by sequential imaging from 2.6 to 69.0 seconds, allows measurement of multiple time-dependent variables.

In several studies, dynamic contrast-enhanced MRI (DCE-MRI) findings correlated well with C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) as well as DAS, Health Assessment Questionnaire scores, and erosions. In follow-up studies, findings correlated with clinical and histologic changes and relapse, with erosions seen at 1 year. DCE-MRI has also been successfully used to compare therapy effectiveness between DMARDs.

**RA JOINT PATHOLOGY**

MRI allows assessment of all the structures involved in RA: synovial membrane, synovial fluid, tendons, tendon sheaths, ligaments, cartilage, and bone. Miniarthroscopy of the metacarpophalangeal joints in patients with RA confirmed the presence of bone pathology in all joints with MRI bone erosions and histologic synovitis in all joints with synovitis. The extent of synovitis in these joints correlated well not only between MRI and macroscopic findings on miniarthroscopy but also with clinical disease activity. Recently, increased synovial vascularity assessed by magnetic resonance angiography has been shown to correlate well with both MRI and ultrasonography-detected synovitis in a pilot study involving 30 patients with early inflammatory arthritis.

Several studies have confirmed that MRI bone edema represents a cellular infiltrate, indicating the presence of osteitis within the subchondral bone. In contrast to radiographic erosions, which reflect fully developed bone damage with a break in the cortical bone, bone marrow edema comprises a link between joint inflammation and bone destruction.

Some remain skeptical as to whether erosions seen by MRI are true erosions. Many studies have confirmed that MRI erosions do reflect actual bone damage. MRI findings correlate closely with histopathologic signs of synovial inflammation. Using high-resolution CT as the gold standard, nonradiographically visible MRI erosions have been proved to be true erosions. At follow-up, these erosions demonstrated a small degree of reversibility by MRI after patients initiated either anti-TNF or rituximab treatment. In wrists and metacarpophalangeal joints, MRI and CT have a concordance of between 77% and 89%, given that CT is often considered the gold standard for detection of bone destruction.

Cartilage assessment was initially excluded in RAMRIS because of poor interreader reliability, but an MRI JSN scoring system proposed by McQueen and colleagues demonstrated excellent interreader and intrareader reliability. However, it was not capable of distinguishing JSN between those with early RA and healthy subjects. Subsequently, the OMERACT MRI group commenced the development of a JSN MRI score as a potential RAMRIS addendum for cartilage assessment. Preliminary use of this scoring method had good intrareader/interreader agreements. A novel MRI technique, delayed gadolinium-enhanced MRI of cartilage, has emerged as most promising to assess cartilage quality.
RA DIAGNOSIS

Synovitis

There are several ways in which MRI can assist the clinician in the diagnosis of RA. MRI is more sensitive than clinical examination, and confirming subclinical synovitis can allow differentiation of the patient with nonspecific joint pain from a patient with true inflammatory synovitis. Synovitis is the primary abnormality in RA, and MRI, unlike radiography, can be used to image the synovium. MRI can assess synovial volume and the level of synovial inflammation. Although clinical examination remains a cornerstone in diagnosing and monitoring disease progression in patients with RA, MRI is more sensitive than clinical examination for identifying synovitis. Sugimoto and colleagues diagnosed 25 of 26 patients at RA disease onset using MRI criteria (presence of contrast enhancement), 23% more patients than were identified using ACR criteria. Another study compared the diagnostic utility of testing for anti–cyclic citrullinated protein (anti-CCP) antibodies with MRI to confirm the diagnosis of RA. This cohort of patients with recent-onset arthritis met at least 3 of the 4 ACR clinical criteria in the absence of serum rheumatoid factor (RF), nodules, or erosions. The presence of MRI synovitis with bone erosions or bone edema of the hand had a specificity of 78% and a sensitivity of 100% for making the diagnosis of RA.

Erosions

MRI can assist in diagnosing RA by revealing erosive disease in the typical RA joint distribution. In 42 patients with early RA (<6 months), McQueen and colleagues found 45% of patients with erosions at baseline by MRI, whereas only 15% showed erosions at baseline on radiography. A 5-year longitudinal study demonstrated that at baseline only 20% of MRI lesions were detected by radiography, in contrast to the 5-year follow-up where 60% of the initial lesions were detected radiographically. In another study comparing MRI with radiography in detecting erosions, only approximately 10% of bone erosions by radiography were classified as small in size. Erosions are visible by MRI at a median of 2 years before being detected by radiography and may become consistently noticeable by radiography of the metacarpophalangeal joints only after 20% to 30% of the bone is eroded on MRI.

Tenosynovitis

MRI is a sensitive tool for detecting inflammation of periarticular tendons (tenosynovitis) (see Fig. 3). Flexor tenosynovitis of the hand diagnosed by MRI is a strong predictor of early RA. Combining flexor tenosynovitis by MRI with positive serology test results (anti-CCP or RF) more strongly predicts early RA.

Bone Marrow Edema (Osteitis)

MRI permits the visualization of subchondral bone abnormality in the form of marrow edema. This is clinically important because marrow edema identified by MRI is often present in patients with early RA. In a cross-sectional study of 40 healthy controls and 40 randomly chosen patients with RA, bilateral hand and wrist magnetic resonance images were assessed by 2 readers blinded to the diagnosis. The presence of bone edema was found to be the best test for RA diagnosis, with a specificity of 82.5% and a sensitivity of 60%, and osteitis of the metacarpophalangeal joints was 100% specific for RA.

Using MRI in the diagnosis of early RA may be most useful when evaluating patients with undifferentiated arthritis (UA) with the ultimate goal to identify those who would...
benefit from earlier treatment. Tamai and colleagues followed up 129 patients with UA for 1 year, with 75 ultimately developing RA. Baseline MRI together with RF and CCP level determination predicted the progression from UA to RA. MRI osteitis was better at predicting RA then synovitis or bone erosions. Duer-Jensen and colleagues followed up 116 patients with UA for 1 year. Similar to the previous study, MRI bone edema independently predicted the development of RA. A prediction model, including clinical hand arthritis, morning stiffness, and positive RF and MRI bone edema score in MTP and wrist joints correctly identified the development of RA versus non-RA in 82% of patients.

**Enthesitis**

Clinical manifestations of the spondyloarthropathies that involve peripheral joints, especially in psoriatic patients presenting with polyarthritis, may be difficult to distinguish from those of RA. Identification of enthesitis (inflammation at the insertions of ligaments and tendons) using MRI may be helpful in making the correct diagnosis when assessing peripheral involvement in patients with spondyloarthritis.

A recent study assessed the value of MRI to diagnose early RA, in which MRI detected nonradiographic lesions. Of 20 patients with early RA (<2 years’ duration), 75% with no radiographic erosions had abnormal results on hand MRI. This review found 36 erosions (50% in the carpal bones) and 55 joints with synovitis (mainly midcarpal and metacarpophalangeal joints). Bone edema was found in the carpal bones, and tenosynovitis most frequently affected the flexor tendons. Ostendorf and colleagues showed similar results in a cohort of 25 patients with early RA (<1 year). Radiographic results were negative in 60%; however, MRI erosions were detected in 36%, and 24% showed pre-erosive features, synovitis, and osteitis. In another study, bone edema, erosions, and synovitis were present in 26 patients with very early (<3 months) RA, with the prevalence being 100%, 96%, and 92%, respectively.

A recent systematic review performed by Suter and colleagues specifically addressed the question of diagnostic utility of MRI in RA. Eleven studies (606 subjects) were analyzed to determine the sensitivity and specificity of the diagnostic utility of MRI. The reported sensitivity and specificity ranged widely between 20% and 100% and 0% and 100%, respectively. The main difficulty in interpreting results across studies was related to nonuniformity in the use of MRI RA criteria, MRI definitions and scoring systems, and magnetic resonance systems. These findings suggest that well-designed studies are still needed in this area.

According to the new ACR/EULAR 2010 classification criteria, definite RA is based on the presence of definite synovitis (tenderness and swelling on clinical examination) in 1 or more joints, absence of an alternative diagnosis that explains the synovitis, and achievement of a total score of 6 or more (range, 0–10) from the individual scores in 4 domains: number/site of involved joints (range, 0–5), serologic abnormalities (range, 0–3), elevated acute phase reactants (range, 0–1), and duration of symptoms (range, 0–1). Despite the fact that imaging is not part of the new RA classification criteria, there is consensus that MRI and ultrasonography may be used to detect synovitis and to count joints in the joint involvement domain.

**RA PROGNOSIS**

There are multiple studies demonstrating that MRI is a useful biomarker for prognosis of early RA. MRI predicts erosive phenotype, worse clinical disease activity, inflammatory activity (higher ESR and CRP level), and functional disability.
Accurately predicting the rate of disease progression is important in the management of early RA. This crucial information allows early aggressive therapeutic intervention. Several studies have reported that MRI of the small joints in early RA predicts progression of erosive disease (Table 2). Some investigators have looked at the short-term predictive value of MRI after 1 year, whereas other studies had up to 10 years of follow-up. Structural progression was assessed by either conventional radiography or MRI. All these studies demonstrated MRI to be a highly significant predictor of structural joint damage.

Data from an uncontrolled prospective cohort of 42 patients demonstrated that baseline MRI bone edema score of the dominant wrist predicted radiographic erosions at 6 years. The levels of CRP was the only clinical measure found to have predictive value, whereas tender and swollen joint scores did not. Boyesen and colleagues showed that both baseline and 1-year cumulative measures of MRI synovitis and bone marrow edema independently predicted 3-year radiographic progression, suggesting these pathologic changes precede radiographic progression in early RA. However, in some studies, MRI synovitis did not reliably predict erosions, as opposed to bone edema, which was found to be the best predictor of structural damage. The largest data set in early RA using MRI is derived from the CIMESTRA (Cyclosporine, Methotrexate, Steroid in RA) trial in which hand and wrist bone edema was the strongest independent predictor of radiographic progression at 2 years. It was superior to conventional radiography, immunologic serology tests (anti-CCP, IgM RF, and IgA RF), environmental factors (smoking, educational level), genetics (shared epitope), and disease activity markers. MRI bone edema and anti-CCP levels predicted radiographic progression in the 5-year extension of this study.

Only one study on established RA (mean disease duration, 7 years), reported by Brown and colleagues, demonstrated that MRI bone edema was less predictive of radiographic erosions in comparison with MRI synovitis. However, the investigators did not use T2-weighted or short tau inversion recovery sequences in their MRI protocol to detect bone edema, as recommended by OMERACT, which may have influenced the results.

**MONITORING OF RA**

The early course of RA is well depicted by MRI because both subchondral edema and synovitis are clearly characterized using this technique (Fig. 4). Recent studies have

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Study Duration (y)</th>
<th>Technique Assessing Structural Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savnik et al,77 2002</td>
<td>22 early, 22 late RA</td>
<td>1</td>
<td>MRI</td>
</tr>
<tr>
<td>McQueen et al,78 2003</td>
<td>42 early RA</td>
<td>6</td>
<td>Radiography</td>
</tr>
<tr>
<td>Tanaka et al,79 2005</td>
<td>114 early RA</td>
<td>10</td>
<td>Radiography</td>
</tr>
<tr>
<td>Palosaari et al,80 2006</td>
<td>27 early RA</td>
<td>2</td>
<td>MRI</td>
</tr>
<tr>
<td>Lindegaard et al,15 2006</td>
<td>25 early RA</td>
<td>1</td>
<td>Radiography</td>
</tr>
<tr>
<td>Haavardsholm et al,66 2008</td>
<td>84 early RA</td>
<td>1</td>
<td>Radiography and MRI</td>
</tr>
<tr>
<td>Mundwiler et al,80 2009</td>
<td>50 early RA (&lt;5 y)</td>
<td>1</td>
<td>Radiography</td>
</tr>
<tr>
<td>Hetland et al,81 2010</td>
<td>139 early RA</td>
<td>5</td>
<td>Radiography</td>
</tr>
<tr>
<td>Boyesen et al,82 2011</td>
<td>84 early RA</td>
<td>1</td>
<td>MRI</td>
</tr>
<tr>
<td>Boyesen et al,83 2011</td>
<td>55 early RA</td>
<td>5</td>
<td>Radiography</td>
</tr>
</tbody>
</table>
shown the important role of early bone injury in determining both progression and long-term functionality in RA. Subchondral edema cannot be assessed on clinical examination, and reproducibility of the clinical examination to determine synovial inflammation is relatively low in comparison with ultrasonography and MRI.86

Ejbjerg and colleagues87 compared MRI with radiographic scores, which were applied to different joint combinations. Independent of the number of joints imaged, MRI was superior in detecting progressive joint destruction. Similar results were seen in another study by Olech and colleagues in patients with early RA,88 adding validity for using MRI as a tool to monitor RA.

In other clinical studies, MRI has been utilized longitudinally in assessing response to therapy. In a 2-year prospective study by Chen and colleagues,16 405 patients being aggressively treated for RA were followed up at 8-months intervals with MRI. Lindergaard and colleagues15 also used MRI in a 1-year follow-up study of patients with early RA who were aggressively treated for RA. Troum and colleagues89 reported that tocilizumab reduced synovitis within 2 weeks and pre-erosive osteitis within 12 weeks in patients with RA using low-field eMRI.

**Subclinical Disease**

Structural damage may be ongoing despite alleviation of pain, signs, and symptoms. MRI is a useful technique in assessing subclinical progression of RA, when synovial inflammation, subchondral edema, and nonradiographically identifiable erosions cannot be detected clinically. In a previously referenced study by Brown and colleagues,90 MRI detected synovitis in 96% and bone marrow edema in 46% of patients with RA in clinical remission. In this group of patients, progression of radiographic joint damage continued in 19% over 1 year despite remaining in remission.85 Gandjbakhch and colleagues91 published pooled data from 6 patient cohorts, including 5 international centers (n = 81), confirming this important observation. These patients with RA were classified as being in clinical remission (DAS28-CRP <2.6) or having low disease activity (DAS28-CRP between 2.6 and 3.2). Wrist and/or hand synovitis and marrow edema on MRI were present in 95% and 35% of the patients, respectively.

The definition of remission in RA varies according to the composite measure utilized. With the advent of new more effective therapies for the treatment of RA, the concept of remission currently invokes more stringent criteria. This change is
reflected in new provisional definitions of remission developed jointly by the American College of Rheumatology (ACR) and the EULAR. A significant limitation in this new definition of remission is that imaging is not included and residual synovitis may exist in many patients whose disease appears inactive based on clinical examination. The accuracy of more stringent remission criteria for assessing the absence of inflammation was described by Saleem and colleagues using ultrasonography as the gold standard. Despite reduced signs and symptoms of inflammation using these more stringent remission criteria, power Doppler activity persisted in joints with no signs or symptoms; these data suggest that clinical criteria are sufficiently insensitive to accurately detect low but clinically relevant levels of inflammation.

MRI AS AN OUTCOME MEASURE IN EARLY RA CLINICAL TRIALS

Although conventional radiography is still the only approved and most widely used imaging tool for monitoring RA progression, MRI offers clear advantages and is increasingly used in clinical trials on RA. This imaging technique assesses structural joint damage (phase III/IV RA trials), evaluates a new compound’s anti-inflammatory efficacy and its impact on pre-erosive lesions (proof-of-concept phase I/II studies), and aids in the diagnosis/prognosis of study subjects. As opposed to radiographic outcomes, multiple randomized clinical trials, including studies on early RA, have used MRI to demonstrate efficacy of various RA therapies in a shorter time frame using fewer subjects (Table 3).

Conaghan and colleagues published the first randomized therapeutic trial using MRI as an outcome measure in early RA. MRI was used to monitor synovitis and erosions in patients randomized to MTX versus MTX plus intra-articular corticosteroids. Reduced MRI synovitis scores and significantly fewer joints with new erosions were found in the combination arm in comparison with MTX monotherapy. Quinn and colleagues assessed efficacy of very early treatment of RA with infliximab added to MTX; synovitis and erosions detected on MRI were reduced significantly by this combination at 1 year in comparison with MTX monotherapy. Durez and colleagues compared MTX, infliximab, and methylprednisolone in early RA (<1 year) using MRI and found significant differences between arms in synovitis, bone edema, and

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Therapy</th>
<th>MRI Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conaghan et al,</td>
<td>40</td>
<td>MTX/intra-articular corticosteroids vs MTX alone</td>
<td>Synovitis &amp; number of joints with new erosions in 3 mo</td>
</tr>
<tr>
<td>Quinn et al,</td>
<td>20</td>
<td>Infliximab/MTX vs placebo/MTX</td>
<td>Synovitis &amp; bone edema at 14 wk, new erosions at 24 wk</td>
</tr>
<tr>
<td>Durez et al,</td>
<td>44</td>
<td>MTX/methylprednisolone vs MTX/infliximab vs MTX alone</td>
<td>Synovitis &amp; bone edema at wk 18</td>
</tr>
<tr>
<td>Emery et al,</td>
<td>56</td>
<td>Placebo vs abatacept</td>
<td>Synovitis, osteitis, erosions at 6 &amp; 12 mo</td>
</tr>
<tr>
<td>Østergaard et al,</td>
<td>318</td>
<td>MTX/golimumab vs MTX alone</td>
<td>Synovitis, osteitis, erosions at 12 &amp; 24 wk</td>
</tr>
</tbody>
</table>
erosions. Abatacept has been studied in 56 anti-CCP–positive patients with undiffer-
entiated or very early RA. Active treatment per protocol was discontinued at 6 months.
Beneficial effects demonstrated by hand/wrist RAMRIS synovitis, erosion, and osteitis
scores persisted for 1 year in the abatacept group, providing evidence that early T-cell
modulation may favorably alter the course of RA. An MRI substudy of the GO-
BEFORE trial evaluated MTX-naive patients with RA randomized to MTX monotherapy
or a combination of MTX with golimumab. Serial measurements of synovitis, bone
edema/osteitis, and bone erosion were obtained using the RAMRIS system. MRI
revealed reductions in synovitis, osteitis, and bone erosion at week 12 and onward
in patients receiving golimumab plus MTX in comparison with those receiving MTX
monotherapy. MRI confirmed clinical and radiographic findings reported for the overall
study population with less than half the follow-up time and half the number of
patients. There are also several early RA MRI studies currently ongoing, and an
interest in incorporating this imaging technique into RA clinical trials has been rapidly
increasing.

SUMMARY

Early diagnosis and treatment have been recognized as essential for improving clinical
outcomes in patients with early RA. MRI is a sensitive modality that can assess both
inflammatory and structural lesions. It is increasingly being utilized in assessing early
RA due to its capacity to help identify the key pathologic features of this disease. MRI
has demonstrated greater sensitivity for detecting synovitis and erosions than both
clinical examination and conventional radiography and can help establish an early
diagnosis of RA. In addition, it may assist in differentiating RA from subsets of periph-
eral spondyloarthropathies by detecting enthesitis. Unique to MRI is the ability to
demonstrate bone marrow edema, a marker of active inflammation and the best
predictor for developing erosions in early RA.

MRI can assist in following the disease course in patients treated with traditional
DMARDs and biological therapies both in the clinic and in research trials. There-
fore, it is expected that MRI becomes the diagnostic imaging modality of choice
in RA clinical trials while remaining a useful tool for clinicians evaluating patients
with RA.

REFERENCES


68. Olech E, Crues JV 3rd, Yocum DE, et al. Bone marrow edema is the most specific finding for rheumatoid arthritis (RA) on noncontrast magnetic resonance imaging of the hands and wrists: a comparison of patients with RA and healthy controls. J Rheumatol 2010;37(2):265–74.


85. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent disso-
ciation between clinical remission and continued structural deterioration in rheu-
ultrasonography: results from a “Tech the teachers” rheumatologist course. Ann
and sensitivity to change of magnetic resonance imaging and radiographic
scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe
joints: a comparison of the OMERACT rheumatoid arthritis magnetic resonance
imaging score applied to different joint combinations and the Sharp/van der
imaging to assess and monitor early rheumatoid arthritis: the optimal joint combi-
89. Troum O, Peterfy C, Kaine J, et al. Tocilizumab reduces synovitis within 2 weeks
and pre-erosive osteitis within 12 weeks in patients with RA: results from a multi-
90. Brown AK, Quinn MA, Karim Z, et al. Presence of significant synovitis in rheuma-
toid arthritis patients with disease modifying antirheumatic drug-induced clinical
91. Gandjbakhch F, Conaghan PG, Ejbjerg B, et al. Synovitis and osteitis are very
frequent in rheumatoid arthritis clinical remission: results from an MRI study of
294 patients in clinical remission or low disease activity state. J Rheumatol
2011;38(9):2039–44.
92. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/Euro-
pean League against Rheumatism provisional definition of remission in rheuma-
93. Saleem B, Brown AK, Keen H, et al. Should imaging be a component of rheuma-
toid arthritis remission criteria? A comparison between traditional and modified
composite remission scores and imaging assessments. Ann Rheum Dis 2011;
94. Olech E. MRI in rheumatoid arthritis clinical trials: expensive imaging techniques
between synovitis and bone damage: a randomized magnetic resonance
imaging study of individual joints in patients with early rheumatoid arthritis.
96. Quinn MA, Conaghan PG, O’Connor PJ, et al. Very early treatment with inflix-
imab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis
reduces magnetic resonance imaging evidence of synovitis and damage,
with sustained benefit after infliximab withdrawal: results from a twelve-month
randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:
27–35.
arthritis: a randomized magnetic resonance imaging study comparing the effects
of methotrexate alone, methotrexate in combination with infliximab, and metho-
trexate in combination with intravenous pulse methylprednisolone. Arthritis
patients with undifferentiated inflammatory arthritis or very early rheumatoid