Anti-TNF therapy in rheumatoid arthritis: Searching for mechanisms of effect
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Improvement of work ability, quality of life, and fatigue in patients with rheumatoid arthritis treated with adalimumab


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ABSTRACT

Objective
To assess the effect of 12-month treatment with adalimumab on work ability, quality of life, and fatigue in patients with active rheumatoid arthritis (RA).

Methods
One hundred twenty-six patients with active RA started treatment with adalimumab. Primary outcome measurements were work ability, assessed by the first item of the Work Ability Index, quality of life, assessed by the Rheumatoid Arthritis Quality of Life (RAQoL) instrument, and fatigue, assessed by the Checklist Individual Strength and the Need for Recovery after work Scale.

Results
All primary outcome measurements showed a significant improvement. The largest improvement for all outcome measurements was gained in the first 6 months of treatment and was sustained over the following 6 months.

Conclusion
Adalimumab improves patient reported outcomes in addition to improving disease activity in established RA.
INTRODUCTION
Several studies in patients with rheumatoid arthritis (RA) have shown that work disability is a common consequence of this disease. In a systematic review, it was reported that 20% to 70% of employees were work disabled 7 to 10 years after disease onset. The great impact of RA on work ability has prompted studies that examined the factors related to work disability and studies that examined the effect of therapy hereon. Treatments with tumor necrosis factor (TNF) inhibitors have been shown to be effective in RA and are recommended for the treatment of active RA, generally after adequate trial of conventional disease-modifying antirheumatic drugs.

The anti-TNF antibody adalimumab has been shown to reduce the signs and symptoms of disease, slow the rate of radiographic progression, and improve self-reported functional disability in both RA refractory to treatment with methotrexate and newly diagnosed RA. These studies have also focused on the patient’s self-reported improvement of quality of life, functional status, and fatigue. Adalimumab therapy was associated with improvements from baseline in both functional disability and fatigue. These improvements exceeded the Minimally Important Clinical Difference.

The social and economic impact of work disability on patients and their families is substantial. In addition, there are major economic consequences for society (indirect costs). Given their beneficial effects, it is plausible that TNF inhibitors will reduce work disability and reduce direct costs of medical care. Recently, some studies have been done to explore the association between employment and treatment with a TNF antagonist, suggesting that the use of TNF inhibitors reduces the chance of becoming unemployed.

Therefore, the objective of this study was to explore the effects of a 12-month period of adalimumab therapy on self-reported work ability, quality of life, and fatigue in a naturalistic design.

PATIENTS AND METHODS
Patient Recruitment and Treatment
In this prospective cohort study, consecutive patients with active RA were recruited from the rheumatology outpatient clinic at the Jan van Breemen Institute, Amsterdam and from the Academic Medical Center, University of Amsterdam, The Netherlands. The protocol was approved by the local Medical Ethics Committee of both participating centers.

All patients met the following inclusion criteria: 1) Their age at time of start of the study was 18 to 62 years (working age). 2) They had a history of RA fulfilling the American College of Rheumatology criteria. 3) They met the criteria for treatment with TNF-alpha inhibitors as required by the guidelines of the Dutch Society for Rheumatology. 4) They all provided informed consent and complied with treatment and follow-up measurements. All patients could continue their disease-modifying antirheumatic drugs, such as methotrexate and non-steroidal anti-inflammatory drugs, as prescribed by the participating rheumatologist. All patients were started on adalimumab subcutaneously 40 mg every other week.
Outcome Measures
At baseline, 6 months, and after 1 year, we evaluated the effects of treatment with adalimumab on work ability, quality of life, fatigue and disease activity were evaluated.

Work Ability
The concept of work ability was defined as the self-perceived ability of a patient to perform his/her job, taking into account the specific work demands, individual health condition, and mental resources\(^{(21)}\). To assess an individual’s work ability, a self-administered questionnaire, the Work Ability Index questionnaire (WAI), was constructed\(^{(22)}\). In this study, the first item of this questionnaire was used. This first item is referred to as WAI or self-perceived workability. The first item of the WAI has previously been used in studies to assess workability in patients with musculoskeletal disorders\(^{(23,24)}\). Patients were asked to assign a value between 0 and 10 to their current work ability (0 points = very low self-perceived work ability and 10 points = best self-perceived work ability ever).

Quality of Life
The Rheumatoid Arthritis Quality of Life (RAQoL) instrument is a well-validated RA specific quality of life instrument\(^{(25)}\). Typical items of this questionnaire are “I have difficulty dressing” and “I feel dependent on others.” It consists of 30 items with a yes/no response format (yes = 1 or no = 0). It measures different areas of life, including moods and emotions, social life, hobbies, every day tasks, personal and social relationships, and physical contact. The overall score was calculated of the sum of the scores of individual items (0 to 30). A higher score indicates worse quality of life. The RAQoL instrument was completed by the patient.

Fatigue
The Checklist Individual Strength (CIS) was used to measure fatigue. It measures several aspects of the patients’ level of fatigue for the previous 2 weeks. The patient scores 20 Likert-items (e.g., I feel tired, I have trouble concentrating) with a seven-point response format (1 = yes, that is true; to 7 = no, that is not true) containing subjective fatigue, reduced motivation, reduced activity, and reduced concentration. The sum scores of the CIS range from 20 to 140. Higher scores indicate more fatigue, with a score >76 points a patient is considered to be fatigued\(^{(26)}\). This questionnaire was validated in the work setting\(^{(26)}\) and demonstrated sensitivity to change in a study of RA patients undergoing cognitive behavioral therapy\(^{(27)}\).

The second fatigue questionnaire was the need for recovery after work scale (NFR). It assesses work-related fatigue and typical items: “at the end of a working day I am really feeling worn-out” and “after a working day I am often too tired to do other activities.” It consists of an 11-point scale with dichotomous answering categories. Scale scores were transformed into scores ranging from 0 to 100. Higher scores indicate a higher work-related fatigue. It can be used both for applications at the individual and at the group (department/organization) level.\(^{(28)}\) The NFR score in the general population is ~27\(^{(28)}\).
Disease Activity

To evaluate clinical efficacy of adalimumab the Disease Activity Score (DAS28) was measured at baseline, 6 months, and 1 year after the start of treatment. Furthermore, the Health Assessment Questionnaire was measured at baseline and at 1 year after baseline.

Descriptive Variables

In an earlier study lack of autonomy, lack of participation in decision making, and lack of supervisor and coworker support were strongly associated with low work ability. Therefore, these psychosocial job characteristics were measured as descriptive variables and the following subscales of the Dutch Questionnaire on the Experience and Assessment of Work (VBBA) were used: psychosocial job demands, lack of autonomy, participation in decision making, and supervisor and coworker support. All items were scored on a four-point scale and summed up (1 = never, 2 = sometimes, 3 = often, and 4 = always). All scale scores were transformed into scales ranging from 0 to 100. The VBBA was validated in the general working population and in employees with chronic diseases. Higher scores reflect worse psychosocial work characteristics. Psychosocial job characteristics are independent of adalimumab therapy. Thus, there should be no change in these items during this study.

Analyses

Statistical test were done using SPSS 16.0. If data were assessed to be normally distributed (ie, CIS, DAS28, and psychosocial job demands), a GLM test for repeated measures was done to assess the differences in outcome measures between baseline, 6 months, and 1 year. Outcome measures that were not normally distributed (ie, WAI, RAQoL instrument, NFR, supervisor support, and independence and coworker support) were tested with the nonparametric Friedman test. For not normally distributed data, post hoc analyses were done using the Wilcoxon signed-ranks test to assess the differences in outcome measures between baseline and 6 months, baseline and 1 year, and between 6 months and 1 year of follow-up. Percentages of improvement in the outcome variables were defined as the calculated difference between two time points compared with the total score. The Need for Recovery after work outcome variable was done only on patients who had a job during their first year of adalimumab treatment (n = 63).

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. During the treatment period, 17 patients (15%) discontinued the treatment with adalimumab. Of these 17 patients, 12 patients (9.5%) stopped because of an insufficient response and 5 patients (4%) stopped because of side effects possibly related to adalimumab (2 headache/fatigue, 1 lupus-like symptom, and 2 were diagnosed with lung carcinoma). Of the patients who discontinued adalimumab treatment, 10 switched to another TNF inhibitor, 2 switched to rituximab treatment, and 5 patients were discontinued on treatment with biologicals. Two patients were lost to follow-up. At baseline, the mean DAS28 was 5.2. After 6 months and 1 year of treatment, the mean DAS28 was 3.4 and 3.1, respectively (p<0.001).
Primary Outcomes

The data on work ability, quality of life, and fatigue are shown in Table 2. Outcome measurements were analyzed if the data for all three time points were present. For all outcome measurements, there was a statistically significant improvement at 6 months and 1 year when compared with baseline. The mean improvement at 6 months in the WAI was 9% (CI, 4% to 14%). In the next 6 months, this improvement is increased further making the total improvement of self-reported workability 11% (CI, 6% to 16%) after 1 year of treatment with adalimumab. After 6 months, the improvement in the RAQoL instrument was 13% (CI, 8% to 18%), which increased over the next 6 months to 15% (CI, 10% to 20%). For the CIS, the same trend was found. The improvement in the first 6 months of treatment was 11% (CI, 6% to 16%). This improvement increased further over the next 6 months to a total of 13% (CI, 8% to 19%) after 1 year of treatment in the NFR score, there was an improvement of 10% (CI, 3% to 17%) in the first 6 months of treatment. The improvement in NFR after 1 year of treatment was 12% (CI, 4% to 20%).

DISCUSSION

The results presented here reveal the effects of adalimumab treatment on work ability in daily clinical practice in a European population. We found improvement of self-reported work ability, quality of life, and fatigue in the first year of treatment in patients with RA. The largest improvement for all

Table 1 Demographic characteristics and characteristics of RA at baseline (N=126)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>Erosive disease</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>DAS(28)</td>
<td></td>
<td>5.2</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td></td>
<td>1.3</td>
</tr>
<tr>
<td>No. previous DMARDs failed</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>No. previous TNF inhibitors failed</td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

Table 2 Work related characteristics at baseline, 6 months and one year

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 months</th>
<th>1 year</th>
<th>P value (T0-T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paid work N (percentage)</td>
<td>54 (55)</td>
<td>50 (51)</td>
<td>52 (53)</td>
<td>0.125</td>
</tr>
<tr>
<td>Independence Mean (SD)</td>
<td>42.4 (23.4)</td>
<td>38.5 (23.2)</td>
<td>39.3 (23.0)</td>
<td>0.533</td>
</tr>
<tr>
<td>Psychosocial demands Mean (SD)</td>
<td>42.0 (13.7)</td>
<td>40.6 (15.1)</td>
<td>39.3 (14.8)</td>
<td>0.187</td>
</tr>
<tr>
<td>Co-worker support Mean (SD)</td>
<td>17.6 (13.8)</td>
<td>19.6 (13.3)</td>
<td>20.6 (12.2)</td>
<td>0.286</td>
</tr>
<tr>
<td>Supervisor support Median (iq range)</td>
<td>14.8 (19.4)</td>
<td>14.8 (27.8)</td>
<td>14.8 (22.2)</td>
<td>0.335</td>
</tr>
</tbody>
</table>
outcome measurements was gained in the first 6 months of treatment and was sustained over the following 6 months. In this period clinical outcome measures, such as disease activity and functional disability, showed a significant improvement as well. Also for these measurements, the largest improvement was seen in the first 6 months of treatment. The importance of patient-reported outcomes in the evaluation of treatment of chronic conditions, such as RA, is gaining importance in the evaluation of new therapies (33-35) and will be increasingly required by the regulatory agencies.

The improvement in work ability after the first year of treatment is consistent with the results of a clinical trial, showing that patients with early arthritis, who were treated with infliximab, were less likely to become unemployed after 1 year of treatment (7). Moreover, patients with established RA using etanercept treatment were less likely to become unemployed than those who did not receive etanercept treatment (8). The follow-up of patients in our study was 1 year. In this time frame, self-assessed workability has been shown to be sensitive to change, which could give opportunities for employment in the future.

Self-assessment of workability has a high predictive value for future work disability (36). However, we could not show an increase of percentage of patients with paid work after 1 year of treatment. This corresponds to the findings of Wolfe (38), who could not find a positive effect of anti-TNF-therapy on the risk of work disability after 5.5 years of follow-up. Obviously, actual employment is dependent on the complex interaction of characteristics of individuals, the nature of their work, and their environment, including the physical workplace, policies related to work accommodation, and labor markets (6). Thus, these studies highlight the importance of the development and implementation of return-to-work programs for this group of patients.

Adalimumab also had a beneficial effect on both general fatigue and work-related fatigue as measured by the CIS and NFR, respectively. Our findings are in agreement with results from randomized clinical in which fatigue was measured by the Functional Assessment of Chronic Illness Therapy fatigue scale (59). In this study, general fatigue, as measured by the CIS, showed a clinically relevant improvement, as the mean score drops below the cutoff point (76 points) for fatigue (26). By measuring fatigue with the NFR, we showed that the beneficial effect of adalimumab treatment on fatigue held up in the work setting. However, even after 1 year of treatment, the work-related fatigue remains much more than in the general population (28).

In our study, the median disease duration at the start of adalimumab treatment was 6.4 years. Previous work has shown that patients with longstanding RA were less likely to improve in employability after effective treatment than those with early disease (37). Probably this is due to the fact that structural damage and comorbidity are more important in affecting work disability in late disease, whereas the effect of disease activity on work disability is reversible in early disease (38-40). Nowadays treatment of RA aims at inducing remission as soon as possible to prevent structural damage and disability. This suggests that with the current early and intensive treatment strategy in RA, maintaining the ability to work will become increasingly feasible.

Using a naturalistic design in a European cohort, we have shown that work ability, quality of life, and fatigue in patients with established RA clearly improved after 1 year of adalimumab therapy. To translate work ability into actual employment, there is a need for the development and implementation of return-to-work programs for RA patients.
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