Effect of Etanercept on Fatigue in Patients With Recent or Established Rheumatoid Arthritis

LARRY W. MORELAND,1 MARK C. GENOVESE,2 REIKO SATO,3 AND AMITABH SINGH3

Objective. To assess the long-term impact of etanercept on fatigue in patients with recent-onset (mean duration 11 months) or established (mean duration 12 years) rheumatoid arthritis (RA).

Methods. Patients participating in either of 2 multicenter, randomized, double-blind clinical trials were included. In one trial, patients with recent-onset RA received either etanercept 25 mg twice weekly or methotrexate in a double-blind fashion for 12 months, then open label for 12 months. All patients then received open-label etanercept. In the second trial, patients with established RA received etanercept 25 mg or placebo twice weekly for 6 months in a double-blinded fashion, then open-label etanercept. Up to 46 months of followup data were included. Fatigue was measured regularly using the Health Assessment Questionnaire vitality domain.

Results. Patients with recent-onset RA who received etanercept had a significantly faster improvement in fatigue than those receiving methotrexate in the first 2 months. Subsequently, patients receiving etanercept and methotrexate had 23–29% and 17–24% reductions in fatigue scores, respectively. In the group with established RA, patients who received etanercept had significantly greater reductions in fatigue than those receiving placebo during the blinded period. Patients initially receiving etanercept sustained a mean fatigue reduction of 25–36% for the entire followup. Patients achieving clinically meaningful improvement in fatigue were more likely to meet the American College of Rheumatology improvement criteria.

Conclusion. Etanercept therapy reduces fatigue in patients with recent-onset or established RA. Improvement in fatigue was sustained for up to 46 months, and correlated with other RA-relevant outcomes.

KEY WORDS. Rheumatoid arthritis; Fatigue; Vitality; Quality of life; Etanercept; Methotrexate; Health Assessment Questionnaire; Short Form 36.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease in which synovial joints, commonly the wrists, knees, and joints in the hands and feet, are chronically inflamed (1). As the disease progresses, the structure of affected joints is damaged and the joints may become deformed (1). RA has a considerable impact on the patient’s quality of life (3), and is associated with substantial pain, gradual loss of mobility, and inability to care for oneself (1). On average, patients with RA have impaired psychological and social functioning and commonly experience anxiety and depression (3,4).

Fatigue is another common symptom of RA that has considerable impact on quality of life. In one study, patients with RA reported higher fatigue levels than age- and sex-matched controls (5). One study involving 628 patients with RA found that 87% reported feeling fatigued; in 42% of patients, this fatigue was considered by investigators to be clinically important (6). In another study, 69% of 446 patients reported feeling severely or very severely fatigued (7). Interviews have revealed that relief of fatigue is one of the outcomes most desired by patients with RA (7,8). In addition, fatigue level has been reported to be more predictive of quality of life than pain, joint tenderness, or disease activity (4).

Although the etiology of RA is not well understood, increased fatigue correlates with pain, depression, anxiety, stress, self efficacy, and well-intentioned but unhelpful social support (5,9–13). Fatigue does not correlate well with objective measures of disease activity, such as number of swollen joints or erythrocyte sedimentation rate,
which are traditionally used to assess antirheumatic therapies (9). Therefore, assessment of impact on fatigue is essential for comprehensive evaluation of novel therapeutic interventions.

In recent years the focus of RA treatment has been on early, aggressive therapy with the goals of disease remission and minimization of joint destruction rather than simple alleviation of symptoms (2,14,15). Use of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine can result in alleviation of symptoms, but progression of the disease is merely slowed in most patients. Typically, patients will discontinue therapy with specific DMARDs after several years because of toxicity or lack of sufficient efficacy (16,17).

More recently developed biologic response modifiers, including etanercept, have targeted proinflammatory cytokines such as tumor necrosis factor (TNF) (15). Etanercept consists of the p75 TNF receptor fused to the constant region of the human IgG1 antibody (14). Etanercept inhibits binding of TNF to its cellular receptors, thereby inhibiting TNF-mediated inflammation and progression of joint abnormalities (15). Several clinical trials have demonstrated the safety and efficacy of etanercept in patients with RA with varying disease characteristics (18–20). Etanercept is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderate to severe RA. However, only one trial specifically considered the effect of etanercept on fatigue, and reported results based on 6 months of therapy (19). Fatigue was also reported to improve in patients with RA treated with methotrexate plus the TNFα antagonist adalimumab relative to patients treated with methotrexate plus placebo in a 24-week trial (21). The objective of the present study was to assess the long-term impact of etanercept on fatigue in patients with either recent-onset or established RA, and to determine the degree of correlation between improvement in fatigue and selected outcomes relevant to RA. Results are reported from patients who enrolled in open-label extensions of previously published etanercept trials (18,19).

**PATIENTS AND METHODS**

**Patients and treatments.** Patients with recent-onset RA (n = 304) were those participating in an open-label extension of the etanercept Early Rheumatoid Arthritis trial (18) (Figure 1A). At the time of enrollment, patients had active RA with disease duration of <3 years and no prior treatment with methotrexate; full details of the protocol can be found in the original trial report (18). Patients were randomly assigned to receive either etanercept 25 mg twice weekly or weekly oral methotrexate (average dose 19 mg) for at least 12 months. After the double-blind phase, patients continued to receive their randomized treatment for up to 1 additional year in an open-label manner. In the subsequent open-label phase, patients originally assigned to the methotrexate group were given 25 mg of subcutaneous etanercept twice weekly and could either continue or discontinue methotrexate treatment (Figure 1A). Sixty-seven percent of patients in the methotrexate arm received 25 mg of etanercept monotherapy. For the current analysis, 20-month data from the open-label extension were available.

Patients with established RA (n = 131) were those who participated in a 6-month, randomized, double-blind trial of patients with established RA and went on to participate in an open-label extension (19) (Figure 1B). At the time of enrollment, patients had active RA and had previously discontinued therapy with 1–4 DMARDs; full details of the protocol can be found in the original trial report (19). Patients received etanercept 25 mg twice weekly or placebo for 6 months during the blinded phase of the trial. During the open-label phase, patients in the placebo group were switched to 25 mg of subcutaneous etanercept twice weekly. Patients who were originally randomly assigned to etanercept continued to receive etanercept (Figure 1B). For the current analysis, 40-month data from the open-label phase are presented.

**Outcomes.** During both trials, fatigue was measured at various time points using the Health Assessment Questionnaire (HAQ) vitality domain (22). This measure consists of 4 questions from the Short Form 36 (SF-36) vitality domain that ask about the patient’s energy level during the previous 4 weeks. The questions are as follows: “Did you feel full of pep?”; “Did you feel worn out?”; “Did you have a lot of energy?”; and “Did you feel tired?” Patients indicated their responses on a 5-point Likert-type scale, ranging from 1 (all of the time) to 5 (none of the time). The HAQ vitality domain differs from the SF-36 vitality domain in that the latter uses a 7-point scale. Patient responses were reported as a score with a range of 0–100. To simplify interpretation, the vitality score was reversed by subtracting it from 100; after this transformation, a higher score indicated a higher level of fatigue. This reversed vitality score will be referred to as the HAQ fatigue score.

Baseline fatigue scores were obtained after the initial washout period and before randomization. When calculat-
ing mean fatigue scores for treatment groups at the various
time points, if no fatigue score was available for a patient
for any time point, the last recorded fatigue score was
carried forward. At each time point in each trial, 2 com-
parisons were made. First, the mean percent change from
baseline in fatigue score of the patients randomly assigned
to the etanercept group was compared with the comparator
group for that trial using a 2-sided Student’s t-test. Second,
the proportion of patients who achieved a clinically mean-
ingful improvement (CMI) in fatigue was compared in
each study group. To define CMI, the upper bound of the
95% confidence interval (95% CI) of the standard error of
measurement (SEM) for the HAQ vitality domain was used
(23). The SEM was calculated using the following equa-
tion:

\[
SEM = s (1 - r)^{1/2}
\]

where \(s\) represents the standard deviation of the baseline
HAQ fatigue scores and \(r\) represents Cronbach’s alpha
coefficient of the baseline HAQ fatigue scores (24). Using
baseline data from the recent-onset RA trial, the upper
bound of the 95% CI of the SEM was calculated to be 18.76
and was rounded off to 20. Therefore, a patient whose
fatigue score decreased by at least 20 points was consid-
ered to have achieved a CMI. At each time point in each
trial, the proportion of patients achieving CMI in the etan-
ercept group was compared with the proportion achieving
CMI in the comparator group using the chi-square test. For
both types of comparisons described above, the alpha
value for significance was adjusted using the Bonferroni
approach to address the issue of multiple testing.

To determine the extent of correlation between HAQ
fatigue score and quality of life outcomes, change in HAQ
fatigue score was compared with both change in pain as
measured on a visual analog scale (VAS) and change in
HAQ disability index. The VAS for pain is a scale from 0
(no pain) to 10 (severe pain) in which patients were asked
to indicate their current level of pain. The HAQ disability
index combines the 8 domains of the HAQ instrument
(activity, arising, dressing, eating, grip, hygiene, reach, and
walking) into 1 aggregate score, with a higher score indic-
ating more disability. Comparisons were performed at the
end of the blinded phase (1 year in patients with recent-
onset RA and 6 months in patients with established RA).
Pearson’s correlation coefficient and Spearman’s rank cor-
relation coefficient were calculated for each comparison.

To further evaluate HAQ fatigue score as an outcome mea-
sure, the proportion of patients meeting the American
College of Rheumatology (ACR) 20%, 50%, or 70% criteria
for improvement (25) and achieving CMI in fatigue at the
end of the blinded phases was determined.

**RESULTS**

Baseline characteristics of patients who participated in the
2 trials and their respective open-label extension phases
are shown in Table 1. There were no statistically signifi-
cant differences in the baseline characteristics in the 2
treatment groups for either trial. For each trial, the mean
baseline HAQ fatigue score of patients who participated in
the open-label extension was not significantly different
from the mean baseline score of those who did not.

In the trial of patients with recent-onset RA, the reduc-
tion of fatigue was more rapid in the etanercept group
compared with the methotrexate group (Figure 2A). A
significant difference in fatigue was observed at weeks 2, 4,
and 8 (Figure 2A). For the remainder of the study, patients
in the etanercept group consistently reported a greater
reduction in fatigue of 23–29% compared with the 17–
24% reduction in patients who started on methotrexate.
Although the difference between the groups did not reach
statistical significance beyond month 2 (except at month
24), reduction in fatigue was sustained throughout the
entire 44 months of followup. Patients in both groups
showed a significant reduction in fatigue relative to base-
line at all time points (\(P < 0.0001\)).

To determine if these reductions in fatigue were clini-
cally significant, the proportion of patients achieving CMI
in fatigue score was calculated for both treatment groups
(Figure 2B). Again, a significantly quicker response was
achieved in the first month in the etanercept group com-
pared with the methotrexate group (Figure 2B). There was
no significant difference in the CMI response between the
2 groups after the first month. The proportion of patients
showing a CMI in fatigue was sustained over the 44
months of followup.

In the trial of patients with established RA, the etan-
ercept group had a significantly greater reduction in fatigue
from baseline compared with the placebo group in the
double-blind phase of the trial, as expected (19) (Figure
3A). Patients originally in the placebo group showed an
immediate reduction in HAQ fatigue scores after being

| Table 1. Baseline characteristics of patients with recent-onset or established RA* |
|---------------------------------|-----------------|-----------------|-----------------|
| Characteristic                  | *     |     |     |     |
|                                 | Recent-onset RA | Established RA |
|                                 | (n = 143) | (n = 161) | (n = 70) | (n = 61) |
| Mean age, years                 | 48    | 50   | 50   | 53   |
| Female sex, %                   | 76    | 73   | 77   | 72   |
| Mean duration of RA             | 11 months | 11 months | 12 years | 12 years |
| Mean number of tender joints    | 30    | 30   | 34   | 32   |
| Mean number of swollen joints   | 24    | 23   | 25   | 26   |
| Mean HAQ fatigue score          | 64    | 64   | 69   | 65   |

* RA = rheumatoid arthritis; HAQ = Health Assessment Questionnaire.
switched to etanercept at month 6. Despite this, patients who initially received placebo had a consistently smaller percent reduction in fatigue score compared with patients who initially received etanercept during the open-label phase, although this difference was not statistically significant. After at least 4 weeks of etanercept treatment, mean reduction in fatigue score was 25–36% in patients who initially received etanercept and 20–27% in patients who initially received placebo (Figure 3A). Similar to the trend observed in the patients with recent-onset RA, the effect of etanercept on fatigue reduction in patients with established RA was sustained throughout 46 months of followup.

The percentage of patients achieving CMI in fatigue was significantly greater in patients receiving etanercept than in those receiving placebo at most time points during the 6-month blinded phase of the trial (Figure 2A). After switching to etanercept, the percentage of patients in the placebo arm who achieved CMI increased but remained lower than the etanercept group, although these differences were not significant. After receiving etanercept therapy for at least 6 months, 34–44% of patients in the placebo group achieved CMI throughout the remainder of the trial. In the etanercept group, 44–56% of patients achieved CMI at all time points after 2 months of therapy to the end of the 46-month followup.

The results presented thus far have demonstrated the long-term impact of etanercept on HAQ fatigue score. To test the validity of HAQ fatigue score as a surrogate marker of improved outcomes, the change in fatigue score from baseline was compared with the changes in pain score and HAQ disability index from baseline (Table 2). For each trial, these comparisons yielded positive correlations, indicating that a decrease in fatigue score correlated with decreases in pain and disability. The correlations were of moderate magnitude, with Pearson’s correlation coefficient and Spearman’s rank correlation coefficient ranging from 0.49 to 0.62.

As a second test of the validity of the HAQ fatigue score, the proportion of patients who met the ACR criteria for...
improvement (25) was determined for patients who achieved and those who did not achieve CMI in fatigue (Table 3). In both trials and for each level of ACR improvement, this proportion was higher among patients who achieved a CMI in fatigue than among those who did not. These results further verify the relevance of the HAQ fatigue score for measuring outcomes in patients with RA.

**DISCUSSION**

This study assessed the long-term effect of etanercept on fatigue in methotrexate-naive patients with recent-onset RA and in patients with established RA based on 2 clinical trials (18,19). Among both patient groups, those randomly assigned to etanercept reported a rapid decrease in fatigue scores that was sustained for the duration of each trial. The reduction in fatigue was clinically meaningful in >31% of patients at any time point after receiving etanercept for at least 2 months.

A minimum reduction of 23% in fatigue score beyond the first 2 months for the etanercept group is quite substantial, considering that it corresponds to an improvement of ~15 points on the HAQ fatigue scale. Given that the standard deviation for baseline HAQ fatigue scores was 17, a 15-point improvement is much larger than half of one standard deviation, which is often cited as a threshold for minimally important difference in outcome measures (26). Similarly, reduction of fatigue by at least 17% in patients initially receiving methotrexate would also be considered an important improvement.

In patients with recent-onset RA, reduction in fatigue was observed more rapidly after initiation of etanercept than methotrexate. This could result from a more rapid action of etanercept, but it may partially be explained by the methotrexate dose escalation that was carried out over the first 2 months of the trial. After month 2, there was no significant difference in fatigue reduction between the 2 treatment groups, with the exception of one time point. In addition, there was no significant difference in the proportion of patients achieving CMI in fatigue between the treatment groups after month 2. This is not surprising, given the efficacy of methotrexate for patients with recent-onset RA.

Despite receiving open-label etanercept for many months, patients with established RA who initially received placebo never achieved the level of fatigue reduction observed in patients who received etanercept for the entire trial (Figure 3A). The difference between the treatment groups may reflect greater disease severity in the placebo group at the time etanercept therapy was initiated. Relative to baseline, patients reported a 7% increase in swollen joints, a 22% increase in pain, and a 23% increase in morning stiffness after receiving placebo for 6 months (19). Similarly, in the patients with recent-onset RA, a nonsignificant but small advantage in fatigue reduction was observed in patients initially receiving etanercept compared with those initially receiving methotrexate (Figure 2A). It is possible that earlier treatment with etanercept has small beneficial effects on fatigue; however, further studies are needed to thoroughly investigate this issue.

In both patient groups, changes in fatigue scores correlated with changes in pain and HAQ disability scores. In

| Table 2. Correlation between change in HAQ fatigue score and quality of life outcomes* |
|------------------------------------|----------|------------|
| **Comparison of change**           | **Pearson’s coefficient** | **Spearman’s coefficient** |
| Patients with recent-onset RA      |                       |                         |
| HAQ fatigue score vs VAS pain score (n = 300) | 0.49    | 0.50       |
| HAQ fatigue score vs HAQ disability score (n = 304) | 0.57    | 0.58       |
| Patients with established RA       |                       |                         |
| HAQ fatigue score vs VAS pain score (n = 131) | 0.56    | 0.56       |
| HAQ fatigue score vs HAQ disability score (n = 131) | 0.62    | 0.58       |

* Comparisons used change between baseline and end of the blinded phase of each trial (1 year in patients with recent-onset RA and 6 months in patients with established RA). Only patients who participated in the trial extensions were included. HAQ = Health Assessment Questionnaire; RA = rheumatoid arthritis; CMI = clinically meaningful improvement.

| Table 3. Proportion of patients meeting the ACR criteria for improvement* |
|------------------------------------|--------|--------|--------|
| **Patients**                       | **ACR20** | **ACR50** | **ACR70** |
| Patients with recent-onset RA      |        |        |        |
| CMI in fatigue achieved (n = 120)  | 85.8   | 62.5   | 40.8   |
| CMI in fatigue not achieved (n = 184) | 56.0   | 32.6   | 12.5   |
| Patients with established RA       |        |        |        |
| CMI in fatigue achieved (n = 39)   | 74.4   | 46.2   | 20.5   |
| CMI in fatigue not achieved (n = 92) | 28.3   | 18.5   | 5.4    |

* Comparisons used data at the end of the blinded phase of each trial (1 year in patients with recent-onset RA and 6 months in patients with established RA). Only patients who participated in the trial extensions were included. Values are the percentage. ACR = American College of Rheumatology; RA = rheumatoid arthritis; CMI = clinically meaningful improvement.
addition, in each trial, a majority of patients who achieved CMI in fatigue also met the ACR criteria for 20% improvement. In previous studies using a variety of assessment instruments, pain (5,6,9,10,12,13) and functional disability (5,6,12,13) have consistently been identified as strong correlates of fatigue in patients with RA. The magnitudes of these correlations were similar to those observed in the present study, with Pearson’s and Spearman’s coefficients ranging from 0.48 to 0.62 for the association between fatigue and pain, and from 0.26 to 0.56 for the association between fatigue and disability (5,9,10,13). Although these correlations were reported in cross-sectional studies, the similar magnitude of correlations in our study further supports the association between fatigue, pain, and disability. Fatigue was found to be a better predictor of disability in patients with recent-onset RA than erythrocyte sedimentation rate, tender joint count, and pain (4). Some researchers have suggested that fatigue may be a useful measure to assess patient distress and to identify problem patients (6).

Fatigue in patients with RA is strongly associated with quality of life, self-assessed overall health status, and work dysfunction (4.6–8), which may have an important impact on the direct and indirect costs of the disease. For example, it was found that patients with higher levels of fatigue made more frequent visits to rheumatologists than did those with less fatigue (12). Another recent study reported that patients with RA and fatigue have significantly higher annual costs of care than those without fatigue ($4,622 versus $2,131 US; P < 0.001), independent of age, sex, disease duration, and level of formal education (27). In addition, patients with RA who reported fatigue missed significantly more days of work and had more days on which they were unable to perform nonemployment-related activities (P < 0.001) (27).

The HAQ vitality domain, used in this study to measure fatigue, is comparable with the SF-36 vitality domain, which has been shown to be reliable and relevant in patients with RA and osteoarthritis (28–31). Our previous analysis has shown that the SF-36 vitality domain has acceptable psychometric properties (32). Furthermore, the SF-36 vitality domain correlates well with other measures of fatigue in patients with RA (13), requires little time, and is easy to administer. Therefore, the HAQ vitality domain can be considered an appropriate and useful tool to measure fatigue in patients with RA.

Considering possible limitations to this work, the SEM-based criterion that was used to define CMI in fatigue is sample independent only in the middle of the sample range (24,33), and thus may not capture all relevant changes in fatigue from baseline. In the patient populations studied here, however, mean fatigue scores were generally in the central region of the 0–100 scale, minimizing potential distortion by extreme scores. In addition, a study carried out to determine minimally important changes in health-related quality of life measurements during RA clinical trials found that patients who reported one level of global improvement (on a 5-level scale) had an average change of 11.1 on the SF-36 vitality domain (on a 0–100 scale) (34). This is far less than our definition of a 20-point change in individual fatigue score as being clinically meaningful.

This investigation has shown that treatment with etanercept leads to rapid, sustained, and clinically meaningful reduction in fatigue in patients with recent-onset or established RA. Reduction in fatigue strongly correlated with reduced pain and HAQ disability scores. In addition, a majority of patients with CMI in fatigue also met the ACR criteria for 20% clinical improvement. The ability of etanercept to improve patients’ long-term fatigue status may have important implications for quality of life, resource utilization, and both direct and indirect costs of care for those with RA (4.6–8).

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REFERENCES

17. Aletaha D, Smolen JS. Effectiveness profiles and dose dependent retention of traditional disease modifying antirheumatic...


