

Importance of 'meeting of the minds': patient-reported outcomes and MRI

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Patient reported outcomes (PROs) are essential to the judicious care of patients with rheumatoid arthritis (RA). Rheumatologists were pioneers in this field with the first papers using PROs published in the 1940s.¹ Exploring the link between PROs, which are potentially subjective, and the more objective radiographic or MRI measures of structural damage and joint inflammation is important. The former describe the patient experience, which is after all the point of clinical medicine, while the latter provide information about the disease process itself, which can be influenced by clinicians using modern therapeutic approaches. The recent paper published by Baker *et al*² highlights a critical demonstration that inhibition of inflammation and progression of structural damage directly impacts reported pain of patients with RA and physical function, and positively influences their assessment of disease activity. This publication is one of several thought-provoking post hoc analyses performed within the MRI sub-studies of the Golimumab Before Employing Methotrexate as the First-Line Option in the Treatment of Rheumatoid Arthritis of Early Onset (GO-BEFORE) and Golimumab in Active Rheumatoid Arthritis Despite Methotrexate Therapy trials.³⁻⁶

EVIDENCE OF THE ASSOCIATION BETWEEN RADIOGRAPHIC DAMAGE AND PROS

The first meta-analyses to examine the link between physical function and radiographic damage were published in 2000 and 2003.^{7, 8} These studies were performed in the prebiologic era, where even small cross-sectional cohort studies demonstrated an association between total radiographic damage and the health assessment questionnaire-disability index (HAQ-DI). A subsequent comprehensive

literature review of publications between 1990 and 2008 (including some postbiologic disease modifying antirheumatic drugs (DMARD) trials) eliminated cross-sectional studies⁹ and provided a synopsis of four key concepts regarding the relationship between structural damage and HAQ: (A) 9/19 randomised controlled trials (RCTs) demonstrated a significant relationship between baseline radiographic damage and end of study HAQ, (B) 10/19 showed significant correlations cross-sectionally across the entire trial duration; 6 other RCTs a significant association only at the later time points, (C) 6/19 demonstrated a significant correlation between change in radiographic progression and end of study HAQ; 1 specifically that changes in erosions predicted functional impairment¹⁰ and (D) 7/19 RCTs revealed that changes in radiographic damage correlated with changes in HAQ. Several trials included in this review examined an independent relationship between erosions and joint space narrowing (JSN) with HAQ, with significant results. Certain early onset RA trials have demonstrated a stronger correlation between JSN and HAQ/work ability,^{11, 12} and others that erosions had a stronger association with functional impairment.¹³

An important short-term observational study of 77 patients with RA explored a method to numerically estimate the component of structural damage within the HAQ that would be considered to be irreversible damage or DAM-HAQ.¹⁴ While the DAM-HAQ calculation was initially met with enthusiasm, analytical appraisal of the concept did not allow for its incorporation into RA RCTs.¹⁵ There were concerns regarding assumption of a linear relationship between JSN and HAQ, recognition of the floor and ceiling effects of the HAQ, and the known skewing of data that occurs with Total Sharp Scores (TSS). Nonetheless, these analyses highlighted the importance of the direct relationship between JSN and worsening functional impairment,¹² a critical observation now that earlier aggressive treatment has the potential to limit progression of structural damage.

More recent publications have presented detailed analyses of structural damage within joint groups over 3 years

in the Rheumatoid Arthritis Prevention of structural Damage RCTs, indicating that both erosive damage of the wrist and JSN in the metacarpophalangeal joints (MCPs) are most likely to demonstrate progression of structural damage in established RA with the highest impact on functional impairment.¹⁶ This pattern of joint involvement confirmed similar findings in other analyses of structural damage in early and established RA. Examination of four RA RCT databases scored by the van der Heijde modification of the Sharp scoring system (vdH TSS) revealed a repetitive pattern of joint groups affected by erosions and JSN—both occurred at all sites; thus reducing the number of joints scored for damage was not a viable option.¹⁷ Erosions in the fifth metatarsophalangeal joints (MTPs) and JSN in the wrist were most likely to demonstrate structural progression. Two subsequent joint-specific analyses of structural damage in patients with early RA in the PREMIER trial demonstrated a similar pattern of involvement¹⁸ and that baseline erosions were independently associated with JSN in MTPs more than MCPs and proximal interphalangeal joints.¹⁹ Altogether these data confirm that radiographic evidence of erosions and JSN preferentially affect certain joints in both early and established RA and are more likely to demonstrate sites where progression of structural damage have the highest potential impact on physical function.

EVIDENCE OF INFLAMMATION AND DAMAGE BY MRI AND PROS

MRI is a sensitive measure capable of assessing both inflammation and damage in RA (detects synovitis, osteitis, tenosynovitis, erosions and JSN).^{20, 21} While evidence cited above supports that structural damage assessed radiographically can be linked to physical function (HAQ), few studies have comprehensively evaluated a similar link between MRI assessments and PROs, specifically pain, patient global assessment (PtGA) of disease activity as well as HAQ. Importantly, those linking MRI with PROs published prior to Baker *et al*,² were small prospective studies and not derived from RCTs.

The first published report in 2004 described an association between MRI and physical function in a cohort of 42 patients with early RA.²² Baseline MRI total (erosions, osteitis, synovitis and tendonitis) and osteitis scores predicted 6-year Medical Outcomes Survey Short Form-36 (SF-36) physical function component scores (PCS) (R²=0.22, p=0.005 and R²=0.16, p=0.02). This was an

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association with what can be considered a more comprehensive measure of physical function including activities of daily living and instrumental ones such as 'shopping' and 'walking a mile' which had not been demonstrated by radiographic studies. This initial study also demonstrated that total MRI scores at 1 year predicted subsequent HAQ scores at 6 years ($R^2=0.04$, $p=0.01$). A subsequent analysis of this cohort demonstrated that MRI evidence of tendinopathy predicted future tendon rupture at 6 years.²³ MRI osteitis and erosion scores (at baseline/1-year time points) predicted future 8-year tendon function assessed by the ability to conduct a specific manoeuvre ($\chi^2=15.3$, $p=0.0005$, $\chi^2=9.23$, $p=0.01$) and hand function by grip strength ($p=0.02$).²⁴ In another small cohort of 19 female patients with RA initiating 14 weeks open-label treatment with infliximab and methotrexate (MTX), significant correlations between MRI synovitis volume and PROs including pain, PtGA and HAQ was demonstrated ($r=0.65$, $r=0.68$ and $r=0.46$, respectively)—the first report of an association between imaging, pain and PtGA.

Despite promising results from these small series, two subsequent reports failed to show a correlation between MRI and PROs. In a cross-sectional MRI substudy of 118 patients in the Treatment of Early Aggressive Rheumatoid Arthritis trial, the total MRI inflammatory score (synovitis, osteitis and tendonitis) at the 2-year visit trended higher in patients who reported HAQ scores >0.5 compared with those with scores <0.5 (considered normative) but was not significant (12.28 vs 10.16, $p=0.37$).²⁵ Another small study of 27 patients with early RA followed by MRI over 2 years failed to demonstrate a significant correlation between erosions and HAQ scores.²⁶

In the recent publication by Baker *et al*,² the authors performed a post hoc analysis to elegantly and comprehensively examine the relationship between MRI measures of inflammation and damage (synovitis, osteitis and erosions) and PROs (HAQ, pain and PtGA) for the first time in an RCT of early RA. The GO-BEFORE study was performed in 637 MTX and biologic-naïve subjects; 291 who had MRIs scored for synovitis, osteitis and/or bone erosions were included in this subanalysis. All MRIs were scored based on the Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis MRI Scoring system (RAMRIS) of the dominant wrist and MCPs 2–5.²⁷ Significant correlations, although relatively small, were seen between PtGA and MRI

synovitis cross-sectionally across visits, with stronger associations at the latter visits (Spearman's correlation: 0.14 week 0, 0.24 week 52). MRI synovitis, osteitis and erosions correlated with HAQ at all time points (0.13–0.24 week 0, 0.22–0.28 week 54). Due to the relatively larger sample size across all treatment groups, multivariate regression analyses were possible and demonstrated an independent association between MRI synovitis and erosions with HAQ. While there were significant univariate correlations between RAMRIS scores and pain and PtGA, only MRI synovitis scores were independently associated with pain and PtGA in multivariate models, which had not been performed in previous studies due to small sample sizes. In contrast, changes in vdH TSS at 52 weeks were not associated with changes in PROs.

This study was not without limitations, as are typical in post hoc analyses. The golimumab studies were not intended to specifically evaluate the relationship between MRI and PROs, and the cross-sectional correlations between MRI measures and PROs were small. The trial time-frame of 1 year was short, and would not provide an opportunity to more firmly establish a model describing early inflammatory MRI findings with later development of structural damage-related functional impairment. An important omission to be noted is that the regression models did not show an association between osteitis and PROs. However, several early onset RA studies have demonstrated the critical importance of osteitis predicting future joint damage,^{28–31} which would later translate to impairment in patient function.^{22 24}

Inhibition of structural damage as well as synovial and bone inflammation linked to improvement in PROs is of critical importance to the care of patients with RA. A clear relationship between radiographic structural damage and PROs has now been similarly demonstrated based on MRI evidence of both damage and inflammation. Inhibition of progression of structural damage is not just clinically important but important to our patients in terms of their pain, physical function and the impact of their disease on daily life. This is of significance with the emerging role of MRI measurement in future RA RCTs (C Peterfy, V Strand, L Tian, *et al*. Short term changes on magnetic resonance imaging predict long-term changes on radiography in rheumatoid arthritis: an analysis by an OMERACT Taskforce of pooled data from four randomized, controlled trials. Submitted). It will be of

interest to see future MRI studies that more fully examine the relationship between osteitis, synovitis, cartilage volume and erosions with PROs.

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