EXTENDED REPORT

Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis

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Methods: 428 patients with active rheumatoid arthritis despite methotrexate treatment received methotrexate alone or with infliximab (3 mg/kg or 10 mg/kg every four or eight weeks) for 54 weeks (the ATTRACT trial). Data on clinical outcomes and physical function (assessed by the health assessment questionnaire [HAQ]) were collected. Structural damage was assessed using the van der Heijde modification of the Sharp score. Odds ratios (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 determined.

Results: Baseline radiographic scores were correlated 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 associated with severe functional disability (HAQ > 2.0), with OR values of 2.00 (1.53 to 2.63), 1.82 (1.15 to 2.87), 1.19 (1.05 to 1.34), and 1.07 (1.01 to 1.13), respectively. In multiple linear regression analysis, physical disability, joint damage, and fatigue at baseline were correlated with less improvement in physical function after treatment. Infliximab treatment was associated with greater improvement in physical function.

Conclusions: Greater joint damage at baseline was associated with poorer physical function at baseline and less improvement in physical function after treatment, underlining the importance of early intervention to slow the progression of joint destruction.

Physical function in patients with rheumatoid arthritis 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. Approximately 50% of patients with rheumatoid arthritis are expected to experience enough loss of function to cause work disability within 10 years after disease onset. Previous studies have shown that multiple factors are associated with functional disability in patients with rheumatoid arthritis, including disease activity, radiographic damage, co-morbidities, and socioeconomic and psychological factors.

The association of radiographic joint damage with physical function may vary with disease phase. In the early stages of rheumatoid arthritis, the link between joint damage and physical function is not well established. However, in established disease, joint damage is known to be a major determinant of functional disability. It is not clear whether pre-existing joint damage affects the extent of improvement in physical function that could be achieved with highly effective treatment. Understanding the factors associated with improvement in physical function may have implications for appropriate disease management of this disease.

In this post-hoc analysis, data collected from ATTRACT (the anti-TNF trial in rheumatoid arthritis with concomitant therapy) 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.

METHODS

Patient eligibility

Patient enrolment criteria and the design of the study have been described in detail previously. Briefly, patients with rheumatoid arthritis who had active disease despite the use of concomitant methotrexate were randomly assigned to receive methotrexate alone or methotrexate plus one of four infliximab treatment regimens (3 mg/kg or 10 mg/kg every four or eight weeks, after a three dose induction phase with infusions at weeks 0, 2, and 6). Treatment outcomes were collected at four week intervals from baseline to week 54.

Clinical and radiographic evaluation

Outcomes, including the number of swollen and tender joints and the erythrocyte sedimentation rate (ESR), were collected from baseline to week 54. Patient and evaluator global assessments of disease activity and patient assessments of fatigue were made using a visual analogue scale (ranging from 0 to 10). The disease activity score based on 28 joints (DAS 28), calculated as 0.56*(swollen joint count) + 0.28*(tender joint count) + 0.7ln(ESR) + 0.014*(patient global assessment of disease activity), was used as a measure of rheumatoid arthritis disease activity. Physical function was measured using the health assessment questionnaire (HAQ).

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). The

Abbreviations: ATTRACT, anti-TNF trial in rheumatoid arthritis with concomitant therapy; HAQ, health assessment questionnaire
total vdH-Sharp score was the average of the scores from two blinded readers and is referred to in this paper 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 the analysis, with the assumption that the impact of baseline factors on improvement in physical function was similar for the two treatment groups. This assumption was tested by including treatment group as a covariate in the logistic regression model. In the statistical model exploring 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 an HAQ value of 2 or higher was correlated with severe disability.17 The odds ratios (OR) and confidence intervals for severe disability (HAQ ≥2.0) were significantly correlated with baseline HAQ score and baseline disease activity score, morning stiffness, and fatigue score (table 3). The correlation between HAQ scores and radiographic scores increased with longer disease duration (<10 years, r = 0.14 v ≥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 v ≥10 years, r = 0.40) (table 2).

In the logistic regression model, sex, baseline joint damage, disease activity score, morning stiffness, and fatigue score were significantly correlated with baseline HAQ score (r = 0.18, p <0.001) and swollen joint counts (r = 0.26, p <0.001) (table 3). The correlation between HAQ and 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.16 For categorical response variables, patient group comparisons were made using the χ² test. Statistical analyses employed the SAS system (SAS Institute, Cary, North Carolina, USA). All statistical tests were two sided, with α = 0.05.

- **Table 1**: Association of baseline radiographic score with health assessment questionnaire score and tender joint and swollen joint counts at baseline

<table>
<thead>
<tr>
<th>Baseline radiological score</th>
<th>HAQ</th>
<th>Disease activity score</th>
<th>Tender joint count</th>
<th>Swollen joint count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;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 to 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 to 113</td>
<td>1.76 (0.62)</td>
<td>6.9 (1.05)</td>
<td>35.2 (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>32.3 (17.0)</td>
<td>26.2 (11.9)</td>
</tr>
</tbody>
</table>

Correlation coefficient*: 0.18 (p <0.001) 0.12 (p = 0.13) 0.08 (p <0.01) 0.26 (p <0.001)

Values are mean (SD)

- **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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
</tr>
<tr>
<td>HAQ scores v radiographic score</td>
<td>0.14 (p &lt;0.05)</td>
</tr>
<tr>
<td>HAQ scores v disease activity score</td>
<td>0.50 (p &lt;0.01)</td>
</tr>
</tbody>
</table>

HAQ, health assessment questionnaire.

- **Table 3**: Baseline variables significantly associated with baseline health assessment questionnaire (HAQ) scores in the linear regression model

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>β</th>
<th>SE (β)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>-0.202</td>
<td>0.064</td>
<td>0.0016</td>
</tr>
<tr>
<td>Radiographic score (0–440)</td>
<td>0.001</td>
<td>0.000</td>
<td>0.0002</td>
</tr>
<tr>
<td>Disease activity score (0–10)</td>
<td>0.202</td>
<td>0.029</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Morning stiffness (min)</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>

β, estimated coefficient; SE (β), estimated standard error of the β.

RESULTS
Association of baseline radiological joint damage with baseline HAQ score and baseline disease activity
Patients were categorised 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 v 1.57, p <0.05), more swollen (26.2 v 19.2, p <0.05) and tender joints (32.2 v 30.7, p <0.05), and more severe disease activity (6.7 v 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 v ≥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 v ≥10 years, r = 0.40) (table 2).

In the linear regression model, sex, baseline joint damage, disease activity score, morning stiffness, and fatigue score were significantly correlated with baseline HAQ score (table 3). In the logistic regression model, a dichotomous variable representing severe functional disability (HAQ >2.0) was used as the dependent variable, and age, male sex (yes or no),
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 showed 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 incorporated into the model.

### DISCUSSION

Rheumatoid arthritis is a chronic, progressive, and destructive disorder. Functional disability increases rapidly in affected individuals, such that about half will experience work disability within 10 years of diagnosis. Previous studies have shown that multiple clinical and non-clinical variables are associated with functional disability, the most important being disease activity and radiographic joint damage. In the early stage of the disease, functional ability may be influenced more by disease activity than by radiographic joint damage. However, as the disease progresses, joint damage becomes a more dominant factor in determining physical function. Clarke et al 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) versus 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 rheumatoid arthritis. Unchecked progression of the disease can eventually lead to functional impairment. Thus controlling only the 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. An association has been observed not only between joint damage and severe functional loss, but also between joint damage and loss of employability and higher mortality in the rheumatoid population. ATTRACT data showed that radiographic joint damage was associated with unemployment, and that patients with a radiographic score of more than 50 had a much lower probability of being employed full time than those with lower radiographic scores. 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 of 20.5 or less had better improvement in physical function (32%) from baseline to week 54 than those with radiographic scores of more than 113 (16%), even though both patient groups had similar improvement in disease activity scores (31% vs 27%). The ATTRACT trial was ideally suited to this study, as 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 relations based on these results should be made with caution. Another limitation was that only patients with moderate to severe rheumatoid arthritis who were inadequately responding to methotrexate were enrolled in the ATTRACT study. Thus caution should be exercised in extrapolating these results beyond this patient population.

Conclusions

The results of our analysis show that the improvement in physical function after one year of treatment in patients with moderate to severe rheumatoid arthritis was correlated with the degree of radiographic joint damage already evident at baseline. If this indicates the relatively lower reversibility of functional loss resulting from structural damage, then these results underline the importance of early treatment to limit joint damage.

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