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Title: Short-term changes on magnetic resonance imaging predict long-term changes on radiography in rheumatoid arthritis: an analysis by an OMERACT Task Force of pooled data from four randomized, controlled trials

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Word count: 3,355
ABSTRACT

Objective: In rheumatoid arthritis (RA), magnetic resonance imaging (MRI) provides earlier detection of structural damage than radiography (X-ray) and more sensitive detection of intra-articular inflammation than clinical examination. This analysis was designed to evaluate the ability of early MRI findings to predict subsequent structural damage by X-ray.

Methods: Pooled data from 4 randomized controlled trials (RCTs) involving 1022 RA hands and wrists in early and established RA were analyzed. X-rays were scored using van der Heijde- or Genant-modified Sharp methods. MRIs were scored using Outcome Measures in Rheumatology (OMERACT) RA MRI Score (RAMRIS). Data were analyzed at the patient level using multivariable logistic regression and Receiver Operating Characteristic (ROC) curve analyses.

Results: Progression of MRI erosion scores at Weeks 12 and 24 predicted progression of X-ray erosions at Weeks 24 and 52, with areas under the curve (AUCs) of 0.64 and 0.74, respectively. Twelve- and 24-week changes in MRI osteitis scores were similarly predictive of 24- and 52-week X-ray erosion progression; pooled AUCs 0.78 and 0.77, respectively. MRI changes in synovitis at Weeks 12 and 24 also predicted progression of X-ray joint damage (erosion and joint-space narrowing) at Weeks 24 and 52 (AUCs = 0.72 and 0.65, respectively).

Conclusion: Early changes in joint damage and inflammation detected with MRI predict changes in joint damage evident on subsequent X-rays. These findings support the use of MRI as a valid method for monitoring structural damage in short-duration RCTs.

Key words: Magnetic Resonance Imaging, Rheumatoid Arthritis, Outcomes research
INTRODUCTION

Radiography has been the standard for assessing structural damage in RA RCTs for many years. Recently, however, discriminating differences in the rates of progression of X-ray damage between treatment arms has become more challenging. The most important reason for this has been recognition that exposing subjects with active RA to placebo for longer than 12 weeks is unethical. \(^1\) Accordingly, current US FDA guidance states that trials of >12 weeks should include an active comparator as the control or make provisions for rescue therapy. \(^2\) This poses a major obstacle to using X-ray in RCTs, because 24 weeks is typically necessary for radiographic demonstration of inhibition of structural progression, and longer treatment duration and larger numbers to resolve differences between active comparators. A method that more reliably detects structural progression within a 3 month time frame would therefore be helpful.

MRI has demonstrated criterion validity for osteitis and synovitis with histology, and construct validity for erosions when compared to computed tomography. \(^3,4\) Numerous studies have demonstrated MRI to be more sensitive than X-ray for detecting joint damage, and to detect synovitis and osteitis more sensitively than clinical examination does. Consequently, there has been a rapid increase in the use of MRI in RA RCTs over the past decade. \(^4\) A recent report by the Imaging Subcommittee of the ACR Clinical Trials Task Force \(^4\) concluded that MRI met the OMERACT validation filter for “truth, discrimination and feasibility.” \(^5,6\) It concluded that “among all of the currently available imaging modalities that have been validated with supportive data, MRI best serves the purpose of achieving sensitive ascertainment of structural
damage in RCTs while also providing objective measures of inflammatory predictors of damage,”. The report proposed analyzing recently completed RCTs that included both MRI and X-ray assessments to evaluate the predictive validity of MRI.

Accordingly, under the auspices of OMERACT, a task force of the members of the Imaging Subcommittee of the ACR Clinical Trials Task Force obtained and pooled data from four RCTs that included both serial MRIs (baseline to 12 and/or 24 weeks) and X-rays (baseline to 24 and/or 52 weeks) to evaluate the ability of MRI to predict long-term structural damage on X-rays at the individual patient level using a statistical meta-analysis approach. The overall prediction performance for the patient population was evaluated by ROC analysis.

**METHODS**

Data from 4 placebo RCTs (Table 1) in active RA patients were included, in which 1022 hands and wrists had both MRI and X-ray erosion scores at baseline. Information included RCT design, MRI protocols and baseline MRI and X-ray scores. Individual patient identification, study identification, and treatment assignments remained blinded. To maintain confidentiality, the RCTs are referred to as Trials A-D. Measurement schedules are summarized in Table 1. Additional methodological details are provided in online Supplementary Information. Multivariable logistic regression analysis coupled with a nonparametric spline method was performed to assess the ability of:

(1) Baseline MRI erosion scores and changes from baseline to Weeks 12 or 24 to predict X-ray progression (increase >0.5 in X-ray erosion scores from baseline to Weeks 24 or 52).
(2) Baseline MRI osteitis scores and changes from baseline to Weeks 12 or 24 to predict X-ray progression (increase >0.5 in X-ray erosion scores from baseline to Weeks 24 or 52).

(3) Baseline MRI synovitis scores and changes from baseline to Weeks 12 or 24 to predict X-ray progression (increases >0.5 in X-ray Total modified Sharp Scores from baseline to Weeks 24 or 52).

Specifically, the regression included three dummy variables indicating the four studies and five basis functions, \( MRI_0, \Delta_{MRI}, \Delta^2_{MRI}, (\Delta_{MRI} - 0.5)_+, (\Delta_{MRI})_+ \) and \( (\Delta_{MRI} + 0.5)_+ \), as independent variables, where \( MRI_0 \) and \( \Delta_{MRI} \) were the baseline MRI measure and short-term change in MRI measure (erosion, osteitis or synovitis score), respectively and \( x_+ \) represented the positive part of \( x \). The dummy variables representing four RCTs accounted for different progression rates among patients enrolled in each trial. The association between baseline and short-term changes in MRI and longer-term X-ray progression was characterized by the estimated linear combination of the aforementioned basis functions. The ROC curves of the estimated linear combination and AUC measurements were derived to determine the discriminative power of early changes in MRI endpoints for detecting subsequent structural progression by X-ray (AUC 0.5-0.7 = poor, 0.7-0.8 = acceptable, 0.8-0.9 = excellent, >0.9 = outstanding discrimination). All statistical analysis were performed using R-3.2.2 (The R foundation of Statistical Computing).

RESULTS

Table 2 shows baseline X-ray and MRI scores of included patients from the four trials. The association between 12-week change in MRI erosion score and 24-week change in X-ray erosion score was examined in trials A, B and C; week-12 MRI data was not available for trial D. After
excluding patients with missing information, the proportions of patients with X-ray erosion progression >0.5 Sharp units at Week 24 in trials A, B, C and the pooled cohort were 5.7% (10/166), 7.5% (69/855), 4.0% (22/534) and 6.1% (101/1555), respectively. ROC curve analysis of the prediction of X-ray progression at Week 24 based on a logistic regression model of baseline MRI erosion score and 12-week MRI progression in erosion score showed an AUC of 0.64 (95% Confidence Intervals (CI) =0.54-0.75) (Fig. 1). Since we were interested in the predictive value of MRI beyond that due to varying progression rates across trials, we also performed a logistic regression with trial indicators as the only independent variables, and the AUC for this was only 0.51 (95% CI=0.41-0.62). Adjusted for trial indicators, the predictiveness of 12-week MRI changes combined with baseline MRI erosion scores was statistically significantly greater than that using the trial indicator alone (p=0.031). Results by trial are shown in Table 3.

The association between 24-week change in MRI erosion score and 52-week change in X-ray erosion score was examined using data from trials B, C and D, as trial A did not include Week 52 X-ray data (Table 1). The proportions of patients with X-ray erosion progression at Week 52 were 9.0% (79/799), 4.3% (22/494), 7.8% (31/364) and 7.4% (132/1657) in trials B, C, D and the pooled cohort, respectively. The AUC for predicting X-ray erosion progression at Week 52 based on MRI erosion scores at baseline and change at Week 24 was 0.74 (95% CI=0.66-0.82) (Fig. 1), which is considered acceptable 7 If the logistic regression model considered only the trial as a variable, the AUC was poor (0.55; 95% CI=0.48-0.62). Adjusted for the trials, the predictiveness of 24-week change combined with baseline MRI erosion scores was highly statistically significantly greater than that using the trial indicator alone (p<0.001). Results by trial are shown in Table 3.
The association between 12-week change in MRI osteitis score and 24-week change in X-ray erosion score was examined in trials A, B and C; trial D did not include osteitis scores. ROC analysis of the prediction of X-ray erosion progression at Week 24 based on 12-week MRI progression in osteitis showed a near excellent AUC of 0.78 (95% CI=0.70-0.86) (Fig. 1). As a reference, if only trial indicators were included as the predictors, the AUC of the logistic regression was very poor (0.51; 95% CI=0.41-0.62) suggesting that trial indicators alone are not predictive of X-ray erosion progression. Adjusted for the trials, the predictiveness of 12-week change and baseline MRI osteitis scores was highly statistically significantly greater than that using the trial indicator alone (p<0.001). The association between 24-week change in MRI osteitis score and 52-week change in X-ray erosion score was examined in trials B and C; trial A lacked Week 52 X-ray data and trial D lacked osteitis scores. The AUC for predicting X-ray erosion progression based on MRI osteitis scores at baseline and for change at Week 24 was also near excellent (0.77; 95% CI=0.66-0.88) (Fig. 1) and again significantly greater (p<0.001) than that observed if only the trial indicator was considered in the regression model (0.57; 95% CI=0.47-0.67).

The association between 12-week change in MRI synovitis score and 24-week change in X-ray Total modified Sharp score was examined in trials A, B and C, as trial D did not include synovitis scores. At week 24, 9.7%(17/159), 9.7%(90/834), 8.6%(48/508) and 9.4%(155/1501) of hands demonstrated X-ray progression in trials A, B, C and the combined cohort, respectively. The AUC for predicting X-ray progression by MRI was acceptable (0.72; 95% CI=0.64-0.81) (Fig. 1), and significantly greater (p<0.001) than that observed if only the trial was considered (0.55; 95% CI=0.47-0.63).
The association between 24-week change in MRI synovitis score and 52-week change in X-ray Total modified Sharp Score was examined in trials B and C; trial A did not include Week 52 X-ray data and trial D did not include synovitis scores. At week 52, 12.0% (105/773), 9.7%(50/466) and 11.1%(155/1239) of hands demonstrated X-ray progression in trials B, C and the pooled cohort, respectively. The AUC of the ROC curve of MRI scores at baseline, week-24 MRI changes and trial data predicting X-ray progression at 52 weeks was 0.65 (95% CI=0.55-0.75) (Fig. 1), compared to 0.51 (95% CI=0.42-0.59, p=0.063) if only the trial was considered in the regression model.

**DISCUSSION**

This analysis shows that changes in joint damage and inflammation detected with MRI as early as 12 weeks predict changes in joint damage evident on subsequent X-rays. The current analysis of pooled data from four RCTs that included both MRI and X-ray demonstrated that progression of MRI erosion scores at Weeks 12 and 24 predict progression of X-ray erosions at Weeks 24 and 52. Twelve- and 24-week changes in MRI osteitis scores and synovitis scores were similarly predictive of 24-week and 52-week X-ray erosion progression. These findings corroborate those of Baker, et al. who further showed that MRI could allow a large reduction in the number of patients needed to assess structural damage in RA RCTs relative to that required with X-ray; MRI has been used in 13 multicenter, placebo RCTs reported to date, involving ten different biologic therapies. Nine RCTs included follow-up intervals ≤12-16 weeks, and in seven of the nine, MRI demonstrated statistically significant inhibition of progression of bone erosions with active treatment compared to placebo within that timeframe or showed a lack of inhibition consistent with later X-ray data within the trial.
Two of the nine RCTs were underpowered, but did show numerical suppression of erosion progression on early MRI (one RCT included only 20-21 patients per arm, and in contrast to the other RCTs, used only a single reader; the second RCT included 28-35 patients per arm, and showed numerical suppression of MRI erosion relative to placebo at 4 and 12 weeks and statistically significant suppression by 24 weeks).

Two of the nine RCTs discussed above and an active-comparator trial included MRI follow-up intervals of 4 weeks or less. Two of these trials demonstrated statistically significant suppression of synovitis and osteitis with MRI after only 2 weeks of active therapy, using 30-32 and 30-31 patients per arm, respectively. Both trials also showed inhibition of erosion with MRI at later time points. The third study was underpowered for RAMRIS, as noted above, but showed numerical decreases in osteitis, synovitis as well as in erosion progression with treatment compared to placebo at 4 weeks.

There were a number of limitations to this analysis. Some trial datasets could not be included because they did not have earlier MRI followed by later X-ray outcomes. Of the three studies referred to above with MRI follow-up intervals <12 weeks, one did not include X-ray and the other used 0.2T rather than 1.5T MRI, so we were unable to examine whether very early MRI inflammation measures would be predictive of X-ray structural outcomes. Another limitation was that all but one of the four datasets rescued placebo patients with active therapy by 24 weeks, confounding analyses based on X-ray data over longer time intervals. This is, however, an issue for all modern RCTs given current restrictions on the duration of placebo treatment. If by 24 weeks the most rapidly progressing patients in the placebo arm of a trial have received rescue
treatment, X-rays acquired at 24 weeks will underestimate the true placebo progression rate and thus the effect size of treatment. This limitation highlights why a method, such as MRI, that is sensitive enough to discriminate treatment effect within only 12 weeks, i.e., before rescue treatment, is needed. Similarly in this analysis, 24-week X-rays of patients rescued prior to 24 weeks will categorize some 12-week MRI progressors incorrectly as false positives, and artificially reduce the AUC. Which patients received rescue therapy was known in two of the four RCTs analyzed. However, removing these patients from analysis in one trial (A) did not significantly change the results (data not shown).

While the nonparametric spline fitting method used in this analysis is a flexible nonparametric approach, the resulting model may not have been optimal, and higher AUCs for the MRI measures could potentially have been attained by including, for example, additional information about the individual patients and more flexible basis functions of the MRI measures. Nevertheless, the estimated predictive value of MRI measures summarized by the AUCs of the ROC curve offers a conservative estimate of the true predictive value.

Lastly, we did not have access to MRI cartilage loss or MRI joint-space narrowing scores for any of the trials included in this analysis. However, the validity of assessing cartilage loss and joint-space narrowing with MRI has been well documented, and six RA RCTs have included MRI scoring of cartilage loss or joint-space narrowing; all have demonstrated good responsiveness.
In summary, on the basis of this analysis and previous studies, we conclude that MRI can detect progression of structural damage in RA RCTs as soon as 3 months and discriminate inhibition of progression of joint damage within this timeframe in placebo-controlled trials with approximately 30-70 patients per treatment arm. We therefore recommend MRI as an imaging modality to assess inflammation and joint damage in short-duration RCTs in RA to reduce the number of patients and trial duration required to demonstrate inhibition of structural damage.
# Tables

## Table 1. Imaging schedule for included trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
<th>Rescue treatment information</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MRI, X-ray</td>
<td>MRI</td>
<td>MRI, X-ray</td>
<td>N/A</td>
<td>Available</td>
</tr>
<tr>
<td>B</td>
<td>MRI, X-ray</td>
<td>MRI</td>
<td>MRI, X-ray</td>
<td>MRI, X-ray</td>
<td>N/A</td>
</tr>
<tr>
<td>C</td>
<td>MRI, X-ray</td>
<td>MRI</td>
<td>MRI, X-ray</td>
<td>MRI, X-ray</td>
<td>N/A</td>
</tr>
<tr>
<td>D</td>
<td>MRI, X-ray</td>
<td>N/A</td>
<td>MRI*, X-ray</td>
<td>X-ray</td>
<td>Available</td>
</tr>
</tbody>
</table>

* Only erosion scores available; N/A, not available
Table 2. Baseline X-ray and MRI scores

<table>
<thead>
<tr>
<th>Trial</th>
<th>X-ray Erosion</th>
<th>X-ray Total</th>
<th>MRI Erosion</th>
<th>MRI Osteitis</th>
<th>MRI Synovitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.25 (3.68),</td>
<td>5.36 (6.52),</td>
<td>13.63 (12.44),</td>
<td>7.23 (8.06),</td>
<td></td>
</tr>
<tr>
<td>(n = 185)</td>
<td>2.00 (0.75, 4.00)</td>
<td>3.00 (1.00, 7.00)</td>
<td>10.00 (4.50, 20.00)</td>
<td>4.50 (1.00, 10.50)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3.50 (6.29),</td>
<td>6.52 (12.40),</td>
<td>22.17 (22.96),</td>
<td>10.02 (11.21),</td>
<td></td>
</tr>
<tr>
<td>(n = 1272)</td>
<td>1.00 (0.50, 3.50)</td>
<td>1.50 (0.50, 6.00)</td>
<td>14.50 (10.50, 23.50)</td>
<td>6.00 (2.50, 13.50)</td>
<td>9.00 (5.00, 13.50)</td>
</tr>
<tr>
<td>C</td>
<td>5.44 (8.97),</td>
<td>12.06 (18.07),</td>
<td>23.50 (24.71),</td>
<td>4.98 (7.54),</td>
<td></td>
</tr>
<tr>
<td>(n = 888)</td>
<td>1.50 (0.00, 7.00)</td>
<td>3.00 (0.50, 16.50)</td>
<td>14.75 (6.88, 30.12)</td>
<td>2.00 (0.00, 6.63)</td>
<td>6.50 (3.50, 9.50)</td>
</tr>
<tr>
<td>D</td>
<td>5.90 (7.07),</td>
<td>12.42 (15.19),</td>
<td>18.72 (18.17),</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>(n = 450)</td>
<td>3.50 (1.00, 8.50)</td>
<td>6.50 (1.50, 18.50)</td>
<td>12.50 (5.25, 26.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>4.47 (7.17),</td>
<td>9.05 (14.62),</td>
<td>19.42 (20.03),</td>
<td>7.76 (9.59),</td>
<td></td>
</tr>
<tr>
<td>(n = 2795)</td>
<td>1.50 (0.50, 3.25)</td>
<td>2.50 (0.50, 11.00)</td>
<td>13.12 (6.50, 25.00)</td>
<td>4.25 (1.00, 11.00)</td>
<td>7.50 (4.50, 11.50)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation), median (upper, lower quartiles); N/A, not available; n, all hands including those with missing measurements at baseline or follow-up
Table 3. AUC (95% CI) values based on ROC curve analysis for individual trials

<table>
<thead>
<tr>
<th></th>
<th>Trial A</th>
<th>Trial B</th>
<th>Trial C</th>
<th>Trial D</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-week MRI erosion vs. 24-week X-ray erosion</td>
<td>0.60 (0.44-0.77)</td>
<td>0.67 (0.46-0.88)</td>
<td>0.65 (0.51-0.78)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>n = 169 hands</td>
<td>n = 218 hands</td>
<td>n = 153 hands</td>
<td></td>
</tr>
<tr>
<td>24-week MRI erosion vs. 52-week X-ray erosion</td>
<td>0.77 (0.62-0.93)</td>
<td>N/A</td>
<td>0.70 (0.44-0.95)</td>
<td>0.73 (0.62-0.85)</td>
</tr>
<tr>
<td></td>
<td>n = 208 hands</td>
<td>n = 148 hands</td>
<td>n = 387 hands</td>
<td></td>
</tr>
<tr>
<td>12-week MRI osteitis vs. 24-week X-ray erosion</td>
<td>0.78 (0.63-0.93)</td>
<td>0.82 (0.71-0.94)</td>
<td>0.51 (0.24-0.78)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>n = 169 hands</td>
<td>n = 218 hands</td>
<td>n = 153 hands</td>
<td></td>
</tr>
<tr>
<td>24-week MRI osteitis vs. 52-week X-ray erosion</td>
<td>N/A</td>
<td>0.77 (0.64-0.90)</td>
<td>0.67 (0.38-0.96)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>n = 208 hands</td>
<td>n = 148 hands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-week MRI synovitis vs. 24-week X-ray total</td>
<td>0.70 (0.56-0.84)</td>
<td>0.69 (0.54-0.84)</td>
<td>0.76 (0.65-0.88)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>n = 169 hands</td>
<td>n = 218 hands</td>
<td>n = 153 hands</td>
<td></td>
</tr>
<tr>
<td>24-week MRI synovitis vs. 52-week X-ray total</td>
<td>N/A</td>
<td>0.66 (0.52-0.80)</td>
<td>0.65 (0.50-0.79)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>n = 208 hands</td>
<td>n = 148 hands</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N/A, not available.
FIGURE LEGENDS

Figure 1. ROC curves for predicting 24-week (A, C, E) and 52-week (B, D, F) change in X-ray erosion (A-D) or Total modified Sharp (E, F) scores using 12-week (A, C, E) or 24-week (B, D, F) MRI changes in erosion (A, B), osteitis (C, D) and synovitis (E, F) scores based on pooled trial data. Red line: only trial information; black line: trial and MRI information (baseline scores and 12-week or 24-week change scores), grey line, theoretical absence of discrimination.

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COMPETING INTERESTS

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