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

Authors: Charles Peterfy MD, PhD[1], Vibeke Strand, MD[2], Lu Tian, PhD[3], Mikkel Østergaard, MD[4], Ying Lu, PhD[3,], Julie DiCarlo, PhD[1], Peter Countryman, PhD[1], Atul Deodhar, MD[5], Robert Landewe, MD[6], Veena K. Ranganath, MD, MS[7], Orrin Troum, MD[8], Philip G. Conaghan, MD[9]

Affiliations:

1. Spire Sciences, Inc. Boca Raton, FL, USA
2. Division of Immunology/Rheumatology, Stanford University, Palo Alto, CA, USA
3. Department of Biomedical Data Science, Stanford University, Palo Alto, CA, USA
4. Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
5. Oregon Health & Science University, Portland, OR, USA
6. Amsterdam Rheumatology & immunology Center (ARC)(amC) & Zuyderland Medical center, Heerlen, the Netherlands
7. Division of Rheumatology, University of California, Los Angeles, California, David Geffen School of Medicine, Los Angeles, CA, USA
8. The Doctors of Saint John's Medical Group, Providence Saint John's Health Center, Santa Monica, CA, USA and Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

9. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK

Address correspondence and reprint requests to:

Charles Peterfy, MD, PhD

Spire Sciences, Inc., 5314 Boca Marina Cir N, Boca Raton, FL 33487

Phone: 415.233.1642

E-mail address: charles.peterfy@spiresciences.com

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, $MRI_0, \Delta_{MRI}, \Delta_{MRI}^2, (\Delta_{MRI} - 0.5)_+, (\Delta_{MRI})_+$ and $(\Delta_{MRI} + 0.5)_+$, as independent variables, where MRI_0 and Δ_{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 [7]). 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. [8] 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; [9]

MRI has been used in 13 multicenter, placebo RCTs reported to date, [10 11 12 13 14 15 16 17 18 19 20 21 22] involving ten different biologic therapies. Nine RCTs [11 13 14 15 16 17 18 21 22] 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 [14 15 17 18] or showed a lack of inhibition consistent with later X-ray data within the trial [16]

[22] or in subsequent trials. [23] 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; [13] 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 [21]).

Two of the nine RCTs discussed above [17 21] and an active-comparator trial [24] 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 [24] and 30-31 [17] patients per arm, respectively. Both trials also showed inhibition of erosion with MRI at later time points. The third study [21] 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 [17] did not include X-ray and the other [24] 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, [25] [26] [27] [28] and six RA RCTs have included MRI scoring of cartilage loss [14] [17] [18] [22] [29] or joint-space narrowing; [20] 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

Trial	Baseline	Week 12	Week 24	Week 52	Rescue treatment information
A	MRI, X-ray	MRI	MRI, X-ray	N/A	Available
B	MRI, X-ray	MRI	MRI, X-ray	MRI, X-ray	N/A
C	MRI, X-ray	MRI	MRI, X-ray	MRI, X-ray	N/A
D	MRI, X-ray	N/A	MRI*, X-ray	X-ray	Available

* Only erosion scores available; N/A, not available

Table 2. Baseline X-ray and MRI scores

Trial	X-ray Erosion	X-ray Total	MRI Erosion	MRI Osteitis	MRI Synovitis
A	3.25 (3.68),	5.36(6.52),	13.63(12.44),	7.23(8.06),	7.82(4.60),
(n = 185)	2.00 (0.75, 4.00)	3.00 (1.00, 7.00)	10.00 (4.50, 20.00)	4.50 (1.00, 10.50)	7.00 (4.50, 11.00)
B	3.50 (6.29),	6.52(12.40),	22.17(22.96),	10.02(11.21),	10.14(6.80),
(n = 1272)	1.00 (0.50, 3.50)	1.50 (0.50, 6.00)	14.50 (10.50, 23.50)	6.00 (2.50, 13.50)	9.00 (5.00, 13.50)
C	5.44(8.97),	12.06(18.07),	23.50(24.71),	4.98(7.54),	7.15(5.26),
(n = 888)	1.50 (0.00, 7.00)	3.00 (0.50, 16.50)	14.75 (6.88, 30.12)	2.00 (0.00, 6.63)	6.50 (3.50, 9.50)
D	5.90(7.07),	12.42(15.19),	18.72(18.17),	N/A	N/A
(n = 450)	3.50 (1.00, 8.50)	6.50 (1.50, 18.50)	12.50 (5.25, 26.31)		
Pooled	4.47(7.17),	9.05(14.62),	19.42(20.03),	7.76(9.59),	8.59(5.92),
(n = 2795)	1.50 (0.50, 3.25)	2.50 (0.50, 11.00)	13.12 (6.50, 25.00)	4.25 (1.00, 11.00)	7.50 (4.50, 11.50)

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

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

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.

FUNDING

Independent grant support was provided by: Bristol-Myers Squibb, Genentech/Roche, Janssen and Pfizer.

Data was provided by: Amgen, Genentech/Roche and Janssen

Study sponsors were not involved in the study design; in the collection, analysis or interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

COMPETING INTERESTS

Dr. Peterfy reports other from Spire Sciences, Inc., outside the submitted work; Dr. Strand reports grants from Bristol-Myers Squibb, grants from Genentech/Roche, grants from Janssen R&D, grants from Pfizer, during the conduct of the study; consulting fees from Abbvie; Amgen; AstraZeneca; Bayer; Boehringer Ingelheim; Bristol-Myers Squibb, Celltrion, Crescendo / Myriad Genetics, Genentech / Roche, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, UCB, outside the submitted work; Dr. Tian reports no conflicts; Prof. Østergaard reports grants from Bristol-Myers Squibb, grants from Genentech/Roche, grants from Janssen R&D, grants from Pfizer, during the conduct of the study; speaking or consulting fees from Abbvie, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Eli-Lilly, Centocor, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo, Orion, Pfizer, Regeneron, Schering-Plough, Roche, Takeda, UCB, Wyeth; Dr. Lu reports no conflicts; Dr. DiCarlo reports other from Spire Sciences, Inc., outside the submitted work; Dr. Countryman reports other from Spire Sciences, Inc., outside the submitted work; Dr. Deodhar reports grants from Eli Lilley, Glaxo-Smith Kline, Janssen, Novartis, Pfizer, UCB, outside the submitted work; Dr. Landewe reports other from Rheumatology Consultancy BV outside the submitted work; Dr. Ranganath reports personal fees

from Bristol-Myers Squibb, grants from Genentech, grants from Pfizer, outside the submitted work; Dr. Troum reports grants and personal fees from Abbvie, grants and personal fees from Amgen, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Novartis, grants and personal fees from Pfizer, grants and personal fees from Roche/Genentech, outside the submitted work; Prof. Conaghan is supported in part by the National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Prof. Conaghan also reports speakers bureau or consulting fees from Abbvie, Bristol-Myers Squibb, Lilly, Novartis, Pfizer and Roche.

REFERENCES

[1] American College of Rheumatology Clinical Trial Priorities and Design Conference, July 22-23, 2010. Arthritis Rheum. 2011; 63:2151-6.

[2] Guidance for Industry: Rheumatoid Arthritis: Developing Drug Products for Treatment**.** http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] Peterfy C, Østergaard M, Conaghan P. MRI comes of age in RA clinical trials. Ann Rheum Dis. 2013; 72:794-6.

[4] ACR/OMERACT Imaging Subcommittee of the ACR Clinical Trials Taskforce. Review: The utility of magnetic resonance imaging for assessing structural damage in randomized controlled trials in rheumatoid arthritis. Arthritis Rheum. 2013; 65:2513-23.

[5] Boers M, Brooks P, Strand V, Tugwell P: The OMERACT Filter for Outcome Measures in Rheumatology. Editorial. J Rheum 1998; 25:198-9.

[6] Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, D'Agostino M-A, Conaghan P, Bingham CO, Brooks P, Landewe R, March L, Simon LS, Singh JA, Strand V, Tugwell P: Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epi 2014, 67(7):745-53

[7] Hosmer, D.W., Lemeshow, S., Sturdivant, R.X. 2013. Applied logistic regression, 3rd ed. Wiley

[8] Baker JF, Østergaard M, Emery P, Hsia EC, Lu J, Baker DG, Conaghan PG. 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. 2014; 73:1968-74

[9] Baker JF, Conaghan PG, Emery P, Baker DG, Østergaard M. Validity of early MRI structural damage end points and potential impact on clinical trial design in rheumatoid arthritis. Ann Rheum Dis. 2015 Jun 19. pii: annrheumdis-2014-206934. doi: 10.1136/annrheumdis-2014-206934. [Epub ahead of print]

[10] Cohen SB, Dore RK, Lane NE, et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a 12-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum 2008; 58:1299–309

[11] Genovese MC, Kavanaugh A, Weinblatt ME, et al. An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. Arthritis Rheum 2011; 63:337–45

[12] Peterfy C, Durez P, Haraoui B, et al. Responses to early rheumatoid arthritis (RA) to treatment with adalimumab plus methotrexate vs. Methotrexate alone: magnetic resonance imaging results from OPTIMA. Ann Rheum Dis 2010; 69(suppl_3):455

[13] Conaghan PG, Durez P, Alten RE, Burmester GR, Tak PP, Klareskog L, Catrina AI, Dicarlo J, Gaillez C, Le Bars M, Zhou X, Peterfy C. Impact of intravenous abatacept on synovitis, osteitis and structural damage in patients with rheumatoid arthritis and an inadequate response to methotrexate: the ASSET randomised controlled trial. Ann Rheum Dis. 2012; 72:1287-94

[14] Peterfy C, Emery P, Tak PP, et al. Rituximab (RTX) plus methotrexate (MTX) prevents bone erosion and joint-space narrowing (JSN) and reduces synovitis, osteitis as shown on MRI: results from a randomized placebo controlled trial in patient (Pts) with rheumatoid arthritis (RA-SCORE). Ann Rheum Dis 2011; 70(suppl_3):152.

[15] 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

[16] 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.

[17] Beals C, Baumgartner R, Peterfy C, Balanescu A, Mirea G, Harabagiu A, Popa S, Cheng A, Feng D, Fox R, Vallee M-Y Ashton E, DiCarlo J, Dardzinski B. Treatment effects measured by dynamic contrast enhanced MRI and RAMRIS for rheumatoid arthritis. Ann Rheum Dis 2013; 72:748.

[18] Peterfy C, Emery P, Genovese MC, Keystone E, Taylor P, Berclaz P-Y, DiCarlo JC, Lee CH, Schlichting D, Beattie SD, Luchi ME, Macias W. Magnetic Resonance Imaging Substudy in a Phase 2b Dose-Ranging Study of Baricitinib, an Oral Janus Kinase 1/Janus Kinase 2 Inhibitor, in Combination with Traditional Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis. Arthritis Rheum 2012; 64(Suppl 10): S1050.

[19] Peterfy C, Burmester G, Bykerk V, Combe B, Furst DE, Huizinga TWJ, Karyekar CS, Wong D, Conaghan PG, Emery P. MRI results from the AVERT study: a randomized, active-controlled trial to evaluate induction of remission and maintenance of drug-free remission using abatacept in combination with methotrexate or as monotherapy in patients with early RA. Ann Rheum Dis 2014; 73(Suppl2):71

[20] Axelsen MB, Eshed I, Hørslev-Petersen K, Stengaard-Pedersen K, Hetland ML, Møller J, Junker P, Pødenphant J, Schlemmer A, Ellingsen T, Ahlquist P, Lindegaard H, Linauskas A, Dam MY, Hansen I, Horn HC, Ammitzbøll CG, Jørgensen A, Krintel SB, Raun J, Krogh NS, Johansen JS, Østergaard M; OPERA study group. A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. Ann Rheum Dis. 2015; 74:867-75

[21] Conaghan PG, Østergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D, Irazoque-Palazuelos F, Soto-Raices O, Hrycaj P, Xie Z, Zhang R, Wyman BT, Bradley J, Soma K, Wilkinson B. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow edema, synovitis, and bone erosion in methotrexate-naïve early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Ann Rheum Dis 2016; 75:1024-33

[22] Genovese MC, Jarosova K, Cieślak D, Alper J, Kivitz A, Hough DR, Maes P, Pineda L, Chen M, Zaidi F. Apremilast in Patients With Active Rheumatoid Arthritis: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. Arthritis Rheumatol. 2015; 67:1703-10

[23] Weinblatt ME, Genovese MC, Ho M, Hollis S, Rosiak-Jedrychowicz K, Kavanaugh A, Millson DS, Leon G, Wang M, van der Heijde D. Effects of fostamatinib, an oral spleen tyrosine kinase inhibitor, in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheumatol. 2014; 66:3255-64

[24] Conaghan PG, Peterfy C, Olech E, Kaine J, Ridley D, Dicarlo J, Friedman J, Devenport J, Troum O. The effects of tocilizumab on osteitis, synovitis and erosion progression in rheumatoid arthritis: results from the ACT-RAY MRI substudy. Ann Rheum Dis. 2014; 73:810-6

[25] Døhn UM, Conaghan PG, Eshed I, Boonen A, Boyesen P, Peterfy CG, Lillegraven S, Ejbjerg B, Gandjbakhch F, Bird P, Foltz V, Genant HK, Haavardsholm E, McQueen FM, Ostergaard M. The OMERACT-RAMRIS Rheumatoid Arthritis Magnetic Resonance Imaging Joint Space Narrowing Score: Intrareader and Interreader Reliability and Agreement with Computed Tomography and Conventional Radiography. J Rheumatol. 2014; 41:392-7

[26] Peterfy CG, Olech E, DiCarlo JC, Merrill JT, Countryman PJ and Gaylis NB. Monitoring cartilage loss in the hands and wrists in rheumatoid arthritis with magnetic resonance imaging in a multi-center clinical trial: IMPRESS (NCT00425932). Arthritis Res Ther. 2013, 15:R44

[27] Peterfy CG, Dicarlo JC, Olech E, Bagnard MA, Gabriele A, Gaylis N. Evaluating joint-space narrowing and cartilage loss in rheumatoid arthritis using MRI. Arthritis Res Ther. 2012; 14:R131

[28] Peterfy CG, van Dijke CF, Lu Y, Nguyen A, Connick T, Kneeland B, Tirman PFJ, Lang P, Dent S, Genant HK. Quantification of articular cartilage in the metacarpophalangeal joints of the hand: accuracy and precision of 3D MR imaging. AJR. 1995; 165: 371-375.

[29] Peterfy CG, Olech E, DiCarlo JC, Merrill JT, Countryman PJ and Gaylis NB. Monitoring cartilage loss in the hands and wrists in rheumatoid arthritis with magnetic resonance imaging in a multi-center clinical trial: IMPRESS (NCT00425932). Arthritis Res Ther. 2013, 15:R44