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Comprehensive Appraisal of MRI Findings in Sustained RA Remission: Sub-Study of the TEAR Trial

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Abstract

Objective—To evaluate the effect of sustained ACR/EULAR Boolean remission on residual joint inflammation assessed by magnetic resonance imaging (MRI) and to secondarily evaluate

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other clinical definitions of remission, within an early seropositive rheumatoid arthritis (RA) cohort.

Methods—A subcohort of 118 RA patients were enrolled from patients who completed the two-year double-blind randomized Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial. Patients received a single contrast enhanced 1.5 Tesla MRI of their most involved wrist. Two readers scored MRI for synovitis, osteitis, tenosynovitis, and erosions. Clinical assessments were performed every three months during the trial and at time of MRI.

Results—The subcohort was 92% seropositive with mean age 51 years, duration 4.1 months, and DAS28-ESR 5.8 at TEAR entry. Total MRI Inflammatory Scores (tenosynovitis+synovitis +osteitis) were lower among patients in clinical remission. Lower MRI scores were correlated with longer duration of CDAI remission (rho=0.22, p=0.03). At the time of MRI, 89 patients had no wrist pain/tenderness/swelling; however, all 118 patients had MRI evidence of residual joint inflammation after two years. No statistically significant differences in damage or MRI inflammatory scores were observed across treatment groups.

Conclusion—This is the first detailed appraisal describing the relationship between clinical remission cut-points and MRI inflammatory scores within a RA RCT. The most stringent remission criteria (2011 ACR/EULAR and CDAI) best differentiate the total MRI inflammatory scores. These results document that 2-years of triple therapy or TNF+methotrexate treatment in early RA does not eliminate MRI evidence of joint inflammation.

Key Indexing Terms

Remission; MRI; Outcome Measures; Rheumatoid arthritis

INTRODUCTION

Despite significant advancements in the therapeutic management of RA patients, subsequent research has suggested that radiographic progression can continue even when clinical remission criteria are achieved (1–4). When combinations of a disease modifying anti-rheumatic drug [DMARD] (usually methotrexate) and a biologic agent result in a prolonged clinical remission or low disease activity, it may be tempting to discontinue the expensive biologic agent. However, it is still unclear which patients are the best candidates for withdrawal (5). Several reports suggest that about half or more of RA patients withdrawn from a biologic do not remain in remission after 12 to 18 months (6, 7).

Some research groups propose defining “true” RA remission by the incorporation of sensitive imaging measures (ultrasound and/or magnetic resonance imaging [MRI]) (3, 8). MRI is one of the most sensitive imaging measures of joint inflammation due to its ability to visualize synovitis, tenosynovitis, and bone marrow edema or lesions (‘osteitis’). Two recently published articles, by the American College of Rheumatology (ACR) RA Clinical Trials Task Force Imaging Group/Outcome Measures in Rheumatology MRI Inflammatory Arthritis Working Group and by the European League Against Rheumatism (EULAR), highlight the significant progress of RA MRI research over the last decade (8, 9): a) MRI is more sensitive in detecting joint inflammation compared to clinical examination, b) MRI osteitis is a strong independent predictor of radiographic progression (10–14), and c) MRI

synovitis and osteitis are responsive to therapy, as seen in several RA randomized controlled clinical trials (RCTs), with several more studies in progress (15–25).

To the best of our knowledge, no studies have assessed MRI findings across different clinical remission criteria in a predominantly seropositive early RA cohort, patients who are at higher risk for radiographic progression of erosive disease. Most importantly, studies using MRI to evaluate clinical remission states have been performed in heterogeneous observational RA cohorts with varied treatment regimens, longer disease duration, and overall low rates of seropositivity.

The purpose of this MRI substudy to the parent Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) Trial was to examine 2 years' of clinical data collected during this randomized double-blind clinical trial (26), to assess the following hypotheses: 1) Clinical remission criteria (ACR/EULAR 2011 Remission Criteria as the primary analyses) correlate with MRI inflammatory scores, 2) Longer duration of clinical remission is associated with lower MRI inflammatory scores, 3) MRI joint inflammatory scores are associated with radiographic disease progression, and 4) MRI joint inflammatory scores of early RA patients are similar across the 4 different arms of the TEAR trial.

PATIENTS AND METHODS

Subjects

The parent TEAR trial enrolled a total of 755 RA patients and 476 patients completed the 2-year trial. Of the 476 RA patient-completers of the TEAR trial with DAS28 scores, 118 patients were enrolled in the MRI sub-study. Details of the TEAR clinical trial have been previously published (26–29). Early seropositive DMARD-naïve RA patients were enrolled into the TEAR trial with the following inclusion criteria: ≥18 years of age, met American College of Rheumatology (ACR) RA 1987 Diagnostic Criteria, TJC28 ≥ 4, SJC 28 ≥ 4, rheumatoid factor (RF) or anti-CCP positive or ≥ 2 erosions, <3 years of disease duration, biologic naïve, and minimal prior use of methotrexate (MTX) (18.6% with <50mg MTX within MRI sub-study), hydroxychloroquine (HCQ) (1.7% within MRI sub-study), or sulfasalazine (SSZ) (<1.7% within MRI sub-study) [Table 1]. Patients were randomized into four treatment arms within a 2 × 2 factorial design: 1A) immediate treatment with MTX and etanercept (ETN) [N=43/159 within MRI sub-study/total number of completers], 1B) immediate treatment with MTX, SSZ, and HCQ [N=14/76 within MRI sub-study], 2A) step-up from MTX alone to addition of ETN (if DAS28-ESR≥3.2) at 6 months [N=42/166 within MRI sub-study], and 2B) step-up from MTX alone to addition of SSZ and HCQ (if DAS28-ESR≥3.2) [N=19/75 within MRI sub-study] at 6 months. In the latter two arms, if DAS28-ESR was less than 3.2 at 6 months, monotherapy with MTX was continued for the duration of the two-year study (in 11 patients from group 2A and 5 patients from group 2B within MRI sub-study).

After completing the two-year controlled clinical trial, the following TEAR patients were eligible to enroll into the MRI study: 1) Patients able to safely obtain MRI; and 2) Patients at sites where 1.5 Tesla MRI was available. Patients were excluded from the MRI study if they experienced: 1) Recent surgery of the wrist joint and/or surgical replacement of the wrist

joint; 2) Pregnancy; 3) Renal insufficiency or dialysis due to reports of nephrogenic systemic fibrosis with use of gadolinium contrast.

The 118 RA patients who completed the two-year multicenter randomized double blind TEAR trial were recruited from 17 U.S. sites for an ancillary MRI sub-study (26). Only 118 of the 476 TEAR patients who completed the study were enrolled due to not all TEAR sites' participation in the sub-study and budgetary constraints.

Design

Both the parent TEAR trial and MRI ancillary study received local IRB approval and participants were consented separately to each study. Patients were blinded to treatment assignment and remission status during the TEAR study. Consenting patients (N=118) received MRI (1.5 Tesla magnet) with gadolinium contrast of the historically most involved wrist after the completion of their week 102 TEAR trial visit at participating TEAR sites between August 15, 2008 and February 28, 2009. MRIs were obtained as per OMERACT guidelines (30). All MRIs utilized a circumferential wrist coil for uniformity. The sequences and plains included were axial T1-weighted, axial fat-saturated T2-weighted, coronal T1-weighted, coronal short tau inversion recovery (STIR), coronal 2D gradient echo (GRE). The slice thickness was 3mm (skip 1 mm) for coronal plains and 4 mm (skip 1 mm) for axial plains with exception of the coronal GRE sequence where the slice thickness was at 1.4 mm (skip 0.2 mm). The field of view was 100 mm for all plains and the matrix 256 ×192 for coronal plains and 258–512 × 160 for the axial plains. MRI scans were done in 70 patients within eight weeks of the week 102 visit, and 48 patients after eight weeks (range 8.8–146 weeks, median 51 weeks, mean 59 weeks). A subgroup analysis was conducted for patients with MRI done within eight weeks of their TEAR week 102 visit to assess the sensitivity of the observed associations to timing of MRI.

Study Measures

RAMRIS and Tenosynovitis Scores—The RA MRI Scoring method (RAMRIS) for the wrists was used to evaluate synovitis, osteitis, and erosions (30–32). Tenosynovitis was scored according to Haavardsholm et al. with grading from 0–3 and range from 0–30 (evaluation of 10 areas) (33). The total MRI inflammatory score was defined as the sum of the synovitis, osteitis, and tenosynovitis scores of the wrist (34). Erosions representing a fixed measure of damage and were not used in the total MRI inflammatory score. Maximum possible scores were 9 for synovitis, 45 for osteitis, 150 for erosions, and 30 for tenosynovitis. The maximum total MRI Inflammatory Score was 84 (the sum of synovitis, osteitis, and tenosynovitis scores).

A rheumatologist and musculoskeletal radiologist (EH and KM) independently scored all 118 MRIs. The average scores of the two readers were used for subsequent analyses. The readers were blinded to the patients' disease activity and treatment assignment. Subsequently, both readers re-read an additional 15 randomly selected MRIs. The inter-reader interclass correlation coefficients (ICC) were 0.50 for total inflammatory MRI score, and intra-reader ICCs were 0.88 and 0.97 respectively for each of the two readers.

Remission RA Measures Evaluated

Self-reported duration and severity of morning stiffness and fatigue (visual analogue scales [VAS] not originally included in the TEAR study) were determined at the time of the MRI to permit determination of all six components of the 1981 ACR remission criteria at that point in time. In addition, patient global VAS, arthritis severity VAS, and pain VAS were determined at the time of the MRI. If the MRI was performed more than two months after the 102 week TEAR visit, the patient's rheumatologist obtained: ESR, TJC28, SJC28, physician global, and list of current DMARDs/biologic agents. The modified Health Assessment Questionnaire (mHAQ) was measured at baseline, and at each of the 12 week visits. The self-reported complete HAQ-Disability Index (HAQ-DI) was also added to the self-administered patient questionnaire at the time of the MRI.

The 2011 ACR Boolean-Based definition of remission was the primary remission criteria evaluated. Patients were considered to be in remission if at any time point patients satisfied all of the following: TJC ≤ 1, SJC ≤ 1, ESR ≤ 25, and patient global assessment ≤ 1 (we used ESR because C-reactive protein (CRP) was not obtained during TEAR or at the time of the MRI). Other remission criteria were also evaluated as secondary analyses: 1981 ACR Remission Criteria, clinical disease activity index (CDAI), DAS28/ESR-4 item (DAS28/ESR), and HAQ-DI. The original 1981 ACR Remission Criteria required that patients meet at least five of the six clinical remission characteristics for two consecutive months: morning stiffness ≤ 15 min, no fatigue, no joint pain (by history), no swollen joints, no tender joints, and ESR ≤ 30 mm/hr for female or 20 mm/hr for male. In this study they were modified slightly to apply to a single point in time, rather than requiring two consecutive months. The DAS28/ESR and CDAI were calculated every 12 weeks throughout the TEAR study. DAS28-ESR (cut-point <2.6), and CDAI (cut-point ≤2.8) published cut-points were utilized to determine remission (35–37). Lastly, previously established cut-point of <0.5 for HAQ-DI was used to define functional remission (38).

Radiographs

Plain radiographic series of the hands, wrists and feet at baseline, 48, and 102 weeks of therapy were scored by 2 independent readers according to the Sharp/van der Heijde method (SHS), as previously described (26). Radiographic progression was defined by a total Sharp/van der Heijde Score increase of one unit or more between baseline and week 102. Paired radiographic data were available for 85 of the 118 patients.

Statistical Analyses

Descriptive statistics were calculated for patients' demographic and clinical characteristics. Clinical disease activity measures and Total Sharp/van der Heijde Score were compared between baseline and time of MRI with paired t-tests.

The primary analysis was to compare MRI measures between subjects meeting/not meeting the ACR/EULAR 2011 remission criteria at the time of the MRI. Additional comparisons used the following alternative remission criteria: ACR 1981 remission criteria, DAS28ESR <2.6, CDAI≤2.8, and HAQ-DI<0.5. The analyses used t-tests to compare total MRI inflammatory scores between patients who did versus those that did not meet the various

remission criteria. Effect sizes (differences in means of those meeting vs not meeting remission definitions divided by the pooled standard deviation) were calculated to contrast the differences in MRI scores across the remission definitions.

Next, patients were separated into four mutually exclusive categories based on the duration of remission over the two-year TEAR study: never in remission, intermittent remission, sustained remission for a period of one year or longer before the MRI, and sustained remission for a period shorter than one year before the MRI. Kruskal-Wallis analyses were used to compare tenosynovitis, synovitis, osteitis, erosion, and total MRI inflammatory scores across the remission duration categories. Pairwise Wilcoxon Rank Sum analyses were conducted to assess score differences between remission duration categories where Kruskal-Wallis analyses were significant.

Kruskal-Wallis analyses were used to evaluate the total MRI inflammatory scores across treatment groups assigned at TEAR entry. Wilcoxon Rank Sum analyses were conducted to compare the tenosynovitis, synovitis, osteitis and total MRI inflammatory scores between patients who had radiographic progression and those who did not.

The association between length of time in remission and total MRI inflammatory Score was assessed through Spearman correlation analyses and visual assessment of scatter plots. The proportion of time in remission between entry into TEAR and time of MRI was estimated by assuming that the 6 weeks before and after each 3 month clinical assessment was represented by that assessment, and that the assessment at the time of the MRI represented half the time between it and week 102 visit. Thus, when patients met remission criteria at the clinical assessment, they were considered in remission for half the time period between the measurement and the immediate prior and subsequent assessment. The sum of the time in remission and the total time under observation were used to calculate the percent of time under observation in remission for each patient.

A subgroup analysis was conducted for the set of patients with MRI performed within eight weeks of their TEAR week 102 visit to assess the sensitivity of the observed associations to the timing of MRI. In addition, all analyses were conducted using the average scores of the two individual MRI readers. The results of the analyses based on individual readers were found to be similar to the results obtained when the average score of the two MRI readers were used.

Statistical analyses were conducted using SAS v9.3 (SAS Institute, Carey, NC) and R v2.15.3 (TheRProject.org) and p-values <0.05 were considered statistically significant.

RESULTS

A total of 118 patients obtained MRI after the 102 week visit of the TEAR study. At entry in to the TEAR study, the average age of the patients was 51 years. Most patients were white (79%), female (75%), with disease duration of less than one year (92%), severe disease activity (mean DAS28-ESR 5.8), functional impairment (mean mHAQ 0.99), and were seropositive for RF/anti-CCP (92%) [Table 1]. Medications prior to study entry included prednisone (31%), non-steroidal anti-inflammatory drugs (NSAIDs) (75%), and minimal

amounts of MTX or HCQ (20%). The baseline characteristics were similar to the overall TEAR study population of 755 RA patients (26). The only statistically significant differences were for pain VAS and prednisone use (pain VAS mean 4.7 [MRI TEAR substudy] vs 5.3 [rest of cohort], prednisone percent use 30% vs 44%, respectively).

Table 1 also describes statistically significant improvement of disease activity measures at the time of the MRI, compared to the baseline values ($p<0.01$). DAS28-ESR was 2.9, SJC/TJC 2.8–2.9, and average mHAQ 0.3. The total Sharp/van der Heijde score was 3.8 at 2 years compared to 3.2 baseline score, with 11.5% patients having a score of 0 ($p=0.10$).

Due to missing data, DAS28/ESR and CDAI was calculable in 115 patients, and ACR/EULAR Boolean in 111 patients with complete records. Total MRI Inflammatory Scores were statistically lower among patients who met 2011 ACR/EULAR Boolean remission criteria and remission by CDAI ($p<0.05$), but not for DAS28-ESR remission [Table 2].

Duration of Sustained Remission

None of the 118 patients had an MRI score of zero for synovitis or erosions; two had zero scores for tenosynovitis, and 30 had zero scores for osteitis (Table 3). Patients were separated into four mutually exclusive remission duration categories for ACR/EULAR Boolean, DAS28-ESR, and CDAI. For the more stringent definitions of remission (2011 ACR/EULAR Remission and CDAI≤2.8), the total MRI inflammatory scores were significantly different across the remission duration categories ($p<0.05$). Patients with sustained remission >1yr or <1yr had the lowest total MRI inflammatory scores, while the ‘never in remission’ and ‘intermittent remission’ categories had higher total MRI inflammatory scores. The DAS28<2.6 remission criteria did not demonstrate any significant differences across the categories. Pairwise comparisons indicated that total MRI inflammatory scores were greater among patients never in remission relative to those in remission at the time of MRI or those with intermittent remission, for CDAI criteria ($p=0.04$) and ACR Boolean-based criteria ($p=0.02$) [Table 3].

Synovitis scores were significantly different across the remission duration categories for ACR Boolean remission ($p<0.05$), while osteitis and erosion scores did not differ across any remission duration categories for DAS28-ESR, CDAI or ACR Boolean. Although only 29 patients had tenderness or swelling on physical examination of the wrist, all 118 patients had some evidence of inflammation of the wrist detected through MRI.

Spearman correlation analyses and visual assessment of scatter plots were used to assess the association between percent of time in remission and total MRI inflammatory score (Figure 1). Scatter plots of total MRI inflammatory score and percent time under observation in remission indicate a weak negative association between the inflammation detected by MRI and time in remission based on the four remission criteria. Spearman correlation coefficients ranged from −0.04 to −0.22, with time in remission based on CDAI criteria demonstrating the strongest and only significant correlation ($p=0.03$).

Lastly, a subgroup analysis was conducted to evaluate the sensitivity of observed associations to the timing of MRI. All analyses were replicated for the subset of patients

with MRI done within eight weeks of TEAR week 102 visit (N=70), and the results were similar to those observed for the overall cohort (not shown). This indicates that the observed associations were not sensitive to the variation in time of MRI.

Radiographic Progression and MRI Total Inflammatory Scores

Among all patients, the mean total Sharp/van der Heijde Score was 3.2 (SD=7.0) at baseline and 3.8 (SD=6.8) at week 102. Patients with radiographic progression (N=14) had higher mean tenosynovitis, synovitis, and osteitis scores than patients without radiographic progression (N=71), although the individual differences were not significant. However, the total MRI inflammatory scores were significantly greater among patients with radiographic progression (mean=13.7, SD=4.8) relative to those without progression (mean=11.3, SD=7.6) (p=0.03).

MRI Total Inflammatory Scores and Treatment Groups

Damage and total MRI inflammatory scores were compared across treatment groups using Kruskal-Wallis analyses based on patients' intention-to-treat group assignment at entry into the TEAR trial (Table 4). There were equal proportions of MTX monotherapy patients in both step-up groups (11 patients in ETN+MTX step up and 5 patients in triple therapy step up group). No statistically significant differences in damage or MRI inflammatory scores were observed among treatment groups. In addition, there were no statistically significant differences across treatment groups when limiting the analyses to the patients meeting DAS<3.2 at 6 months (Table 4b).

Discussion

In this early RA cohort of 118 patients treated over a 2-year period during an RCT, not a single patient was devoid of MRI inflammatory findings (tenosynovitis, osteitis, or synovitis) at the study end. This study demonstrates that total MRI inflammatory scores are best differentiated by the most stringent clinical remission criteria (CDAI and 2010 ACR Boolean Criteria). However, there were no differences in MRI findings between patients meeting DAS28-ESR 2.6 cutpoint and those who did not. The small cohort of patients with radiographic progression of SHS≥1 had higher total MRI inflammatory scores compared to patients without radiographic progression. However, it is understandable that the extraarticular tenosynovitis component of the total MRI inflammatory score may not directly contribute to joint erosions. There was also a weak but statistically significant correlation between a longer duration of CDAI remission and lower total MRI inflammatory scores. This study is first to report MRI findings across triple therapy and ETN plus MTX groups after 2 years of therapy. Although statistical power was limited given relatively small sample sizes, no significant differences in damage or MRI inflammatory scores were observed among treatment groups: immediate ETN plus MTX, immediate triple therapy, step up ETN plus MTX, and step up triple therapy. After 2-years of treatment, the step-up groups did not demonstrate higher MRI inflammatory score findings compared to the immediate start groups, supporting the MTX-first recommendations of O'Dell et al. for the TEAR trial (29).

In an observational cohort study, Brown et al. evaluated 107 RA patients with 1.5T wrist MRI who were deemed to be in clinical remission by their rheumatologist; 57% of patients met DAS28 and 55% 1981 ACR remission (39). For the patients achieving DAS28<2.6, 96% demonstrated MRI synovitis, 52% osteitis, and 26% tenosynovitis, while patients achieving 1981 ACR remission had slightly lower rates of osteitis and tenosynovitis. Compared with our study, their patient population was more heterogeneous: longer mean disease duration (mean 7 years), lower rate of rheumatoid factor positivity 64%, and less than 25% of patients were on combination therapy (even fewer on biologic therapy). The MRI findings in our early seropositive RA patient-cohort demonstrated overall high rates of synovitis (100%), osteitis (76%), and tenosynovitis (98%) for patients meeting DAS28 remission after 2 years of therapy. The lower MRI inflammation rates seen by the Brown et al. group may be partly due to the fact that the research group did not use T2-weighted or STIR sequences as recommended by OMERACT RAMRIS and/or due to the inherent differences in the study populations.

Another study published by Gandjbakhch et al., assessed MRIs of the wrists and/or MCPs of 294 RA patients from 6 cohorts within 5 international centers across CDAI, SDAI, and DAS28 remission cutpoints (included the Brown et al cohort) (40). The field strength varied across the 6 cohorts from 0.2T to 1.5T, the average disease duration was 2.3 years, 57% of patients were rheumatoid factor positive, and only 15% of patients were on biologics. All patients meeting remission cutpoints demonstrated high rates of synovitis (88–90%), but lower rates of osteitis (23–32%). Our results show similar high rates of synovitis for patients who achieve remission cutpoints, but our osteitis rates were more than double this study's findings.

We evaluated the hypothesis that longer duration of clinical remission is associated with lower MRI inflammatory scores by examining subcategories with >1 year and ≤1 year of remission prior to the MRI and calculating the proportion of time in remission with MRI scores. There does not appear to be a strong relationship between duration of remission and MRI inflammation, although patients who did not achieve remission had higher MRI scores. Only 16% of patients in our study had progression of radiographic damage (≥1 SHS) during the prior 2 years, yet 78% had evidence of osteitis on MRI. Since osteitis is considered the strongest predictor of future radiographic progression in early RA, this finding may be consistent with published reports of radiographic progression during clinical remission (1–4). In a follow-up paper, Brown et al. showed that MRI synovitis at baseline was significantly associated with radiographic progression 1-year later (41). Another MRI study by Gandjbakhch et al of 85 RA patients in either remission or low disease activity, assessed 0.2T MRI of the wrist and hand at baseline, 6 months, and 12 months (42). The authors demonstrated that MRI osteitis was predictive of future MRI erosive disease.

Our study is limited to patients with early RA treated with combination of DMARDs and/or etanercept, who completed the TEAR trial. The 118 patients in the MRI study had tolerated the assigned aggressive DMARD/biologic regimens without serious adverse effects requiring discontinuation and with sufficient benefit to have continued the blinded treatment for 24 months. While all of the patients in our cohort demonstrated some evidence of MRI inflammation, it is still unclear what the long-term prognostic implications are of these

findings since the protocol did not allow for long-term follow up. In addition, our inter-reader reliability was low compared to recent MRI studies. However, similar results were obtained when evaluating each of the MRI scorers independently. Lastly, our study only evaluated MRIs of the wrist without including the MCPs, while several recent randomized RA clinical trials have included MCP1–5 as well as the wrist.

Some studies have evaluated control subjects without RA and have demonstrated low levels of synovitis, osteitis, and/or tenosynovitis (39, 43). One study evaluated 10 healthy volunteers with 3T dynamic contrast enhanced MRI at baseline, 12 weeks, 24 weeks, and 52 weeks, and suggested a small and stable inherent variability of MRI inflammatory measures over time. We were not able to directly relate the normal findings seen in healthy controls with our cohort. Minimally clinically significant differences for MRI osteitis, synovitis and tenosynovitis have not yet been established. Thus, the clinical importance of the observed high rates of osteitis is not certain, especially in the setting of aggressive treat-to-target management.

In conclusion, our study provides a detailed, comprehensive appraisal of MRI inflammatory findings after 2-years of aggressive sustained therapy with either ETN plus MTX or triple therapy in a well-defined seropositive early RA cohort. MRI inflammatory scores were lower during clinical remission, but did not reach zero for any patients, regardless of the duration of remission or treatment assignment prior to the MRI. Of all remission definitions, the 2010 ACR/EULAR Boolean and CDAI remission criteria best differentiate MRI inflammatory findings. It is still unclear whether attainment of clinical remission justifies the promotion of drug holidays or cessation of RA treatment. With strong prior published data suggesting that osteitis predicts future radiographic progression and our observation of high rates of osteitis despite attaining clinical remission, it is currently ill-advised to discontinue therapy until future studies suggest otherwise.

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SIGNIFICANCE AND INNOVATION

1. Experts highlight significant progress of RA MRI research over the last decade and demonstrate that MRI osteitis is a strong predictor of radiographic progression. No RCT studies have examined MRI findings with clinical remission and evaluated impact of remission duration.
2. After 2 years of treatment with triple therapy or TNF inhibitor plus methotrexate, all 118 patients had evidence of residual MRI inflammation. Evidence of osteitis was present in 78% of patients.
3. The ACR/EULAR 2011 Boolean and CDAI remission criteria best differentiated the total MRI inflammatory score, where 23% of patients met ACR/EULAR 2011 remission criteria after 2 years of therapy.
4. This is the first study to evaluate MRI findings between triple therapy and TNF inhibitor plus methotrexate. While the sample size was small and future studies will be required to validate these findings, there were no perceived differences in MRI findings between the groups.

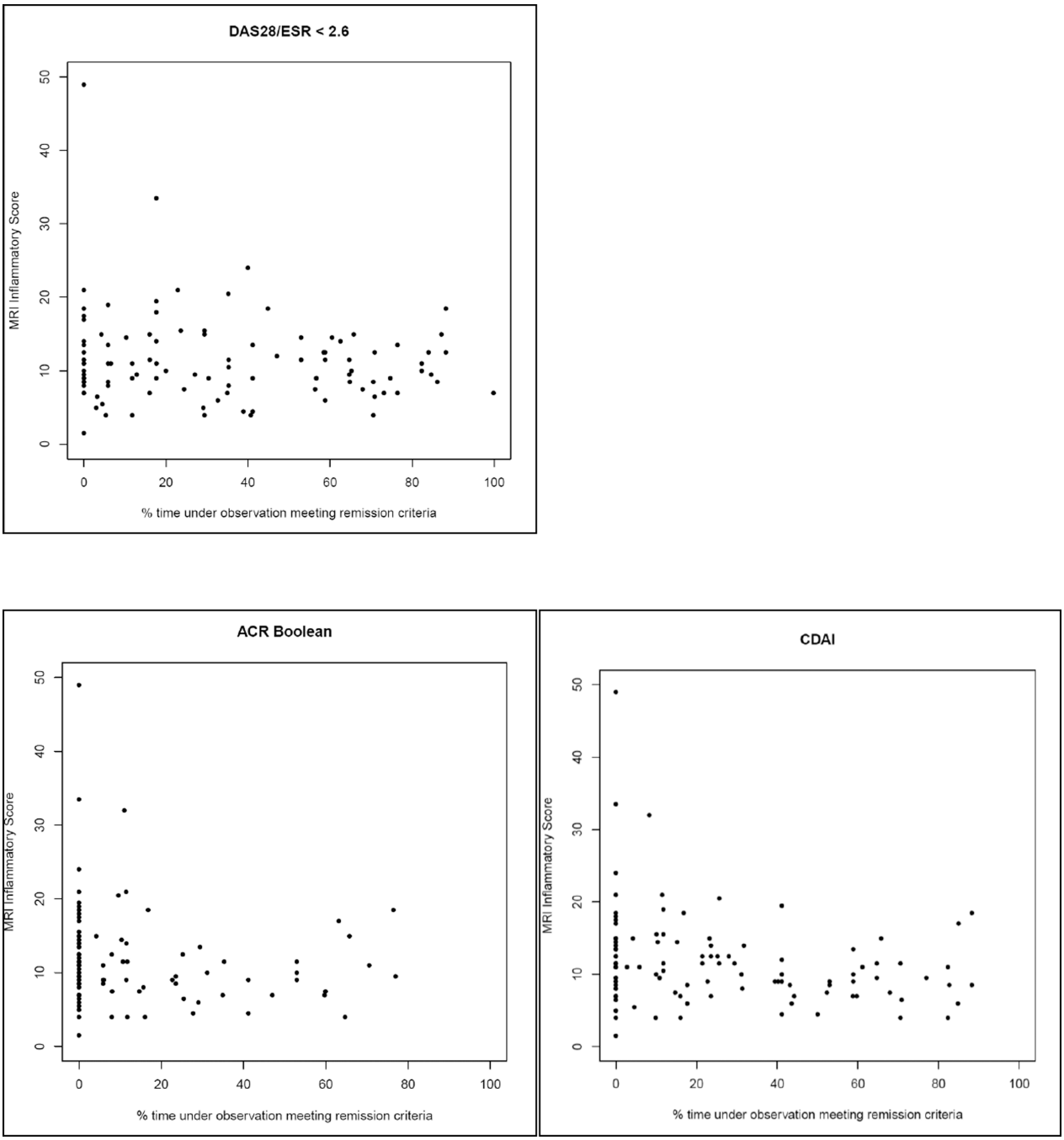

Figure 1.

Scatter plots display the association between percentage of time in remission and total MRI Inflammatory Score for DAS28-ESR<2.6, ACR/EULAR Boolean remission, and CDAI remission criteria. Spearman correlation analyses were conducted to quantify this association percent of time in remission and total MRI Inflammatory Score for the DAS28-ESR<2.6 ($\rho=-0.044$, $p=0.650$), ACR/EULAR Boolean remission ($\rho=-0.178$, $p=0.067$), and CDAI ($\rho=-0.216$, $p=0.025$) remission criteria.

Table 1

Characteristics of RA Subjects in MRI Sub-study

	Baseline	Time of MRI
Age (years), mean (SD)	50.5 (13.0)	
Female, %	74.6	
Race, %		
White	78.8	
African-American	9.3	
Other	11.9	
Disease Duration (years), %		
≤ 1 year	92.4	
1 – 3 years	7.6	
Prior Medications to Study Entry, %		
Prior Prednisone	31.4	
Prior NSAIDS	74.6	
Prior MTX (<50mg total)	18.6	
Prior HCQ (<1 month)	1.7	
Prior Other DMARD (<1 month)	1.7	
Family History of RA, %	31.4	
Rheumatoid Factor or Anti-Cyclic Citrullinated Peptide Antibody Positive, %	91.5	
DAS28 item, mean (SD)	5.8 (1.0)	2.9 (1.4)†
Pain VAS (1–10), mean (SD)	6.4 (2.3)	3.2 (2.3)†
Patient global VAS (1–10), mean (SD)	5.6 (2.2)	2.8 (2.0)†
Physician global VAS (1–10), mean (SD)	6.5 (1.5)	2.4 (1.6)†
Tender joint count (28), mean (SD)	13.5 (6.4)	2.9 (4.8)†
Swollen joint count (28), mean (SD)	12.5 (5.4)	2.8 (4.4)†
mHAQ, mean (SD)	0.99 (0.32)	0.3 (0.4)†
Total Sharp/van der Heijde Score mean (SD)*	3.2 (7.0)	3.8 (6.8)

NSAIDs= non-steroidal anti-inflammatory drugs, MTX= methotrexate, HCQ= hydroxychloroquine, DMARD= disease modifying anti-rheumatic drugs, DAS= Disease activity score, ESR= erythrocyte sedimentation rate, VAS= visual analogue scale, mHAQ= modified health assessment questionnaire

*Radiographic assessments were conducted at baseline and week 102

†Paired t-test p-value<0.01.

Table 2

Comparison of Total MRI Inflammatory Scores for Remission Criteria at the Time of the MRI

	Remission Criteria Met					
Remission Criteria	**No**		**Yes**			
	N	**Total Inflammatory MRI Score Mean (SD)**	**N**	**Total Inflammatory MRI Score Mean (SD)**	**p-value**	**Effect Size**
DAS28/ESR <2.6	63	11.71 (6.9)	51	11.10 (4.9)	0.60	0.10
CDAI ≤2.8	75	12.71 (7.6)	40	9.48 (3.6)	<0.01	0.61
1981 ACR Remission Criteria	86	12.01 (7.0)	18	9.36 (3.6)	0.08	0.50
2011 ACR/EULAR Boolean-Based Remission Definition	86	12.37 (6.9)	25	9.28 (3.5)	0.03	0.59
HAQ-DI < 0.5*	78	12.28 (7.5)	34	10.16 (4.0)	0.17	0.37

* Functional remission

Table 3

MRI Inflammatory/Damage Scores Categorized by Time Prior to MRI for Remission Criteria

A) DAS28 Remission < 2.6

	Never in remission		Intermittent remission		Sustained Remission ≤ 1yr		Sustained Remission > 1yr		p-value
	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	
Tenosynovitis	24	6.0 (2.5) / (1)	39	5.5 (3.5) / (0)	27	5.5 (3.5) / (1)	24	4.8 (3.0) / (0)	0.55
Synovitis	24	3.5 (1.3) / (0)	39	3.5 (1.5) / (0)	27	3.0 (1.5) / (0)	24	3.3 (1.0) / (0)	0.30
Osteitis	25	1.5 (4.0) / (7)	39	1.0 (2.5) / (10)	27	0.5 (4.0) / (7)	24	1.0 (1.8) / (5)	0.98
Erosions	25	7.5 (5.0) / (0)	39	7.5 (7.0) / (0)	27	6.5 (9.0) / (0)	24	7.3 (3.8) / (0)	0.80
Total Inflammatory Score	24	11.0 (6.3) / (0)	39	10.0 (7.5) / (0)	27	10.5 (7.0) / (0)	24	10.0 (4.5) / (0)	0.71

B) Clinical Disease Activity Index Remission ≤ 2.8

	Never in remission		Intermittent remission		Sustained Remission ≤ 1yr		Sustained Remission > 1yr		p-value
	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	
Tenosynovitis	39	5.5 (3.5) / (1)	36	6.3 (4.0) / (0)	25	5.0 (4.0) / (1)	15	4.5 (2.0) / (0)	0.11
Synovitis	39	3.5 (1.0) / (0)	36	3.5 (1.0) / (0)	25	3.0 (1.5) / (0)	15	3.0 (1.5) / (0)	0.13
Osteitis	40	1.8 (5.0) / (9)	36	1.0 (2.8) / (8)	25	0.5 (2.0) / (9)	15	0.5 (1.0) / (4)	0.13
Erosions	40	8.5 (8.0) / (0)	36	7.8 (4.0) / (0)	25	6.5 (5.0) / (0)	15	7.6 (5.0) / (0)	0.10
Total Inflammatory Score	39	11.5 (6.5) / (0)	36	11.0 (6.3) / (0)	25	9.0 (4.5) / (0)	15	8.5 (3.0) / (0)	**0.05***

C) 2011 ACR/EULAR Boolean-Based Remission Definition

	Never in remission		Intermittent remission		Sustained Remission ≤ 1yr		Sustained Remission > 1yr		p-value
	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	
Tenosynovitis	60	6.0 (3.3) / (1)	26	5.3 (3.5) / (0)	17	4.5 (3.5) / (1)	8	5.3 (1.3) / (0)	0.41

C) 2011 ACR/EULAR Boolean-Based Remission Definition									
					Sustained Remission				p-value
	Never in remission		Intermittent remission		≤ 1yr		> 1yr		
	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	N	Median (IQR) / (# zeroes)	
Synovitis	60	3.5 (1.0) / (0)	26	3.5 (1.0) / (0)	17	2.5 (3.5) / (0)	8	3.0 (0.8) / (0)	**0.03***
Osteitis	61	1.5 (3.5) / (14)	26	0.8 (3.5) / (7)	17	1.0 (2.0) / (5)	8	0.5 (0.8) / (2)	0.41
Erosions	61	8.5 (6.0) / (0)	26	7.0 (7.5) / (0)	17	6.5 (5.0) / (0)	8	6.0 (3.5) / (0)	0.15
Total Inflammatory Score	60	11.5 (5.8) / (0)	26	9.3 (7.0) / (0)	17	8.5 (4.5) / (0)	8	9.3 (2.8) / (0)	**0.05***

Asterisk (*) indicates $p<0.05$

Table 4

a. MRI Inflammatory/Damage Scores Categorized by Treatment Group					
	ETN + MTX Immediate Median (IQR) N=43	**MTX+SSZ+HCQ Immediate Median (IQR) N=14**	**ETN + MTX Step-up Median (IQR) N=42**	**MTX+SSZ+HCQ Step-up Median (IQR) N=19**	**p-value**
Tenosynovitis	4.5 (3.0)	6.5 (3.5)	6.0 (2.5)	4.5 (3.0)	0.09
Synovitis	3.0 (1.0)	4.0 (3.0)	3.5 (1.0)	3.5 (1.0)	0.19
Osteitis	1.0 (5.0)	2.3 (8.0)	0.5 (1.5)	1.5 (2.5)	0.35
Erosions	7.0 (5.5)	11.3 (8.5)	7.0 (5.0)	7.5 (6.5)	0.27
Total Inflammatory Score	9.5 (8.0)	13.5 (9.5)	9.5 (3.0)	10.0 (5.5)	0.20

b. Patients with DAS score <3.2 at week 24 by treatment group assignment					
	ETN + MTX Immediate Median (IQR) N=18	**MTX+SSZ+HCQ Immediate Median (IQR) N=5**	**ETN + MTX Step-up Median (IQR) N=11**	**MTX+SSZ+HCQ Step-up Median (IQR) N=5**	**p-value**
Tenosynovitis	4.8 (3.0)	7.5 (1.5)	6.5 (2.5)	5.0 (2.0)	0.16
Synovitis	3.3 (1.5)	3.0 (2.5)	3.0 (1.5)	3.5 (0.5)	0.99
Osteitis	1.3 (5.0)	2.5 (6.0)	0.5 (1.5)	1.5 (3.0)	0.24
Erosions	9.0 (5.0)	13.0 (8.5)	7.0 (4.0)	6.5 (5.5)	0.30
Total Inflammatory Score	11.5 (8.0)	13.5 (8.0)	10.0 (3.0)	9.0 (1.0)	0.42