Association Between Baseline Radiographic Damage and Improvement in Physical Function After Treatment of Patients with Rheumatoid Arthritis

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Extended Report

Association Between Baseline Radiographic Damage and Improvement in Physical Function After Treatment of Patients with Rheumatoid Arthritis

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Abstract

Objectives: The objectives of this study were to identify the factors associated with poor physical function in patients with rheumatoid arthritis (RA) and to assess whether baseline joint damage has an impact on improvement in physical function after patients were treated with infliximab plus methotrexate (MTX) or placebo plus MTX.

Methods: ATTRACT (Anti-TNF Trial in RA with Concomitant Therapy) was a placebo-controlled, randomized trial in which a total of 428 patients with active RA despite MTX therapy received placebo (i.e., MTX alone) or infliximab at 3 mg/kg or 10 mg/kg every 4 or 8 weeks along with MTX for 54 weeks. Clinical outcomes and physical function as measured by the Health Assessment Questionnaire (HAQ) were collected from baseline through week 54. Structural damage was assessed using the van der Heijde modification of the Sharp score. The odds ratio (OR) for factors associated with severe functional disability (HAQ≥2.0) at baseline were estimated using multiple logistic regression analyses, and baseline factors related to the change in physical function after treatment at week 54 were examined using multiple regression analyses.

Results: Baseline radiographic scores were significantly associated with baseline HAQ scores. After adjustment for demographic characteristics in the logistic regression model, baseline disease activity scores, radiological joint damage, fatigue, and morning stiffness were found to be significantly associated with severe functional disability (HAQ>2.0), with OR values of 2.00 (1.53-2.63), 1.82 (1.15-2.87), 1.19 (1.05-1.34), and 1.07 (1.01-1.13), respectively. In the multiple linear regression model, physical disability, joint damage, and fatigue at baseline were significantly correlated with less improvement in physical function after treatment. Furthermore, infliximab treatment was associated with significantly greater improvement in physical function.

Conclusion: Greater joint damage at baseline was significantly associated with both poorer physical function at baseline and less improvement in physical function after treatment. These results underscore the potential importance of early intervention to slow the progression of joint destruction.

Key indexing terms: Health Assessment Questionnaire, physical disability, radiographic damage, rheumatoid arthritis, risk factors
Introduction

Physical function in patients with rheumatoid arthritis (RA) deteriorates progressively throughout the course of the disease, starting with functional limitations and progressing to physical disability, if no effective treatment intervention is introduced in a timely manner [1]. Approximately 50% of patients with RA are expected to experience enough loss of function to cause work disability within 10 years after disease onset [2]. Previous studies have shown that multiple factors are associated with functional disability in patients with RA, including disease activity, radiographic damage, comorbidities, and socioeconomic and psychological factors [3-6].

The association of radiographic joint damage with physical function may vary with disease phase. In the early stages of RA, the link between joint damage and physical function is not well established [7-11]. However, in established RA, joint damage is known to be a major determinant of functional disability [4-6]. It is not known whether pre-existing joint damage affects the potential extent of improvement in physical function that might be achieved with highly effective therapies. Understanding factors associated with improvement in physical function may have implications for appropriate disease management of RA.

In this post-hoc analysis, data collected from the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) were used to evaluate the association between radiological joint damage and physical function at baseline, as well as the association of baseline radiological damage with improvement in physical function after one year of treatment.
Patients and Methods

Patient eligibility. Patient enrollment criteria and design of the study have been described in detail previously [12,13]. Briefly, patients with RA who had active disease despite the use of concomitant methotrexate (MTX) were randomly assigned to receive MTX alone or MTX plus one of four infliximab treatment regimens (3 mg/kg or 10 mg/kg every 4 or 8 weeks, after a 3-dose induction phase with infusions at week 0, 2 and 6). Treatment outcomes were collected at 4-week intervals from baseline through week 54.

Clinical and Radiographic Evaluations. Outcomes, including number of swollen and tender joints and erythrocyte sedimentation rate (ESR) were collected from baseline through week 54. Patient and evaluator global assessments of disease activity and patient assessments of fatigue were evaluated using a visual analog scale (VAS, ranging from 0 to 10). The Disease Activity Score based on 28 joints (DAS28), calculated as 0.56*SQR(T(Tender Joint Count) + 0.28*SQR(T(Swollen Joint Count) +0.7ln(ESR) + 0.014*(patient global assessment of disease activity), [14] was used as a measurement of RA disease activity. Physical function was measured using the Health Assessment Questionnaire (HAQ) [15]. Structural damage of the hands and feet was assessed using the van der Heijde modification of the Sharp score (vdH-Sharp Score ranging from 0 to 440) [16]. The total vdh-Sharp score was the average of the scores from two blinded readers and, in this paper, is referred to as the total radiographic score.

Statistical Analysis. Patients with radiographs of both the hands and feet at baseline and week 54 were included in the analysis. Data from patients in both the placebo and infliximab groups were used in this analysis with the assumption that the impact of baseline factors on improvement of physical function was similar for the two treatment groups. This assumption was tested by including treatment group as a covariate in the regression model. In the statistical model, to explore the factors associated with baseline HAQ, multivariate linear regression and logistic regression analyses were employed to adjust for the confounding effect of correlated variables. In the logistic regression analysis, patients were classified into two groups based on the HAQ scores at baseline, HAQ < 2.0 (moderate disability) and HAQ ≥ 2.0 (severe disability). This value was chosen based on data indicating that a HAQ score of 2 or higher was correlated with severe disability [17]. The odds ratio (OR) and confidence interval for severe disability were estimated. After treatment at week 54, the correlation of change in physical function with baseline clinical and radiographic joint damage was analyzed using multiple linear regression models. DAS28 was used to represent disease activity in all multiple regression models. Erythrocyte sedimentation rate (ESR), numbers of swollen and tender joints, and patient assessments of disease activity were not included in the model because these variables are included in the DAS28 calculation. Missing values in clinical measures other than radiographic scores at week 54 were imputed using the last-observation-carried-forward method. Analysis of variance on the van der Waerden normal scores was used to compare the results among patient groups for continuous variables [18]. For categorical response parameters, patient group comparisons were made using the chi-square test. Statistical analyses were performed using the SAS system (SAS Institute, Cary, NC). All statistical tests were two-sided and were performed at α=0.05.
Results

Association of baseline radiological joint damage with baseline HAQ score and baseline disease activity

Patients were categorized into four groups of approximately the same size based on quartiles of baseline radiographic scores. Compared with patients in the lowest quartile of radiographic score (≤20.5), patients in the highest quartile of radiographic score (>113) had a significantly higher HAQ score (1.86 vs 1.57, p<0.05), had more swollen (26.2 vs 19.2, p<0.05) and tender (32.3 vs 30.7, p>0.05) joints, and demonstrated more severe disease activity (6.7 vs 6.5, p <0.05). Furthermore, baseline radiographic damage was significantly correlated with baseline HAQ scores (r=0.18, p<0.001) and swollen joint counts (r=0.26, p<0.001) (Table 1). The correlation between HAQ scores and radiographic scores increased with longer disease duration (<10 years, r=0.14 vs. ≥10 years, r=0.20); whereas, the correlation between HAQ scores and disease activity scores decreased with longer disease duration (<10 years, r=0.50 vs. ≥10 years, r=0.40) (Table 2).

Table 1. Association of baseline radiographic score with HAQ and tender joint and swollen joint counts at baseline

<table>
<thead>
<tr>
<th>Baseline Total Radiologic Score</th>
<th>HAQ Mean (SD)</th>
<th>Disease activity Mean (SD)</th>
<th>Tender joint Mean (SD)</th>
<th>Swollen joint Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20.5</td>
<td>1.57 (0.54)</td>
<td>6.5 (0.96)</td>
<td>30.7 (16.2)</td>
<td>19.2 (11.3)</td>
</tr>
<tr>
<td>20.6-51.5</td>
<td>1.62 (0.66)</td>
<td>6.7 (0.99)</td>
<td>30.3 (16.5)</td>
<td>21.6 (11.5)</td>
</tr>
<tr>
<td>51.6 – 113</td>
<td>1.76(0.62)</td>
<td>6.9 (1.05)</td>
<td>35.22(16.9)</td>
<td>23.7 (12.7)</td>
</tr>
<tr>
<td>&gt; 113</td>
<td>1.86(0.64)</td>
<td>6.7 (1.06)</td>
<td>32.31(17.0)</td>
<td>26.2 (11.9)</td>
</tr>
<tr>
<td>Correlation coefficient*</td>
<td>0.18 (p&lt;0.001)</td>
<td>0.12 (p=0.13)</td>
<td>0.08 (p&gt;0.05)</td>
<td>0.26 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

SD = standard deviation
*Spearmann's correlation coefficients of baseline total radiographic score with HAQ, DAS, and swollen and tender joint counts.

Table 2. Spearman correlations between baseline HAQ scores and baseline radiographic scores or disease activity by disease duration

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Disease Duration (years)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>≥10</td>
</tr>
<tr>
<td>HAQ scores vs Radiographic scores</td>
<td>0.14 (p&lt;0.05)</td>
<td>0.20 (p=0.01)</td>
</tr>
<tr>
<td>HAQ scores vs Disease activity scores</td>
<td>0.50 (p&lt;0.01)</td>
<td>0.40 (p&lt;0.01)</td>
</tr>
</tbody>
</table>

In the linear regression model, gender, baseline joint damage, disease activity score, morning stiffness and fatigue score were statistically significantly correlated with baseline HAQ score (Table 3).
Table 3. Baseline variables significantly associated with baseline HAQ scores in the linear regression model

<table>
<thead>
<tr>
<th>Explanatory Variables</th>
<th>$\beta$</th>
<th>SE ($\beta$)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male</td>
<td>-0.202</td>
<td>0.064</td>
<td>0.0016</td>
</tr>
<tr>
<td>Radiographic scores (0-440)</td>
<td>0.001</td>
<td>0.000</td>
<td>0.0002</td>
</tr>
<tr>
<td>Disease activity scores (0-10)</td>
<td>0.202</td>
<td>0.029</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Morning stiffness (minutes)</td>
<td>0.012</td>
<td>0.006</td>
<td>0.0404</td>
</tr>
<tr>
<td>Fatigue (0-10)</td>
<td>0.064</td>
<td>0.013</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

$\beta =$ estimated coefficient  
SE ($\beta$) = estimated standard error of the $\beta$

In the logistic regression model, a dichotomous variable representing severe functional disability (HAQ $\geq$ 2.0) was used as the dependent variable, and age, male gender (yes or no), disease duration, disease activity (DAS28 score), radiographic score $>$50 (yes or no), morning stiffness (minutes), and fatigue score were used as independent variables. In the final model, using stepwise selection, baseline disease activity and radiographic joint damage were the most significant risk factors for severe functional disability at baseline. The odds ratio for severe functional disability for patients with severe joint damage (radiographic score $>$ 50) was 1.82 (1.15-2.87, p = 0.01). The odds ratio for severe functional disability for patients with higher disease activity (per unit increase) was 2.0 (1.53-2.63, p < 0.01). Fatigue and morning stiffness also showed significant association with severe functional disability. Men were less likely to have severe functional disability compared with women. Disease duration was not a significant factor in the model after adjusting for the other factors; therefore, it was not selected into the model (Table 4).

Table 4. Baseline variables significantly associated with severe physical disability (HAQ≥2.0) in the logistic regression model

<table>
<thead>
<tr>
<th>Explanatory Variables</th>
<th>$\beta$</th>
<th>SE ($\beta$)</th>
<th>P value</th>
<th>OR</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.025</td>
<td>0.010</td>
<td>0.02</td>
<td>1.004</td>
<td>1.01 - 1.05</td>
</tr>
<tr>
<td>Gender: male</td>
<td>-0.780</td>
<td>0.292</td>
<td>&lt;0.01</td>
<td>0.46</td>
<td>0.26 - 0.81</td>
</tr>
<tr>
<td>Radiological joint damage (radiographic score&gt;50)</td>
<td>0.598</td>
<td>0.233</td>
<td>0.01</td>
<td>1.82</td>
<td>1.15 - 2.87</td>
</tr>
<tr>
<td>Disease activity scores (per unit)</td>
<td>0.694</td>
<td>0.139</td>
<td>&lt;0.01</td>
<td>2.00</td>
<td>1.53 - 2.63</td>
</tr>
<tr>
<td>Morning stiffness (per minute)</td>
<td>0.065</td>
<td>0.029</td>
<td>0.02</td>
<td>1.07</td>
<td>1.01 - 1.13</td>
</tr>
<tr>
<td>Fatigue (per unit)</td>
<td>0.170</td>
<td>0.062</td>
<td>&lt;0.01</td>
<td>1.19</td>
<td>1.05 - 1.34</td>
</tr>
</tbody>
</table>

$\beta =$ estimated coefficient  
SE ($\beta$) = estimated standard error of the $\beta$  
OR = odds ratio  
OR 95% CI = 95% confidence interval of the odds ratio

Association of baseline joint damage and treatment outcomes

The mean percent improvement in physical function was significantly associated with baseline radiographic scores, with patients in the highest radiographic score quartile having significantly smaller improvements in HAQ than patients in the lowest radiographic score quartile (16% vs. 32%, p < 0.01). In contrast, the mean percent
Improvement in disease activity, the number of tender joints, and the number of swollen joints was not significantly different among groups defined by radiographic score quartiles (Figure 1).

Since patients in the infliximab plus MTX group had greater improvement in physical function in each radiographic score quartile than those in the placebo plus MTX group, the correlation of improvement in physical function at week 54 with baseline factors was further analyzed using a multiple linear regression analysis with treatment as one of the covariates. In the final regression model, using stepwise model selection, infliximab treatment was significantly correlated with improvement in HAQ score at week 54. Age, baseline HAQ scores, baseline joint damage, and baseline fatigue were also independently associated with the change (improvement) in physical function, regardless of the treatment group assignment (Table 5). Greater radiographic joint damage and more severe fatigue at baseline were associated with less improvement in physical function at week 54 (p<0.05). In addition, patients with greater disability at baseline demonstrated a greater improvement in physical function after treatment at week 54 (p<0.01). Baseline disease activity and morning stiffness were not significant factors in predicting improvement in physical function at week 54 after adjustment for other baseline factors; therefore, they were not selected into the model.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>$\beta$</th>
<th>SE ((\beta))</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.009</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline HAQ scores</td>
<td>0.180</td>
<td>0.050</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline radiographic scores</td>
<td>-0.001</td>
<td>0.000</td>
<td>0.019</td>
</tr>
<tr>
<td>Baseline fatigue score</td>
<td>-0.035</td>
<td>0.014</td>
<td>0.014</td>
</tr>
<tr>
<td>Treatment (infliximab)</td>
<td>0.302</td>
<td>0.070</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$\beta$ = estimated coefficient
SE (\(\beta\)) = estimated standard error of the $\beta$
Discussion

RA is a chronic, progressive, and destructive disorder. Functional disability deteriorates rapidly in patients with RA such that about half will experience work disability within ten years after diagnosis [2]. Previous studies have shown that multiple clinical and non-clinical variables are associated with functional disability, with the most important factors being disease activity and radiographic joint damage [3,6]. In the early stage of the disease, functional ability may be influenced more by disease activity than by radiographic joint damage [7]. However, as the disease progresses, joint damage becomes a more dominant factor in determining physical function [6]. Clarke et al. [3] reported that the correlation between radiographic scores and HAQ scores tends to increase with disease duration from 0.15 after 0 to 5 years of disease onset to 0.42 after 10 to 15 years. The ATTRACT baseline data showed a similar trend, with the correlation between HAQ scores and radiographic scores increasing from 0.14 to 0.20 with an increase in disease duration (< 10 years vs. ≥ 10 years).

In general, traditional disease-modifying antirheumatic drug (DMARD) treatments can slow disease progression but may not prevent the bone and cartilage erosion associated with RA [19]. Unchecked progression of RA can eventually lead to functional impairment. Therefore, controlling only clinical signs and symptoms may not be adequate to retain the patient’s long-term physical function. Understanding and managing the risk factors related to long-term functional impairment is critical for better treatment outcomes.

In the past decade, joint damage as assessed by radiography has been considered one of the critical measurements in the evaluation of disease severity and treatment efficacy in clinical trials [20]. An association has been observed not only between joint damage and severe functional loss, but also between joint damage and loss of employability [21] higher mortality in the RA population [22]. ATTRACT data showed that radiographic joint damage was associated with unemployment, and that patients with a radiographic score of greater than 50 had a much lower probability of being employed full-time, compared with patients with lower radiographic scores [23]. As demonstrated in this analysis, baseline radiographic joint damage is related to baseline physical function and is also a significant predictor of improvement in physical function after treatment. Patients with radiographic scores that were 20.5 or less had better improvement in physical function (32%) from baseline to week 54 compared with those with radiographic scores that were greater than 113 (16%), even though both patient groups demonstrated similar improvement in disease activity scores (31% vs. 27%). The ATTRACT trial was ideally suited for this study, since the range of radiographic scores at baseline in ATTRACT was larger than that of the study populations in other trials. The results of this analysis strongly support the association between radiographic damage and physical disability in patients with established disease. Furthermore, the results indicate that physical disability caused by joint damage from erosions and joint space narrowing is less likely to be reversible at later disease stages.

A major limitation of the study was that it was a post-hoc exploratory analysis, examining the association between joint damage and physical function. Any conclusions
regarding causal relationships based on these results should be made with caution. Another limitation was that only patients with moderate-to-severe RA who were inadequately responding to MTX were enrolled in the ATTRACT study. Therefore, caution should be exercised in extrapolating these results beyond this patient population.

In conclusion, the results of this analysis demonstrated that the improvement in physical function after 1 year of treatment in patients with moderate-to-severe RA was correlated with the degree of radiographic joint damage already evident at baseline. If this does indicate the relatively lower reversibility of functional loss resulting from structural damage, then these results may underscore the importance of early treatment to limit joint damage.
Acknowledgments
The ATTRACT study was sponsored by Centocor, Inc. Drs. Breedveld, Kavanaugh, Maini, and van der Heijde have received research support from and served as consultants to Centocor, Inc. Drs. Han, Bala, and Baker are employees of Centocor, Inc.
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23. Kavanaugh AF, Han C, Bala M. Improvement in functional status results in increased employability and reduced costs of RA: Analysis of the minimum clinically important difference in Health Assessment questionnaire in the ATTRACT study, Arthritis Rheum 2002;46(Suppl 9):S575.
Figure Legends

Figure 1: Percent improvement in HAQ, disease activity, and tender and swollen joint counts from baseline to week 54 by baseline radiological score
Figure 1

- HAQ
- DAS
- Tender Joint
- Swollen Joint
Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis

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