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Relationship of Patient-Reported Outcomes with Magnetic Resonance Imaging Measures in Rheumatoid Arthritis

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Abstract

Purpose

We assessed whether magnetic resonance imaging (MRI) measures of inflammation and damage were associated with patient-reported outcomes (PROs) in a longitudinal clinical trial setting.

Methods

This longitudinal cohort was derived from the MRI sub-study of the GO-BEFORE randomized clinical trial of golimumab among methotrexate-naïve patients. Correlations between RAMRIS scores (synovitis, osteitis, bone erosion) and disability (Health Assessment Questionnaire), pain, and global patient scores were determined at 0, 12, 24, and 52 weeks. Correlations between interval changes were also assessed. Multivariable regression models using robust generalized estimating equations evaluated associations over all time-points and their relationship to other clinical disease activity measures.

Results

Greater synovitis, osteitis, and bone erosion scores were positively associated with disability at all time-points (all $p < 0.05$) and with pain and patient global scores at 24 and 52 weeks. Over all visits, synovitis was associated with disability, pain, and patient global scores ($p \leq 0.03$) independent of clinical disease activity measures. Improvements in synovitis and bone erosion were also associated with improvements in PROs. Less improvement in synovitis and progression in MRI erosion at 52 weeks were both independently associated with worsening in all PROs at 52 weeks while progression on x-ray was not associated. Similar associations were observed across treatment groups.

Conclusions

MRI measures of inflammation and structural damage correlate independently with disability, pain, and patient global assessments. These observations support the validity of MRI biomarkers.

Key Words: magnetic resonance imaging; rheumatoid arthritis; disability; pain; patient-reported outcomes

Introduction

The use of patient-reported outcomes (PROs) in clinical care of patients with rheumatoid arthritis (RA) enhances communication between patients and their providers. However, PROs are not always reflective of the inflammatory disease burden and may be influenced by comorbid conditions and other factors with disagreement between patients and their providers being common.[1-3] In addition, patients who feel well and are in clinical remission can have structural damage progression.[4] Thus objective measures of disease activity are of interest. Because objective outcomes might be expected to correlate more modestly with patient assessments, it is important to determine whether a reduction in objective measures translates to improvement in PROs. Magnetic Resonance Imaging (MRI) measures of synovitis, osteitis, and bone erosion correlate with clinical disease activity and predict progression of structural damage.[5-7] However, the relationship between MRI measures and PROs has been poorly described.

Studies previously showed that patients who experience structural damage progression as imaged by X-ray have greater disability as measured by the Health Assessment Questionnaire (HAQ).[8, 9] Averaged over 9 years, an annual increase of 6 units in the van der Heijde-Sharp (vdHS) score was associated with an approximate increase in 0.2 in the HAQ.[10] However, while progression of damage on X-ray at one year has been an important clinical trial endpoint for many years, it is not clear that progression on X-ray at one year is associated with functional decline.

One small study reported that MRI measures at baseline could predict functional outcomes.[11] However, we are aware of no studies that have comprehensively assessed associations between longitudinal MRI measures and changes in PROs. The aims of this study were to determine the extent to which MRI measures are associated with PROs including physical functioning, pain, and patient global assessment of

disease activity (PtGI) and to determine if changes in MRI measures are associated with changes in these PROs.

Methods

This study was a secondary analysis of the GO-BEFORE (Clintrials.gov identifier NCT00361335) randomized trial MRI sub-study. Details of the trial design and results have been previously published.[12-14] 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.

Patients 18 years or older who met 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. Eligible patients were randomly assigned to receive placebo subcutaneous injection with methotrexate (MTX) (group 1), golimumab 100 mg injection with placebo (group 2), golimumab 50 mg injection with MTX (group 3), or golimumab 100 mg injection with MTX (group 4). Subjects remained in their assigned group for 28 weeks and were then allowed pre-defined increases in treatment intensity (early escape) if they had less than 20% improvement in both swollen and tender joint counts. Overall, 43/291 (15%) met the early escape criteria between 28 and 52 weeks, including 14/77 (20%) in group 1, 8/70 (11%) in group 2, 10/71 (14%) in group 3, and 13/73 (15%) in group 4. An additional 55 (71%) from group 1 were started on golimumab after 52 weeks. Similarly, an additional 38 (62%) patients in group 2 crossed over from placebo to MTX at 52 weeks.

Data collection at each visit included independent, blinded assessments of disease activity using the DAS28 with CRP [DAS28(CRP)], completion of the Health Assessment Questionnaire (HAQ), as well as assessment of pain and PtGI scores using visual analogue scale (VAS).

Magnetic Resonance Imaging

The details of the acquisition of MRI images has been described elsewhere. [7, 8, 15] Briefly, MRIs of the patient's dominant wrist and 2nd-5th metacarpophalangeal (MCP) joints were obtained using 1.5T MRI with contrast enhancement. Images were scored by two independent readers who were blinded to the image time-point or sequence, patient identity, and treatment group. The average score of 2 readers was determined for synovitis (0–21 for wrist plus MCP joints), osteitis (0–69) and bone erosion (0–230), using the RAMRIS system.[7, 16] Progression in the MRI erosion score was defined as a change >0.5, as previously described.[7, 8, 17]

Radiographs of Hands and Feet

Radiographs of hands and feet were performed at baseline, week 24, and week 52 and scored by two blinded, centralized readers using the vdHS method as previously described.[18, 19] X-ray progression was defined as a change in vdHS score of greater than 0.5 as in previous studies.[7, 15, 17, 20-22]

Statistical Analysis

Data were analyzed with STATA 14 software (StataCorp, LP, College Station, TX). Correlations between synovitis, osteitis, and bone erosion scores on MRI were assessed at individual time-points using Spearman's correlations and over all observations using robust linear models incorporating Generalized Estimating Equations (GEE) in order to cluster on patient. The changes in HAQ, pain, and PtGI scores were also determined over the 12-, 24-, 52-, and 104-week intervals. Correlation between changes in PROs and changes in MRI measures were determined. Finally, independent

associations between changes in synovitis, MRI progression, and X-ray progression and changes in PROs at 1 year were assessed using multivariable linear regression. Assessment for altered associations across treatment groups was performed by testing the significance of multiplicative interaction terms.

Results

The basic characteristics of the study cohort are shown in Table 1 and have been previously described.[7, 17, 23] The correlations between MRI measures (synovitis, osteitis, bone erosion) with PROs (HAQ, pain, and PtGI scores) are presented in **Table 2**. MRI measures were associated with HAQ over all time-points. MRI measures were increasingly associated with pain and PtGI scores at later follow-up times.

Spearman correlations between observed changes in MRI measures and changes in the PROs are shown in **Figure 1**. Improvements in synovitis at 12, 24, and 52 weeks were generally associated with greater improvements in HAQ, pain, and PtGI scores. Changes in osteitis were not significantly associated with changes in PROs at any follow-up time. Changes in bone erosion were associated positively with changes in pain and patient global at later follow-up times. In contrast, changes in vdHS at 52 weeks were not associated with changes in PROs and the relationship was numerically inverse.

In longitudinal models incorporating all study observations, synovitis was significantly associated with HAQ, and this was independent of the DAS28(CRP) (**Table 3**). Synovitis was also associated with pain and PtGI scores independent of CRP, swollen, and tender joint counts. Greater bone erosion was associated with greater HAQ independent of synovitis and DAS28(CRP).

Univariate and multivariable association between synovitis, bone erosion progression, and x-ray progression are presented in **Table 4**. In multivariable models,

significant associations were observed between the change in synovitis at 1-year and the change in HAQ [β : 0.053 (0.029, 0.077) $p < 0.001$], pain [β : 0.16 (0.058, 0.25) $p = 0.002$], and PtGI score [β : 0.16 (0.066, 0.25) $p = 0.001$] over the same interval. MRI erosion progression was associated with greater increase in HAQ, pain, and PtGI scores (all $p < 0.01$), while X-ray progression was not associated (all $p > 0.11$). In a similar analysis, a unit change of 1 in the MRI erosion score at one year was associated with a positive change in HAQ [β : 0.045 (0.014, 0.076) $p = 0.005$].

There was substantial overall improvement in HAQ over the first 52 weeks of the clinical trial [-0.75 (0.73)] while no significant improvement occurred between 52 and 104 weeks [-0.042 (0.34)]. There was similar correlation between the change in MRI erosion and the change in HAQ in the first ($\rho = 0.13$) and second year ($\rho = 0.13$) of follow up. In contrast, while there was a strong correlation between change in synovitis and change in HAQ over year 1 ($\rho = 0.24$), poor correlation was seen in year 2 ($\rho = 0.032$). These relationships were similar across treatment groups

In these analyses no attenuation of the coefficients were noted with adjustment for treatment group. In addition, no significant interactions by treatment group were noted.

Discussion

The current study is the first to systematically assess relationships between MRI measures of synovitis, osteitis, and bone erosion with PROs in a large clinical trial setting. MRI measures correlated with physical functioning over the entire study period, and it was observed that 1) less improvement in synovitis and 2) MRI erosion progression were independently associated with unfavorable changes in HAQ, pain, and PtGI score at one year.

Over all study visits, synovitis was associated with all PROs independent of clinical disease activity. Greater bone erosion scores were also associated independently with higher HAQ. Thus for two individuals with similar clinical assessments, the individual with greater synovitis on MRI is likely to have worse pain and function. These data indicate that synovitis and bone erosion are complementary to other clinical parameters in terms of relevance to the patient experience.

Improvements in MRI measures of synovitis were generally correlated with greater improvements in all PROs. Specifically, at 52 weeks, the reduction in synovitis noted on MRI was significantly correlated with improvements in HAQ, pain, and patient global scores. The correlations between PROs and MRI measures were similar across treatments received. These observations suggest that MRI measures of synovitis may be a reasonable surrogate endpoint in observational and early interventional studies.

While synovitis showed strong correlations with PROs, osteitis was not significantly associated. One previous study evaluated associations between osteitis and HAQ and found that, while there was correlation at baseline, there was no correlation after 6 years of follow-up.[11] The current study, which found poor correlation between the change in HAQ and change in osteitis over time, supports this previous observation

An important additional observation is that MRI erosion progression was independently associated with greater increases in PROs. We recently showed that MRI erosion has improved discriminative characteristics in the identification of the effective treatment arm.[8] The observations from the current study show that short-term progression in bone erosion on MRI is also associated with declines in physical functioning. The current study suggests that progression in the MRI erosion score (>0.5) is associated with a change in HAQ of 0.35 at 1 year. In addition, a 4.4 unit change in MRI erosion score would translate to a change in HAQ of 0.2. The present study did not identify a relation between X-ray progression and functional decline over 1 year.

However, as noted, earlier studies have observed such an association averaged over 9 years (6 units of vdHS = 0.2 units of HAQ).[10] Our results suggest that MRI provides comparable, if not improved, discrimination of functional decline. Of note, we found that changes in synovitis were more strongly correlated with HAQ during the treatment of active inflammation in year 1, while changes in bone erosion were correlated with similarly throughout the 2-year period.

The current study is within a clinical trial population and thus may not be entirely generalizable to other populations. Further study in longitudinal observational studies may be helpful to characterize these associations in other populations. This study was also limited in the evaluation of PROs that were available as part of the original clinical trial. Future study should consider incorporating additional PROs in order to better understand their relationships with MRI measures. In addition, there have been advances in MRI techniques since this study was performed that may improve the visualization of inflammatory and structural changes.

In conclusion, MRI measures of synovitis and bone erosion correlate with patient-reported outcomes. Improvements over time in MRI inflammation and deterioration in MRI damage correlate with changes in function, pain, and patient global scores suggesting that these objective measures reflect how patients experience their disease.

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Conflicts of Interest

JF Baker has nothing to disclose. PG Conaghan has done speakers bureaus or consultancies for Abbvie, BMS, Janssen, Lilly, Novartis, Pfizer, and Roche. P Emery has received consulting fees, speaking fees, and/or honoraria from Pfizer, Merck, Abbvie, UCB, Roche, BMS, Lilly, and Novartis (less than \$10,000 each). DG Baker is an employee of Janssen Biotech, Inc. M Østergaard has received fees for consultancy or speaker fees and/or research support from Abbott, AbbVie, BMS, Boehringer-Ingelheim, Celgene, Centocor, Eli-Lilly, GSK, Janssen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche, UCB, Takeda and Wyeth.

Tables

Table 1: Basic characteristics of the study population.

	GO-BEFORE MRI Sub-Study
N	291
Age (years)	49.0 (12.6)
Female, N (%)	237 (81.4)
Race	
Asian, N (%)	75 (25.8)
White, N (%)	190 (65.3)
Disease Duration (years)	1.2 (0.6, 3.3)
DAS28(CRP)	5.60 (1.06)
CRP (mg/dl)	1.2 (0.5, 2.7)
HAQ, Baseline	1.56 (0.69)
HAQ, 104 weeks	0.76 (0.75)
CCP Positive, N(%)	222 (76.3)
vdHS, Baseline	5.5 (2, 21.5)
RAMRIS Scores	
Synovitis, Baseline	9.5 (5.0)
Osteitis, Baseline	10.0 (10.0)
Bone Erosion, Baseline	14.5 (10, 22.5)

Table 2: Spearman correlations at 0, 12, 24, and 52 weeks between synovitis, osteitis, bone erosion, and HAQ, pain, and patient global.

HAQ				
	<u>Week 0</u>	<u>Week 12</u>	<u>Week 24</u>	<u>Week 52</u>
Synovitis	0.24 ‡	0.20 ‡	0.26 ‡	0.27 ‡
Osteitis	0.13 †	0.19 †	0.23 ‡	0.22 ‡
Bone Erosion	0.18 †	0.23 ‡	0.27 ‡	0.28 ‡
Pain				
	<u>Week 0</u>	<u>Week 12</u>	<u>Week 24</u>	<u>Week 52</u>
Synovitis	0.093	0.13 *	0.17 †	0.21 †
Osteitis	0.0073	0.14 *	0.14 *	0.21 †
Bone Erosion	0.072	0.12 *	0.14 *	0.20 †
Patient Global				
	<u>Week 0</u>	<u>Week 12</u>	<u>Week 24</u>	<u>Week 52</u>
Synovitis	0.14 *	0.16 †	0.18 †	0.24 ‡
Osteitis	0.046	0.16 †	0.14 *	0.23 ‡
Bone Erosion	0.11	0.15 *	0.15 *	0.21 †

* p<0.05; † p<0.01; ‡ p<0.001

Table 3: Longitudinal univariate and multivariable regression models using robust generalized estimating equations assessing independent associations of synovitis, osteitis, and bone erosion with HAQ scores, pain and patient global, over all visits. Treatment interactions with MRI measures were tested and non-significant.

	HAQ Univariate Associations		HAQ Multivariable Model	
	B (95% CI)	p	B (95% CI)	p
Synovitis	0.045 (0.032, 0.058)	<0.001	0.017 (0.0050, 0.029)	0.005
Ln(osteitis)	0.14 (0.079, 0.20)	<0.001	-0.017 (-0.075, 0.041)	0.56
Ln(erosion)	0.19 (0.11, 0.26)	<0.001	0.093 (0.001, 0.19)	0.047
DAS28(CRP)	0.28 (0.26, 0.30)	<0.001	0.27 (0.24, 0.29)	<0.001

	Pain (VAS) Univariate Associations		Pain (VAS) Multivariable Model	
	B (95% CI)	p	B (95% CI)	p
Synovitis	0.14 (0.093, 0.18)	<0.001	0.047 (0.0040, 0.084)	0.03
Ln(osteitis)	0.25 (0.080, 0.42)	0.004	0.10 (-0.13, 0.33)	0.31
Ln(erosion)	0.40 (0.17, 0.62)	0.001	0.27 (-0.031, 0.57)	0.08
Ln(CRP)	0.81 (0.69, 0.93)	<0.001	0.59 (0.42, 0.75)	<0.001
Swollen Joints	0.18 (0.16, 0.20)	<0.001	0.042 (0.021, 0.063)	<0.001
Tender Joints	0.18 (0.17, 0.19)	<0.001	0.057 (0.044, 0.071)	<0.001

	Patient Global (VAS) Univariate Associations		Patient Global (VAS) Multivariable Model	
	B (95% CI)	p	B (95% CI)	p
Synovitis	0.15 (0.11, 0.19)	<0.001	0.052 (0.012, 0.093)	0.01
Ln(osteitis)	0.31 (0.13, 0.48)	0.001	-0.052 (-0.25, 0.14)	0.60
Ln(erosion)	0.39 (0.15, 0.62)	0.001	0.18 (-0.13, 0.50)	0.26
Ln(CRP)	0.77 (0.67, 0.90)	<0.001	0.56 (0.40, 0.73)	<0.001
Swollen Joints	0.17 (0.15, 0.20)	<0.001	0.039 (0.018, 0.061)	0.002
Tender Joints	0.18 (0.17, 0.20)	<0.001	0.065 (0.052, 0.077)	<0.001

Table 4: Multivariable regression to identify independent associations between MRI and X-ray progression with change in PROs at 52 weeks of follow-up. Osteitis was not associated independently (not shown). Treatment interactions with MRI measures were tested and non-significant.

	Change in HAQ *		Change in HAQ *	
	Univariate Associations		Multivariable	
	B (95% CI)	p	B (95% CI)	p
Δ Synovitis (per 1 unit)	0.046 (0.022, 0.069)	<0.001	0.053 (0.029, 0.077)	<0.001
MRI Erosion Progression	0.35 (0.13, 0.57)	0.002	0.36 (0.12, 0.59)	0.003
X-ray Progression	0.081 (-0.13, 0.29)	0.45	-0.063 (-0.28, 0.15)	0.56

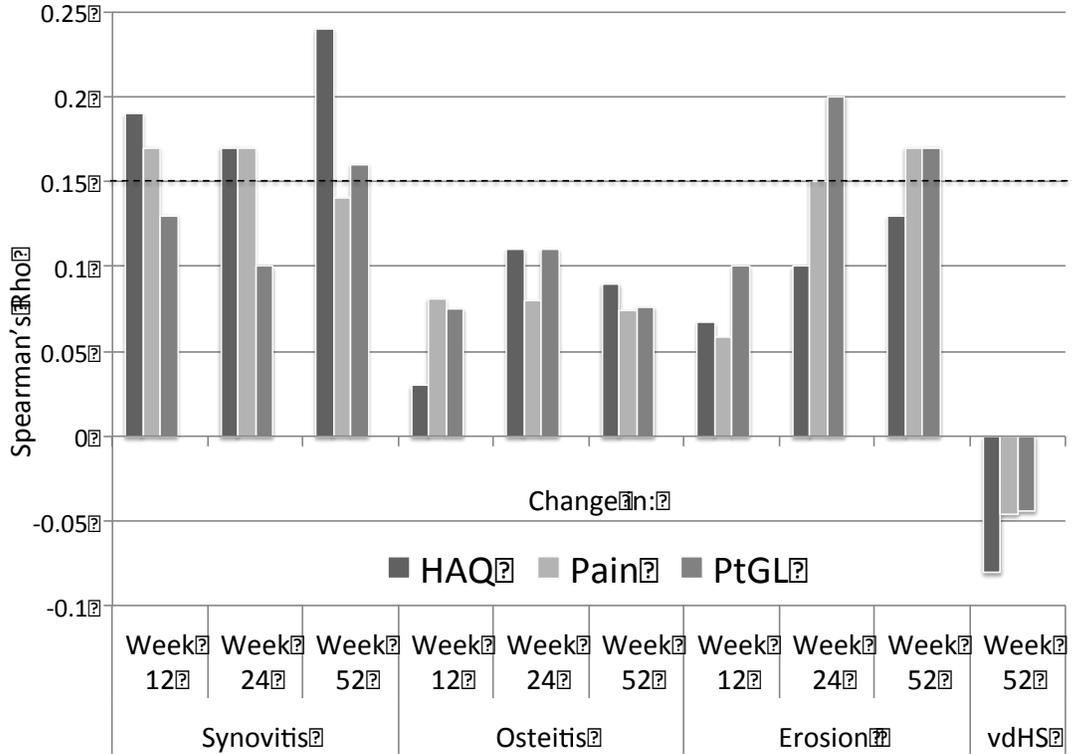
	Change Pain (VAS)*		Change in Pain (VAS)*	
	Univariate		Multivariable	
	B (95% CI)	p	B (95% CI)	p
Δ Synovitis (per 1 unit)	0.15 (0.054, 0.25)	0.002	0.16 (0.058, 0.25)	0.002
MRI Erosion Progression	1.47 (0.57, 2.36)	0.001	1.42 (0.47, 2.37)	0.004
X-ray Progression	0.59 (-0.25, 1.43)	0.17	-0.067 (-0.93, 0.80)	0.88

	Change Patient Global (VAS)*		Change in Patient Global (VAS)*	
	Univariate		Multivariable	
	B (95% CI)	p	B (95% CI)	p
Δ Synovitis (per 1 unit)	0.16 (0.066, 0.25)	0.001	0.16 (0.066, 0.25)	0.001
MRI Erosion Progression	1.47 (0.61, 2.33)	0.001	1.35 (0.44, 2.25)	0.004
X-ray Progression	0.66 (-0.15, 1.46)	0.11	0.029 (-0.79, 0.85)	0.95

*adjusted for baseline value

Figures

Figure 1: Spearman correlations between changes MRI measures of synovitis, osteitis, and bone erosion with patient-reported outcomes including HAQ, pain, and patient global scores over 12, 24, and 52 weeks of follow-up. The dashed line represents a p-value of 0.05.



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