

Towards Imaging Remission: Determining an MRI Inflammatory Activity-Acceptable State in RA

Written by Toni Rizzo

Treatment of rheumatoid arthritis (RA) has improved substantially in the past decade, and a state of remission (generally defined as the absence of inflammatory activity, based on clinical criteria) or low disease activity (LDA) is now a realistic goal that is achieved by a substantial proportion of patients. Although patients may be in clinical remission or have LDA, radiographic structural progression may occur and has been noted in magnetic resonance imaging (MRI) findings. It has also been suggested that patients with MRI findings that are indicative of inflammation are more likely to progress to radiographic joint destruction. Taken together, these observations suggest that the inclusion of a definition of MRI remission may be clinically relevant to future definitions of remission in patients with RA. What is not clear, however, is whether or not there is a critical amount of MRI inflammation (eg, synovitis and/or bone edema) below which RA is not likely to progress to joint destruction.

Espan A. Haavardsholm, MD, Diakonhjemmet Hospital, Oslo, Norway, reported results from a series of studies that assessed the use of MRI to identify subclinical inflammation. The objectives of the study were to define the MRI characteristics of clinical remission and LDA (Outcome Measures in Rheumatoid Arthritis Clinical Trials [OMERACT] 10 criteria), to determine the predictive factors for structural progression in these patients, and to identify an MRI cutoff for nonprogression.

Databases from 6 cohorts were collected from 5 international centers. The study assessed 294 RA patients (70% women, median age 55 years, disease duration 2.3 years, Disease Activity Score 28-C-reactive protein [DAS28-CRP] 2.2, Simplified Disease Activity Index [SDAI] 3.9, and Clinical Disease Activity Index [CDAI] 3.1). More than half (57%) of the participants were rheumatoid factor (RF)-positive; 54% were anti-cyclic citrullinated peptide-positive; 66% had radiographic erosions. A total of 213 patients (74%; 213/287) were considered to be in clinical remission (DAS28-CRP <2.6); 81 were classified as having LDA (DAS28-CRP $2.6 \leq$ but <3.2). MRIs were assessed according to the OMERACT RA MRI scoring system (RAMRIS). MRI inflammatory activity in wrist and/or metacarpophalangeal joints was observed in the majority (synovitis, 95%; bone edema [osteitis], 35%) of patients. The median (IQR) RAMRIS score was 6 (3 to 9) for synovitis and 0 (0 to 2) for osteitis. Synovitis and osteitis were not less frequent in DAS28 clinical remission (synovitis/osteitis 96%/35%) than in LDA (91%/36%). A trend toward lower frequencies of osteitis in patients in SDAI and CDAI remission was observed [Gandjbakhch F et al. *J Rheumatol* 2011].

The following steps were undertaken using an underlying conditional logistic regression model that was stratified per cohort, with radiographic progression as the dependent variable:

- Step 1: Multivariate stepwise regression with baseline DAS28-CRP, age, disease duration, RF status, disease activity (low vs remission), biologic treatment, disease-modifying antirheumatic drugs (DMARD) treatment, RAMRIS synovitis, erosions and bone marrow edema
- Step 2: Receiver operating characteristic analysis used to identify the best cutoff point(s)
- Step 3: Analysis with the identified cutoff point(s) in the model
- Step 4: Identification of possible interaction effects (several possible effects were included, such as disease activity (low/remission), biologic/DMARD treatment, and RF)
- Step 5: Final model with interaction effects

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Following Step 1, only RAMRIS synovitis was identified as a significant predictor and was entered into the next model ($p < 0.01$). A simple ROC analysis identified a cutoff value for RAMRIS synovitis of 6 (0 to 6 vs ≥ 7); however, after an additional analysis to test different models with possible cutoffs in the range of 4 to 7 and applying Akaike's Information Criterion, the model with the best fit was the model with a synovitis cutoff of ≥ 6 versus 0 to 5. Step 3 yielded a significant model with an odds ratio for progression of 2.42 (95% CI, 1.236 to 4.724; $p = 0.01$) for above versus below the cutoff value of synovitis. In Step 4, RF status yielded a significant interaction with synovitis (interaction $p = 0.044$). The final estimates show that patients who are RF-positive and have a RAMRIS synovitis score of ≥ 6 have an odds ratio of 4.4 for radiographic progression versus those with a synovitis score of ≤ 5 (Table 1).

Table 1. Final Estimates.

Wald Confidence Interval for Odds Ratios		
Label	Estimate	95% CI*
Synovitis RAMRIS 6 vs 0–5 at RF=positive	4.412	1.715 to 11.352
Synovitis RAMRIS 6 vs 0–5 for RF=negative	1.090	0.399 to 2.979

*CI=confidence limits; RF=rheumatoid factor.

Less than 20% ($n = 21$) of RF-negative patients progressed radiographically, while 27% ($n = 36$) of RF-positive patients progressed. Of the RF-positive patients who did progress, 42% ($n = 28$) had a RAMRIS synovitis score > 5 , whereas $< 12\%$ ($n = 8$) of RF-positive patients with RAMRIS synovitis score 0 to 5 progressed.

The strengths of this study include a large patient population and the use of experienced readers and RAMRIS at all centers. The results may be limited by the fact that there were multiple readers, the follow-up times differed at the individual centers (6 to 12 months), and different joint areas were assessed by radiograph and MRI.

The investigators concluded that RF-negative patients and RF-positive patients who are in remission or have LDA and who have a RAMRIS synovitis score ≤ 5 have a favorable prognosis with regard to nonprogression of radiographic damage. High RAMRIS synovitis score is a strong predictor of radiographic progression.

The authors further concluded that, from a clinical perspective, RF-positive patients who are in clinical remission or have LDA could benefit from an MRI scan for risk stratification. They recommend that RF-positive patients with RAMRIS synovitis scores ≥ 6 should continue to be closely monitored, while patients with scores of ≤ 5 may be candidates for less rigorous follow-up and possible step-down therapy.



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