Development and validation of rheumatoid arthritis magnetic resonance imaging inflammation thresholds associated with lack of damage progression

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Abstract

Objective

To determine thresholds for rheumatoid arthritis (RA) magnetic resonance imaging scores (RAMRIS) associated with a low risk of structural damage progression.

Methods

MRI of the dominant hand was performed and RAMRIS scores determined at weeks 0, 24, and 52. X-rays were performed and van der Heijde-Sharp scores (vdHS) determined. In a development cohort (n=297) the changes in MRI erosion score and vdHS score were determined over the 24-week to 52-week interval and progression was defined as change >0.5. We identified 24-week thresholds for synovitis and osteitis that provided >90% sensitivity for imaging progression over the 24 to 52-week interval. The performance of these cut-offs was tested in a validation cohort (n=217).

Results

In the development cohort, synovitis or osteitis scores ≤3 by 24 weeks were associated with a low probability of progression on MRI and x-ray. The coefficient for osteitis was stronger than that of synovitis in models predicting x-ray and MRI progression. Therefore, a total inflammation score was weighted on osteitis (x2). An inflammation score ≤9 was more frequently attained than DAS28 remission (64 vs. 38) and was associated with low probability of progression regardless of attainment of clinical remission. In the validation cohort, there was a low odds of MRI progression among those with low synovitis [OR 0.27 (0.086,0.82) p=0.02], osteitis [OR 0.20 (0.085, 0.49) p<0.001] and inflammation scores [OR 0.12 (0.033, 0.41) p=0.001].

Conclusion

Attainment of low MRI single-hand synovitis and osteitis is not uncommon and predicts a lack of structural progression in RA, independent of clinical remission.

Key words

rheumatoid arthritis, magnetic resonance imaging, structural damage, clinical trials

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Introduction

Determining levels of rheumatoid arthritis (RA) disease activity that are associated with improved long-term outcomes including a low risk of structural damage progression is of interest. A number of different criteria to define clinical remission have been defined. For example, patients that meet a state of comprehensive disease control, consisting of low disability, low disease activity, and halting of radiographic progression, are noted to have improved short-term and long-term outcomes (1).

Magnetic resonance imaging (MRI) has been used to accurately measure inflammatory activity in the joints and has been used in a number of clinical trials to assess the effectiveness of therapies for rheumatoid arthritis (RA). Previous studies have shown that MRI measures of synovitis and osteitis, as well as early changes in these measures, are reliable, sensitive to change, and predictive of subsequent radiographic joint damage progression independent of clinical disease activity (2-5). MRI has also established the concept of subclinical inflammation, even in apparent clinical low disease activity states (6).

To date, it remains unclear how best to define a low activity state based on MRI findings. One previous study defined an inflammatory activity acceptable state for synovitis by assessing a cut-off to determine radiographic progressors using pooled MRI cohorts (7). However, it remains unclear what thresholds for both synovitis and osteitis should be utilised to identify patients with minimal to no risk of progression. Such thresholds would have implications for clinical trials, where these dichotomous outcomes might be used as surrogate endpoints for non-progression. Furthermore, the identification of low activity states based on MRI could have important implications for the potential future use of MRI in clinical care.

The objective of this study was to define and validate thresholds of synovitis and osteitis based on the RA MRI Scoring (RAMRIS) system that are associated with a very low risk of subsequent radiographic progression (with greater than 90% sensitivity) and to determine if these thresholds are predictive beyond that of clinical thresholds.

Methods

Study setting

This study is a secondary analysis of the GO-BEFORE (Clinicaltrials.gov identifier NCT00361335), and GO-FORWARD (NCT00264550) randomised clinical trials. Both were multicenter, double-blind, placebo-controlled trials that evaluated the efficacy of golimumab (GLM), a fully human monoclonal antibody to tumour necrosis factor alpha (TNF-α), for the treatment of RA. The trial results have been previously published (8-10). Both studies evaluated the effect of golimumab in combination with methotrexate compared to methotrexate and golimumab monotherapy. The GO-BEFORE study was performed in 637 methotrexate (MTX) and biologic-naïve subjects; 291 of these were included in this analysis who had MRIs scored for synovitis, osteitis, and/or bone erosion. GO-FORWARD included 444 subjects who previously had inadequate response to methotrexate; 217 had MRIs that were performed and scored. The trial was conducted according to the principles of the Declaration of Helsinki. As such, all patients provided written informed consent before participating in the study. This secondary analysis of de-identified data was considered exempt by the Internal Review Board at the University of Pennsylvania.

Patients 18 years or older who met the American College of Rheumatology (ACR) 1987 criteria for RA for at least the past 3 months and had active disease were recruited into the MRI sub-study at participating sites. Patient visits occurred at regular 4-week intervals as part of the original trial. Data collection at each visit included independent, blinded assessments of disease activity using the DAS28 with CRP [DAS28(CRP)].

Magnetic resonance imaging

The details of the acquisition of MRI images has been described in detail elsewhere (2). Briefly, MRIs of the patient's dominant wrist and 2nd-5th metacarpophalangeal (MCP) joints were obtained using 1.5T MRI with contrast en-

hancement. The MR sequences were as follows: axial T1 fast spin echo (FSE) pre-contrast, coronal T1 FSE pre-contrast, coronal short tau inversion recovery (STIR) (or T2 fat-suppressed pre-contrast) and coronal T1 fat-suppressed post-contrast.

Images were scored by two independent readers who were blinded to the image time-point or sequence (visit number), patient identity, and treatment group. The average score of 2 readers was determined for synovitis (0–9 for wrist joint, 0–21 for wrist plus MCP joints), osteitis (0–69) and bone erosions (0–230), using the RAMRIS system). The change in MRI erosion between 24 and 52 weeks was determined and structural damage progression was defined as a change in MRI erosion score of >0.5 as previously described (2, 12). A change of >0.5 demonstrated the best test characteristics in predicting later radiographic progression (2).

Radiographs of hands and feet

Radiographs of hands and feet were performed at baseline, week 24, and week 52. Radiographs were scored by two blinded readers using the van der Heijde-Sharp (vdHS) method. Change from baseline in vdHS scores at 24 and 52 weeks was determined using centralised readers and standardised methods, as previously described (13, 14). X-ray progression was defined as a change in vdHS score of greater than 0.5. This cut-off has previously been chosen to reduce misclassification error (1, 2, 12, 15-17). Also studied was another frequently used definition of progression: a change in vdHS of >3 units (18).

Statistical analysis

The data were analysed with STATA 14 software *(StataCorp, LP, College Station, TX)*. In a development cohort (GO-BEFORE; methotrexate-naive) the changes in MRI erosion score and vdHS score were determined over the 24-week to 52-week interval. We aimed to identify 24-week thresholds for synovitis (total possible score 21) and osteitis (possible score 230) that provided greater than 90% sensitivity for MRI erosion progression and vdHS progression over the 24 to 52 week interval. The coefficient for osteitis was stronger than that of synovitis in multivariable models predicting x-ray and MRI progression. Therefore, when these scores were combined into a single total inflammation score, the score was weighted on osteitis (x2). Rates of progression were illustrated over the range of synovitis, osteitis, and the total inflammation score at the beginning of the interval. The proportions progressing below different cut-points were described and the log-odds of progression was illustrated using lowess curves.

The performance of the cut-offs was then tested in a validation cohort (GO-FORWARD; methotrexate failures). The rate of MRI erosion progression from weeks 24 to 52 among those above and below the identified thresholds was defined. In addition, the proportion with vdHS progression from 24 to 52 weeks was defined. The odds ratios for progression among those who reached the specified thresholds were determined using logistic regression adjusting for treatment allocation and clinical disease activity at week 24. Finally, the odds ratios for radiographic progression from baseline to week 52 (the primary trial outcome) among those who reached the identified thresholds by 24 weeks were also determined.

Table I. Basic characteristics of the study population.

	GO-BEFORE (Development)	GO-FORWARD (Validation)
n	291	217
Age (years)	49.0 (12.6)	50.5 (10.9)
Female, n (%)	237 (81.4)	180 (83.0)
Race		
Asian, n (%)	75 (25.8)	60 (27.7)
White, n (%)	190 (65.3)	136 (62.7)
Disease duration (years)	1.2 (0.6, 3.3)	6.3 (3, 12.5)
DAS28(CRP)	5.60 (1.06)	5.28 (1.01)
CRP (mg/dl)	1.2 (0.5, 2.7)	0.8 (0.1, 2)
HAQ, baseline	1.56 (0.69)	1.35 (0.69)
CCP positive, n (%)	222 (76.3)	178 (82.0)
vdHS, baseline	5.5 (2, 21.5)	16.5 (2.5, 50.5)
RAMRIS scores		
Synovitis, baseline	9.5 (5.0)	7.0 (4.3)
Osteitis, baseline	6.5 (2.5, 15.5)	2 (0, 10.7)
Bone erosion, baseline	14.5 (10, 22.5)	13.8 (10, 22.5)

Results

Characteristics of the study population in the MRI sub-study are shown in Table I, and have been previously described in detail ([2, 13, 17, 19, 20).

Establishment of cut-offs in the development cohort

In the development cohort, the association between synovitis, osteitis, and the total inflammation score at 24 weeks with the log-odds of progression on MRI and x-ray over the 24 to 52 week interval is illustrated in Figure 1 and in Supplementary Figures 1 and 2. The actual proportions progressing between 24 and 52 weeks among those with synovitis, osteitis, and total inflammation scores below different cut-offs at week 24 are also shown in Table II. For both synovitis and for osteitis, the approximate cut-off below which the probability of progression was less than 0.10 for MRI or x-ray in the development cohort from 24 weeks to 52 weeks was ≤3. For synovitis, the rate of progression from 24 to 52 weeks on MRI was 2.6% (1/39) among those with synovitis scores ≤3 by 24 weeks. For osteitis, the proportion with progression from 24 to 52 weeks on MRI was 2.9% (2/70) among those with osteitis scores ≤3. Furthermore, the proportion with progression on x-ray (both hands and both feet) between 24 and 52 weeks was 7.9% (3/38) among those with synovitis scores ≤3 and 5.9% (4/68) among those with osteitis scores ≤3. The percent of subjects with radiographic progression ≥3 units in vdHS among those with low synovitis and osteitis scores were 0% (0/38) and 0% (0/68), respectively.

For the total inflammation score, the cut-off below which very few subjects

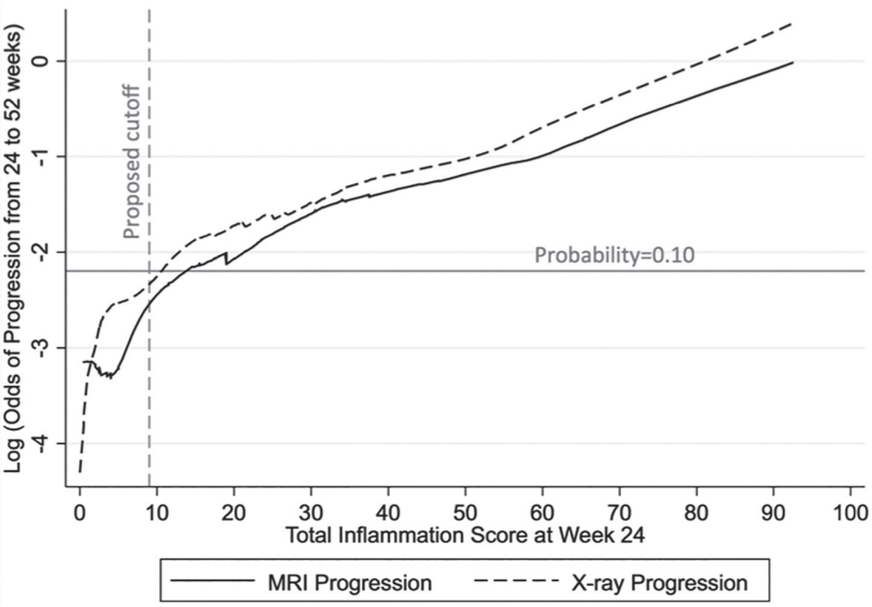

Fig. 1. Lowess plot of association between 24-week measures of MRI total inflammation scores with log-odds of progression in MRI erosion score and vdHS score from 24 to 52 weeks.

Table II. Actual number of subjects below MRI and clinical thresholds at 24 weeks and the actual number who progress on MRI and x-ray between 24 and 52 weeks in the development cohort (GO-BEFORE).

	Number (%) Below cut-off	MRI Erosion	MRI Erosion >3 units	X-ray	X-ray >3 units
Synovitis score (n=206)					
≤1	10 (5%)	0%	0%	10.0%	0%
≤3	39 (19%)	2.6%	0%	7.9%	0%
≤5	74 (36%)	9.5%	0%	11.0%	2.7%
≤7	111 (54%)	10.9%	1.8%	12.7%	1.8%
≤10	159 (77%)	12.0%	3.1%	13.4%	2.6%
Osteitis score (n=216)					
≤1	44 (20%)	4.6%	0%	5.7%	0%
≤3	70 (32%)	2.9%	0%	5.9%	0%
≤5	102 (47%)	6.9%	0%	8.0%	0%
≤7	125 (58%)	9.6%	0%	8.1%	0.8%
≤10	150 (69%)	9.3%	0.7%	10.8%	1.4%
Inflammation score (n=206)					
≤3	15 (7%)	0%	0%	6.7%	0%
≤9	53 (26%)	3.8%	0%	6.8%	0%
≤15	81 (39%)	7.8%	0%	6.9%	0%
≤21	111 (54%)	10.6%	0%	9.7%	0%
≤30	139 (67%)	11.9%	2.2%	11.9%	1.5%
Clinical remission (n=216)					
DAS28 <2.6	59 (27%)	5.1%	0%	8.6%	5.2%

would be expected to progress was ≤9 (Table II, Fig. 1). The proportion progressed on MRI from 24 to 52 weeks among those with inflammation scores ≤9 was 3.8% (2/53). In addition, progression on x-ray (both hands and both feet) was 5.9% (3/48). The proportion with radiographic progression ≥3 units in vdHS among those with low inflammation scores was 0% (0/51).

Evaluation of cut-offs in the validation cohort

The actual proportions progressing between 24 and 52 weeks among those with synovitis, osteitis, and total inflammation scores below different cut-offs at week 24 in the validation cohort are shown in Table III. The proportion that progressed on MRI between 24 and 52 weeks among subjects who reached synovitis scores ≤3 by week 24 was 7.8% (4/51) (Table IV). Among those above this threshold at 24 weeks, the proportion demonstrating MRI progression was 25.7% (19/74). This translates into lower odds of progression in MRI bone erosion over the 24 to 52 week interval compared to those who did not reach that threshold [OR 0.25 (0.078, 0.78) p=0.02] (Table IV).

Similarly a low osteitis score at 24 weeks was associated with a low percent with progression of 9.0% (9/100) and a lower odds of progression in bone erosion over the 24 to 52 week interval [OR 0.20 (0.085, 0.48) p<0.001]. Finally, a low inflammation score at 24 weeks was associated with a low rate of MRI progression (4.7%, 3/64) and much lower odds of MRI progression over the 24 to 52 week interval [OR 0.12 (0.033, 0.41) p=0.001] (Table IV). In addition, rates of x-ray progression between 24 and 52 weeks in the trial (both hands and both feet) were lower among those reaching low synovitis, osteitis, or inflammation scores by 24 weeks (Table III), with lower odds of radiographic progression compared to those who did not reach these thresholds (Table IV). There was no x-ray progression from 24 to 52 weeks >3 vdHS units among those who reached low synovitis, osteitis, or total inflammation scores by week 24 (not shown). Furthermore, there was less radiographic progression between 0 and 52 weeks (the primary trial endpoint) among those who reached low activity as defined by synovitis, osteitis, and total inflammation score by week 24 (Table IV). Associations between low measures of synovitis, osteitis, and total inflammation and the odds of MRI or x-ray progression were not attenuated with adjustment for treatment group or the DAS28(CRP) at week 24.

Comparison to clinical remission

In GO-BEFORE (methotrexate naïve patients) there was fair to poor agreement between clinical remission based on the DAS28(CRP) and low activity based on MRI synovitis (Kappa: 0.21, p=0.001), osteitis (Kappa: 0.13, 0.01), and total inflammation score (Kappa: 0.17, p=0.003). For example, among

Table III. Actual proportion progressing on MRI and x-ray among patients who reach clinical remission and/or MRI low activity in the GO-FORWARD study.

MRI Progression (24 to 52 weeks)			
	Clinical remission	No clinical remission	Total
Synovitis score			
Low	1/13 (7.7%)	3/38 (7.9%)	4/51 (7.8%)
Not low	2/20 (10%)	21/74 (28.4%)	21/94 (22.3%)
Total	3/33 (9.1%)	24/112 (21.4%)	
Osteitis score			
Low	1/23 (4.4%)	8/77 (10.4%)	9/100 (9%)
Not low	3/13 (21%)	17/47 (36.2%)	20/60 (33%)
Total	4/36 (11%)	25/124 (20.2%)	
Total inflammation Score			
Low	0/15 (0%)	3/49 (6.1%)	3/64 (4.7%)
Not low	3/18 (16.7%)	21/63 (33.3%)	24/81 (29.6%)
Total	3/33 (9.1%)	24/112 (21.4%)	
X-ray progression (24 to 52 weeks)			
	Clinical remission	No clinical remission	Total
Synovitis score			
Low	2/12 (16.7%)	1/27 (3.7%)	3/39 (6.5%)
Not low	1/20 (5%)	11/62 (17.7%)	12/82 (14.6%)
Total	3/32 (9.4%)	12/89 (13.4%)	
Osteitis score			
Low	1/19 (5.3%)	4/58 (6.9%)	5/77 (6.5%)
Not low	2/14 (14.3%)	8/37 (21.6%)	10/51 (19.6%)
Total	3/33 (9.1%)	12/95 (12.6%)	
Total inflammation score			
Low	1/14 (7.1%)	1/40 (2.5%)	2/54 (3.7%)
Not low	2/18 (11.1%)	11/49 (22.5%)	13/47 (27.7%)
Total	3/32 (9.4%)	12/89 (13.4%)	

Table IV. Percentage of subjects progressing on MRI and x-ray among those who reached the defined thresholds in the validation cohort (GO-FORWARD). Odds of progression also shown after adjusting for treatment allocation and clinical disease activity (DAS28) at 24 weeks.

Percentage and odds of MRI progression between 24 to 52 weeks by 24-week MRI score (n=161)						
	Synovitis		Osteitis		Synovitis + (2*Osteitis)	
	Low (<=3)	Not low	Low (≤3)	Not low	Low (≤9)	Not low
Week 24 MRI score	7.8% OR=0.26 (0.082, 0.80)*	24.5%	9.0% OR=0.19 (0.077, 0.46)***	32.8%	4.7% OR=0.11 (0.030, 0.39)***	29.6%
Percentage and odds of x-ray progression between 24 to 52 weeks by 24-week MRI score (n=128)						
	Synovitis		Osteitis		Synovitis + (2*Osteitis)	
	Low (<=3)	Not low	Low (≤3)	Not low	Low (≤9)	Not low
Week 24 MRI score	7.7% OR= 0.47 (0.12, 1.83)	15.1%	6.5% OR= 0.28 (0.091, 0.90)*	19.6%	3.7% OR= 0.16 (0.034, 0.74)*	19.4%
Percentage and odds of x-ray progression 0 to 52 weeks by 24-week MRI score (n=159)						
	Synovitis		Osteitis		Synovitis + (2*Osteitis)	
	Low (<=3)	Not low	Low (≤3)	Not low	Low (≤9)	Not low
Week 24 MRI score	8.3% OR= 0.17 (0.056, 0.54)**	35.4%	14.4% OR= 0.21 (0.95, 0.47)***	41.3%	11.1% OR= 0.22 (0.086, 0.55)***	35.7%

*p<0.05, **p<0.01, ***p<0.001.

150 subjects who were not in clinical remission at week 24, 31 (21%) had reached low activity based on the total inflammation score. Only 1 of these subjects (3%) progressed. Overall, progression rates for those reaching clinical remission were low (Table II).

There was no significant agreement between clinical remission based on DAS28(CRP) and low activity based on MRI synovitis (Kappa: 0.042, p=0.31), osteitis (Kappa: 0.0004, p=0.50), or total inflammation score (Kap:0.013, p=0.43) at week 24 in GO-FORWARD (methotrexate failures). Overall, approximately 2–3 times more subjects achieved MRI remission than clinical disease remission (Table III). Among individuals achieving clinical remission, those that also had achieved MRI low activity generally had marginally lower progression rates. In contrast, among those who did not achieve DAS28 clinical remission, patients who reached a low total inflammation score had a much lower risk of progression on both x-ray and MRI (Table III).

The MRI activity cut-offs demonstrated greater discrimination of 24–52 week progressors on MRI and x-ray. For example, the areas-under-the-curve (AUCs) for MRI progression for DAS28(CRP) remission and low total inflammation score on MRI were 0.57 and 0.70, respectively (p for comparison = 0.02). The AUCs for x-ray progression for DAS28 remission and a low total inflammation score were 0.54 and 0.68 respectively (p for comparison = 0.04).

Discussion

This study demonstrated that individuals who reach a low level of MRI inflammation (synovitis or osteitis) during a clinical trial are substantially less likely to demonstrate structural damage progression, supporting the importance of low levels of MRI-detected inflammation. Cut-offs for synovitis, osteitis and combined inflammation scores identified individuals who were low risk of progression and predicted structural damage progression independently of clinical disease activity and clinical remission.

Interestingly, there was poor or absent agreement between measures of low

activity on MRI and clinical remission. This suggests that MRI measures of low activity are not redundant in the context of clinical remission. Overall the proportions progressing among those with low activity based on MRI were consistently lower than those seen with DAS28(CRP) clinical remission. Furthermore, the prediction of radiographic progression for these imaging definitions of low activity was superior and independent of clinical disease activity measures alone. In particular, among patients who do not meet criteria for clinical remission by 24 weeks, those that meet MRI criteria for low activity have substantially lower overall risk.

The definition of low activity based on MRI measures has several immediate implications. Firstly, this study suggests that achievement of low activity on MRI by 24 weeks may be a reasonable surrogate for other long-term outcomes such as radiographic progression. Early phase clinical trials assessing efficacy of new drugs might consider the achievement of low MRI measures as a surrogate outcome for halting of structural damage progression. Secondly, in theory, use of MRI definitions of low activity could be used to inform treatment decisions, particularly in difficult cases. Despite the cost of MRI, low activity on MRI might reassure a physician to hold off on escalation of therapy and this could lead to a reduction in overall costs. In this study, many more patients achieved MRI remission than clinical remission, suggesting that low MRI activity may frequently occur when clinical disease activity scores do not meet criteria for remission. Future study is needed to determine if and how MRI, including definitions of low activity, might fit into clinical care algorithms.

There are several limitations to the current study. While this MRI sub-study is relatively large in comparison to other similar sub-studies, relatively few patients reach clinical remission and low MRI activity and thus the estimates of the proportion progressing is subject to imprecision. Furthermore, because so few patients reach SDAI or CDAI remission, it was difficult to accurately assess the risk of progression in these groups. The use of a development and validation cohort is a significant strength and should be reassuring that the observations here are not the result of chance alone. In addition, there have been advances in MRI techniques since this study was performed that may improve the visualisation of synovitis and osteitis. Future studies incorporating newer technologies and objective and automated quantitative methods may also be of interest in the future.

In conclusion, definitions of low activity based on MRI estimates of synovitis, osteitis, and total inflammation can identify individuals with RA who are at very low risk of radiographic progression independent of clinical disease activity. Future studies should assess the role of these endpoints as surrogates for the halting of structural damage progression.

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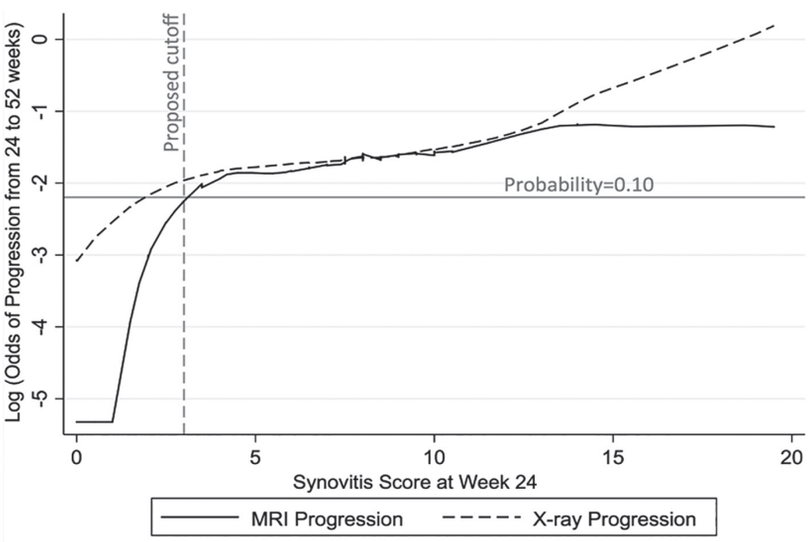
References

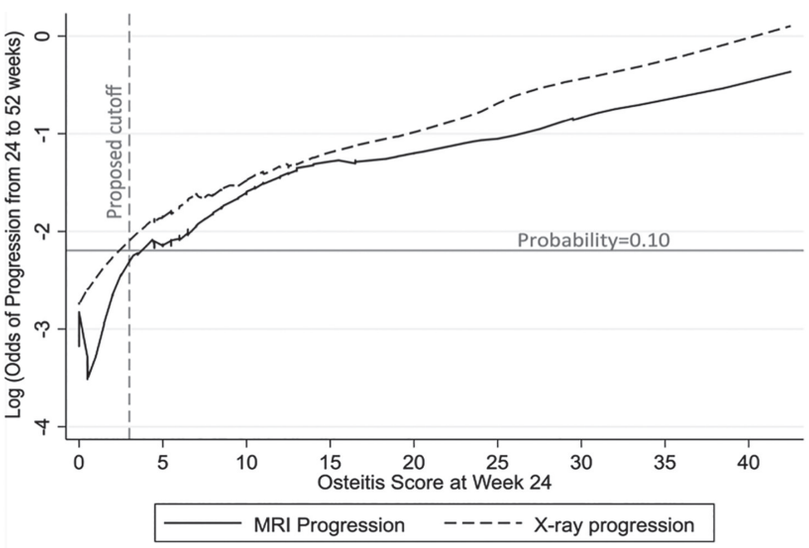
1. EMERY P, KAVANAUGH A, BAO Y, GANGULI A, MULANI P: Comprehensive disease control (CDC): what does achieving CDC mean for patients with rheumatoid arthritis? *Ann Rheum Dis* 2014.
2. BAKER JF, OSTERGAARD M, EMERY P *et al*.: Early MRI measures independently predict 1-year and 2-year radiographic progression in rheumatoid arthritis: secondary analysis from a large clinical trial. *Ann Rheum Dis* 2013; 73: 1968-74.
3. OSTERGAARD M, EMERY P, CONAGHAN PG *et al*.: Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. *Arthritis Rheum* 2011; 63: 3712-22.
4. CONAGHAN PG, EMERY P, OSTERGAARD M *et al*.: Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. *Ann Rheum Dis* 2011; 70: 1968-74.
5. PETERFY C, EMERY P, TAK PP *et al*.: MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. *Ann Rheum Dis* 2014.
6. GANDJBAKHCH F, FOLTZ V, MALLET A, BOURGEOIS P, FAUTREL B: Bone marrow oedema predicts structural progression in a 1-year follow-up of 85 patients with RA in remission or with low disease activity with low-field MRI. *Ann Rheum Dis* 2011; 70: 2159-62.
7. GANDJBAKHCH F, HAAVARDSHOLM EA, CONAGHAN PG *et al*.: Determining a magnetic resonance imaging inflammatory activity acceptable state without subsequent radiographic progression in rheumatoid arthritis: results from a followup MRI study of 254 patients in clinical remission or low disease activity. *J Rheumatol* 2014; 41: 398-406.
8. KEYSTONE EC, GENOVESE MC, KLARESKOG L *et al*.: Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009; 68: 789-96.
9. KEYSTONE E, GENOVESE MC, KLARESKOG L *et al*.: Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* 2010; 69: 1129-35.
10. EMERY P, FLEISCHMANN RM, MORELAND LW *et al*.: Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 2272-83.
11. OSTERGAARD M, PETERFY C, CONAGHAN P *et al*.: OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol* 2003; 30: 1385-6.
12. BAKER JF, OSTERGAARD M, GEORGE M *et al*.: Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years. *Ann Rheum Dis* 2014; 73: 1923-8.
13. EMERY P, FLEISCHMANN R, VAN DER HEIJDE D *et al*.: The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011; 63: 1200-10.
14. KREMER J, RITCHLIN C, MENDELSOHN A *et al*.: Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered

intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2010; 62: 917-28.
15. EMERY P, BREEDVELD F, VAN DER HEIJDE D *et al*.: Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. *Arthritis Rheum* 2010; 62: 674-82.
16. ALETAHA D, SMOLEN JS: Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. *Arthritis Rheum* 2011; 63: 3702-11.
17. BAKER JF, CONAGHAN PG, SMOLEN J *et al*.: Development and validation of modified disease activity scores in rheumatoid arthritis: Superior correlation with MRI synovitis and x-ray progression. *Arthritis Rheum* 2014; 66: 794-802.
18. VAN DER HELM-VAN MIL AH, KNEVEL R, CAVET G, HUIZINGA TW, HANEY DJ: An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. *Rheumatology* (Oxford) 2013; 52: 839-46.
19. BAKER JF, BAKER DG, TOEDTER G, SHULTS J, VON FELDT JM, LEONARD MB: Associations between vitamin D, disease activity, and clinical response to therapy in rheumatoid arthritis. *Clin Exp Rheumatol* 2012; 30: 658-64.
20. BAKER JF, MEHTA NN, BAKER DG *et al*.: Vitamin D, metabolic dyslipidemia, and metabolic syndrome in rheumatoid arthritis. *Am J Med* 2012; 125: 1036 e9- e15.

Supplementary figures



Supplementary Fig. 1.
Lowess plots of associations between 24-week measures of synovitis with log-odds of progression in MRI erosion score and vdHS score from 24 to 52 weeks.



Supplementary Fig. 2.
Lowess plots of associations between 24-week measures of osteitis with log-odds of progression in MRI erosion score and vdHS score from 24 to 52 weeks.