Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis

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Abstract

Objectives

Fatigue is an important systemic symptom of rheumatoid arthritis (RA) but has rarely been evaluated consistently after initiation of treatment in RA patients. This study examined the effects of adalimumab (HUMIRA®, Abbott Laboratories, Abbott Park, IL, USA), a fully human, anti-tumor necrosis factor (anti-TNF) monoclonal antibody, on reducing fatigue in patients with RA.

Methods

A total of 1526 patients with RA were enrolled in 3 randomized, placebo-controlled clinical trials of adalimumab versus placebo plus methotrexate (MTX) or placebo plus standard antirheumatic therapies. Fatigue was assessed with the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale questionnaire (which has been validated in RA) at baseline, mid-study, and at the end of the study. Logistic regression models were constructed using baseline demographic variables to test for treatment effect. In addition, sensitivity analyses were performed to determine the robustness of the data.

Results

At baseline in the 3 trials, patients' fatigue ranged from 27.9–29.7, representing considerable fatigue on the FACIT fatigue scale. Fatigue was significantly and consistently reduced in adalimumab-treated patients in the 3 clinical trials. Relative to placebo plus MTX, the adalimumab 40-mg-every-other-week dosage group reported statistically significantly less fatigue at all time points post-baseline. Improvements between adalimumab and placebo ranged from 3–7 points across all 3 trials, with a 3–4-point change representing a minimum clinically important difference.

Conclusion

Adalimumab treatment was shown to significantly reduce fatigue in patients with moderate to severe RA. Changes in fatigue in all 3 trials were found to be clinically important.

Key words

Fatigue, rheumatoid arthritis, adalimumab, randomized controlled trial, patient-reported outcomes.

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Abbott Laboratories was responsible for the design of the studies reported in this manuscript, as well as for the collection of the data and the decision to submit the manuscript for publication. The sponsor did not have responsibility for conducting the analyses, interpretation of the data or writing of this manuscript, all of which were supported by a grant from Abbott Laboratories.

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Received on January 15, 2007; accepted in revised form on May 16, 2007.

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Conflict of interest: Drs. Chartash and Sengupta are former employees of Abbott Laboratories, the sponsor of this study. Drs. Cella, Yount, Grober and (formerly) Sorenson are employees of Evanston Northwestern Healthcare, which was the recipient of the research grant from Abbott. Drs. Cella and Grober have declared no competing interests.

Introduction

Fatigue is a common symptom of rheumatoid arthritis (RA), reported at varying degrees of severity in more than 80% of patients (1-3). Although every RA patient has joint pain, many have identified fatigue as the most problematic aspect of their disease (4). This may be especially true for patients with recent-onset disease (5, 6). Fatigue contributes to inability to work, recreate, participate in rehabilitation programs, and maintain social relationships (3). Reduction in fatigue correlates with improvement in quality of life and should be a goal of therapy.

Fatigue is a subjective experience of debilitating tiredness or weakness that interferes with normal activity. Although it can be estimated through related indicators, such as hemoglobin or exercise tolerance (7), by definition, fatigue is measured by direct patient queries. These include the fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT) multidimensional quality-of-life (QOL) instrument (8, 9); the Brief Fatigue Inventory (10); the Piper Fatigue Scale (11); the Multidimensional Fatigue Inventory (12); the Fatigue Symptom Inventory (13); various linear analog scales (14); and RA-specific measures such as the Multidimensional Assessment of Fatigue (15). The FACIT, in particular, has shown strong associations with hemoglobin concentrations, functional status, and overall patient QOL (8, 16-18) and has been validated for use in RA (9).

Despite its prevalence and ranking as a priority symptom by patients with RA, fatigue has rarely been measured in RA studies or by clinicians during assessment of patients. A shortcoming of RA clinical trials has been the omission of a separate assessment of fatigue among the patient-reported outcomes collected. Although considered a relevant clinical criterion, fatigue is not specifically included among the outcome measures proposed by the American College of Rheumatology (ACR) (19) and Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Committee (20). From a clinical perspective, nearly 90% of rheumatologists have reported that they do not assess fatigue during their clinical visits with patients, and a mere 4% assess it at least 75% of the time (21).

The purpose of this study was to examine the effects of adalimumab, a fully human, anti-TNF monoclonal antibody, on reducing patient-reported fatigue. Data were obtained from 3 clinical trials involving patients with RA who were treated with adalimumab in combination with methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs). Because the research designs of the trials were different (*e.g.*, data collected at different times), the results are reported separately for all 3 trials. Fatigue was assessed with the 13-item fatigue scale of the FACIT (7, 8), which has been validated in RA (9).

Methods

Patient populations

Data were collected from 3 randomized, double-blind, placebo-controlled, clinical trials of adalimumab, a TNF antagonist administered subcutaneously. A central Independent Ethics Committee/ Institutional Review Board approved the study protocol, and all patients provided written informed consent. Within each trial, the treatment arms had approximately equal sample sizes. The ARMADA (Anti-TNF Research Program of the Monoclonal Antibody Adalimumab in Rheumatoid Arthritis) trial enrolled 271 patients who had failed prior DMARD therapy and currently had active RA despite concomitant treatment with MTX. Treatment groups were randomized to placebo plus MTX or 1 of 3 adalimumab arms (20 mg every other week [eow] plus MTX; 40 mg eow plus MTX; or 80 mg eow plus MTX) (22). The DE019 trial enrolled 619 patients who had persistent RA activity after being on MTX for at least 3 months and who were randomized to 1 of 3 treatment arms (placebo plus MTX; adalimumab 20 mg weekly plus MTX; or adalimumab 40 mg eow plus MTX) (23). STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) enrolled 636 patients who were treated with standard of care that could include 1 or more DMARDs, nonsteroidal anti-inflammatory medications, or corticosteroids (prednisone equivalent

≤10 mg/day), and continued to have RA activity. Patients in STAR were randomized to receive either placebo plus current antirheumatic therapies or adalimumab 40 mg eow plus their current antirheumatic therapies (24).

Measures

Fatigue was measured in these studies using the 13-item fatigue scale of the FACIT Measurement System (25). On this instrument, scores range from 0–52, with greater scores reflecting less fatigue. The FACIT-Fatigue questionnaire was originally developed to assess the fatigue associated with anemia in patients with cancer. For this group, the FACIT-F scale has been demonstrated to have excellent stability (test-retest reliability) and internal consistency, as well as the ability to predict group differences in hemoglobin concentration and performance status (8). More recently, the FACIT-F has been validated as a measure of fatigue in RA patients (9).

The FACIT fatigue scale was administered on slightly different schedules during each trial. In addition to baseline (pretreatment), ARMADA assessed fatigue at Weeks 4, 12, and 24; DE019 administered the FACIT fatigue scale at Weeks 12, 24, and 52; and fatigue data were collected in STAR at Weeks 12 and 24. All 3 trials had an option for patients to adjust treatment if the study drug was ineffective. The rescue therapy in each study was available to patients at slightly different time periods and included different treatment options. While fatigue assessments continued for some patients who had rescue therapy or entered open-label follow-up studies, the results reported here include data only from the blinded trial assessments.

Analyses

Demographics, clinical variables, and fatigue measurements at baseline were analyzed to determine if there were any significant differences across treatment arms. All patients were analyzed as randomized (intention-to-treat analysis), and analyses were conducted with the treatment arms blinded. The primary fatigue endpoint analyses evaluated the change in FACIT fatigue scale scores over time. Patterns of missing data were evaluated to determine the need for and the most appropriate imputation strategies.

Multivariate, repeated-measures, mixed-effects models (26, 27) were used to evaluate the change from baseline in FACIT fatigue scale scores over time for the treatment arms in each study. The basic analytical model included fixed effects (treatment arm, body mass index (BMI) (kg/m^2), patient age (centered on mean age), baseline C-reactive protein (CRP) concentration (log-transformed to normalize the distribution), gender, time, and a treatment time interaction term); and random effects (patient, time, and $time^2$) to account for the intercept and rate of change for each patient. A quadratic effect ($time^2$) was used to evaluate the possibility of nonlinear change over time. Statistical tests of treatment arm differences were conducted using least-squares adjusted means and standard errors at each assessment point. Multivariate contrast tests were performed to test for change from baseline score within treatment groups. No adjustments were made for multiple comparisons.

To ensure that estimated mean fatigue differences between treatment arms could be validly and consistently detected by different analytic methods, a sensitivity analysis was conducted using last observation carried forward (LOCF) and analysis of covariance (ANCOVA) methods. The baseline score served as a covariate and the treatment group as the main effect. For computation of treatment group differences and changes from baseline using LOCF, the final FACIT fatigue scale assessments were used (Week 24 for ARMADA and STAR, and Week 52 for DE019). If the FACIT fatigue scale score for the final assessment was missing, then the last post-baseline score was used.

Results

Demographics

The demographics and baseline clinical characteristics of the 3 study populations are summarized in Table I. The median age among the patient samples was approximately 56 years. At baseline, the median and range of tender joint counts across samples were similar (median 26, range 7–68). ARMADA had a slightly lower median and a more limited range of swollen joints (median 15, range 2–43) than did DE019 (median 17, range 6–65) and STAR (median 19, range 6–66). The most significant differences among the samples were in median values of serum CRP concentration, an index of acute and chronic inflammation. ARMADA had a greater median value and a broader range (median 22 mg/L, range 0.5–226) than either DE019 (median 10 mg/L, range, 4–188) or STAR (median 9 mg/L, range 4–197) ($p < 0.001$). Because the trials featured different dosages and dosing schedules, results are reported separately for each trial.

Overall, patient demographic characteristics were similar for completers and noncompleters. In ARMADA, the baseline median swollen joint count (0–66) was greater in the completer group (swollen joint count (SJC) = 17) than in the noncompleter group (SJC = 13) ($p < 0.01$). In DE019, noncompleters had significantly lower FACIT fatigue scale scores (*i.e.*, greater fatigue) (27.7) than completers (30.1) ($p < 0.05$). In STAR, a marginally greater number of swollen joints (0-66) were observed in completers (SJC = 18) than for noncompleters (SJC = 21) ($p < 0.05$).

Based on the FACIT fatigue scale, at baseline in all 3 trials, women were more fatigued than men, with the fatigue scores of women 3–7 points lower than those of men (*i.e.*, more fatigue). In ARMADA, the differences were limited to the adalimumab 40-mg group ($p = 0.012$) and the adalimumab 80-mg group ($p = 0.066$) and persisted to Week 24 of the trial. In DE019, there were baseline gender differences in fatigue scores for the adalimumab 20-mg group ($p = 0.008$) at all time points, but not for the adalimumab 40-mg or placebo groups. In STAR, there was a gender difference for the adalimumab 40-mg group ($p = 0.002$) at baseline only. For the placebo group, the difference was apparent from baseline ($p = 0.032$) through Week 12 ($p = 0.034$).

Influence of fatigue on the Health Assessment Questionnaire

Prior to the planned analyses of fatigue score changes by treatment arm, a

Table I. Demographic and baseline clinical characteristics of study samples.

	ARMADA (N = 271)	DE019 (N = 619)	STAR (N = 636)
Gender			
Male, n (%)	63 (23)	154 (25)	130 (21)
Female, n (%)	208 (77)	462 (75)	501 (79)
Race/ethnicity			
White, non-Hispanic, n (%)	220 (81)	517 (84)	553 (88)
Black, non-Hispanic, n (%)	23 (9)	39 (6)	31 (5)
Other, n (%)	28 (10)	60 (10)	47 (7)
Age (years), median (range)	56 (28–84)	57 (21–87)	56 (21–86)
Disease duration (years), median (range)	10 (0.3–57)	8 (0.2–52)	8 (0.1–59)
C-reactive protein (mg/L), median (range), (normal range <10 mg/L) (**28**)	22 (0.5–226)	10 (4–188)	9 (4–197)
Tender joint count, n (of 68 joints), median (range)	26 (9–68)	26 (7–68)	25 (7–68)
Swollen joint count, n (of 66 joints), median (range)	15 (2–43)	17 (6–65)	19 (66)
Baseline FACIT fatigue scale score, mean (SD)	27.9 (11.0)	29.7 (10.9)	29.2 (11.1)

preliminary check on the relevance and uniqueness of fatigue as an endpoint was conducted on pooled data from all trials using the Health Assessment Questionnaire (HAQ) Disability Index (29) as the outcome. All of the baseline predictor variables in the model (age, gender, BMI, CRP concentration, physician-assessed disease activity, patient-assessed pain, tender and swollen joint counts, and FACIT fatigue scale score) were significantly associated with HAQ score ($p < 0.001$). The entire model explained 49% of the variability in HAQ scores, with the FACIT fatigue scale score entering the model first and accounting for 29% of the variance in baseline HAQ scores. Even when forced into the model after all other variables had entered (hierarchical entry), FACIT fatigue scale scores contributed to 9% of the variability in the HAQ score ($p < 0.001$). Thus, although fatigue is related to the HAQ at baseline — more so than the other variables in these trials — it also contributes unique information about RA-related disability, underscoring its relevance as a patient-reported outcome.

ARMADA

The ARMADA trial included 271 patients in 4 treatment groups. At 24 weeks, 161 remained in the study, 92 patients entered an open-label extension study between Weeks 16 and 24, and 18 patients withdrew from the study before Week 16. Four patients had no fatigue data post-baseline and 1 patient had no baseline assessment (and was not included in analyses). In summary, the mixed-effects model included data on 270 of the 271 patients enrolled in ARMADA.

Observed and adjusted (for model parameters) mean fatigue scores by treatment arm are summarized in Table II and illustrated in Figure 1. Observed scores are useful for clinical interpretation and comparison with other studies. There were no significant differences in baseline FACIT fatigue scale scores among dosages. As early as Week 4, fatigue scores for the adalimumab 80-mg ($p = 0.029$) and 40-mg ($p = 0.009$) dosage groups were greater (*i.e.*, less fatigue) than those in the placebo group. At Weeks 12 and 24, the fatigue scores in the adalimumab 80-mg and 40-mg dosage groups were significantly greater than in the placebo group ($p < 0.05$). Fatigue scores for the adalimumab 20-mg group were not significantly different from the other dosage groups (including placebo) at any time point.

There were significant improvements in fatigue scores from baseline for all treatment arms. At Week 24, fatigue scores for patients had increased from baseline by 11 points ($p < 0.001$) in the adalimumab 80-mg group, by 10 points ($p < 0.001$) in the adalimumab 40-mg dosage group, by 8 points ($p < 0.001$) in the adalimumab 20-mg dosage group, and, finally, by 6 points ($p = 0.017$) in the placebo group (Fig. 2). Further, the 24-week, adjusted FACIT fatigue score in the adalimumab 40-mg eow group of 40.0 (Table II) approaches 43.6, the value observed in the general population (30). Similarly, patients in the 40-mg eow arm of the DE019 study (discussed below) also neared the normal fatigue value of the general population.

DE019

DE019 consisted of 3 arms and 619 patients. A total of 496 patients completed assessments at baseline and had at least 1 post-baseline assessment. Subsequently, 152 patients withdrew from the study, including 1 death. Of the 152, five patients had no baseline fatigue data (and were not included in the model), 75 had no fatigue data post-baseline, and 43 patients did not complete the Week 52 assessment. Thus, the model incorporated data on a total of 614 patients, including those 75 patients who had baseline observations alone as well as the 43 patients who did not complete the final assessment. Post-baseline data for these 75 patients were imputed based on mixed-model analyses. They were excluded from sensitivity analyses, which were conducted using LOCF data. Results from the mixed-model analyses were confirmed by the sensitivity and other follow-up analyses that excluded these patients.

There were no significant baseline differences in FACIT fatigue scale scores among the 3 treatment arms. However, at Weeks 12, 24, and 52, the adalimumab 40-mg eow and 20-mg weekly dosage groups had significantly greater fatigue scores (*i.e.*, less fatigue) than the placebo group ($p < 0.001$) (Table II, Fig. 3). At Week 52, these fatigue score differences between the adalimumab 40-mg eow and 20-mg weekly groups relative to the placebo group were 5 and 4.8, respectively, which exceed the minimum clinically important difference of 3–4 points (9). At Week 24, the 40-mg eow and 20-mg weekly treatment groups had fatigue scores that were 8 and 9 points greater (*i.e.*, less fatigue) than at baseline, whereas the placebo group had scores 6 points higher.

In addition to differences among treatment arms, all treatment arms displayed

Table II. FACIT fatigue scale observed and adjusted scores at baseline and weeks 12, 24, and 52; and change scores from baseline.

Trial/Treatment Arm	FACIT Fatigue Scale Score Mean (SD)										Change Scores (Baseline to End of Study)[¥]
	Baseline		Week 12			Week 24			Week 52		
	n	Observed Scores	n	Observed Scores	Adjusted Scores[*]	n	Observed Scores	Adjusted Scores[*]	n	Observed Scores	Adjusted Scores[*]	
ARMADA												
Adalimumab 80 mg every other week + MTX	73	26.6 (12.4)	71	36.7 (11.6)	38.3[**]	54	39.0 (9.8)	39.3[**]				11.16
Adalimumab 40 mg every other week + MTX	66	28.4 (11.3)	66	36.6 (10.2)	37.4[**]	49	39.6 (9.0)	40.0[**]				10.34
Adalimumab 20 mg every other week + MTX	69	28.6 (10.5)	66	35.3 (11.5)	34.5	40	38.2 (10.9)	36.3				7.71
Placebo + MTX	62	28.1 (9.4)	52	32.1 (11.5)	31.2	18	36.5 (8.9)	33.3				5.57
DE019												
Adalimumab 40 mg every other week + MTX	204	30.6 (10.6)	183	37.6 (9.9)	37.7[‖]	170	38.51 (10.1)	38.7[‖]	158	39.4 (9.8)	39.0[‖]	8.4
Adalimumab 20 mg weekly + MTX	211	30.1 (10.8)	195	37.5 (37.5)	38.1[‖]	179	37.9 (9.9)	39.1[‖]	165	39.3 (9.3)	38.8[‖]	8.7
Placebo + MTX	199	28.3 (11.4)	160	32.9 (10.8)	33.2	149	34.2 (10.8)	34.1	136	33.7 (11.4)	34.0	5.7
STAR												
Adalimumab 40 mg every other week + current antirheumatic therapy	316	29.4 (11.1)	301	36.2 (10.8)	36.8[‖]	290	36.7 (10.7)	36.8[‖]				5.93
Placebo + current antirheumatic therapy	315	28.9 (11.0)	294	32.5 (11.7)	32.9	286	32.7 (11.4)	33.1				3.37

MTX: methotrexate.
[*]Adjusted scores computed using a mixed-effects model. The values are least-square means, adjusted for age, gender, body mass index, and baseline C-reactive protein concentration.
[¥]Change scores are computed from the multivariate mixed-effects model; therefore, estimates of change differ slightly from those computed using the baseline observed scores presented above.
[**]$p < 0.05$.
[‖]$p < 0.001$ for comparisons with placebo.

significant longitudinal improvements in fatigue scores from baseline. Compared with baseline, Week 52 fatigue scores for the adalimumab 40-mg eow and 20-mg weekly groups increased by 8 ($p < 0.001$) and 9 ($p < 0.001$) points, respectively, and placebo group fatigue scores were 6 points ($p < 0.001$) greater than baseline (Fig. 4).

STAR

STAR included 636 patients. A total of 574 patients had fatigue data at baseline and Weeks 12 and 24. Before Week 24, 57 patients had left the study, and 5 patients had no baseline fatigue data.

There were no significant differences in FACIT fatigue scale scores between the 2 treatment arms at baseline. The adalimumab 40-mg dosage arm was 4 points greater (*i.e.*, less fatigue) than placebo both at Week 12 ($p < 0.001$) and at Week 24 ($p < 0.001$) (Table II, Fig. 5). Both treatment arms demonstrated sig-

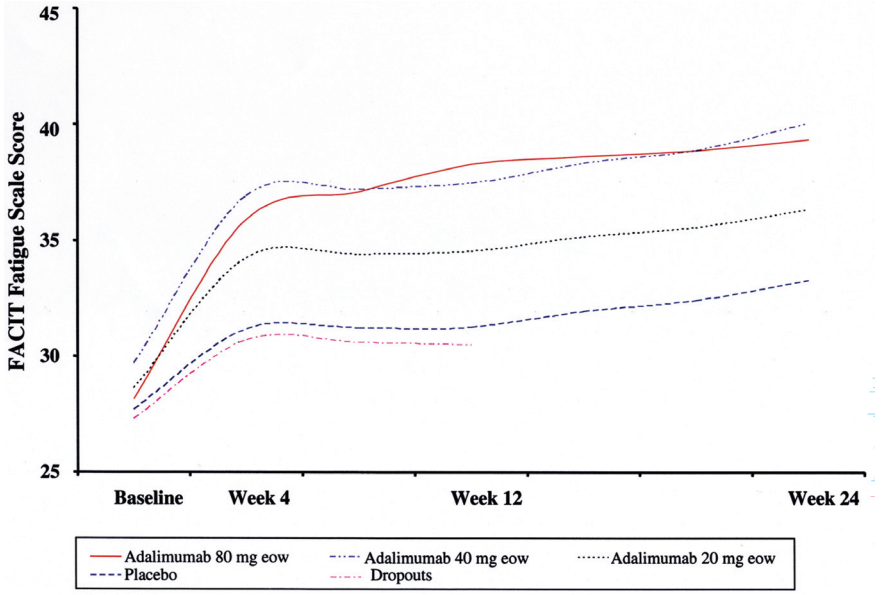

Fig. 1. ARMADA Trial FACIT fatigue scale scores by treatment arms.
Graph lines represent adjusted means of FACIT fatigue scale scores by treatment arm in ARMADA. Includes estimated means of scores of patients who withdrew from the study up to the point where no further fatigue assessments were collected.
ARMADA: Anti-TNF Research Program of the Monoclonal Antibody D2E7 Adalimumab in Rheumatoid Arthritis; eow: every other week; FACIT: Functional Assessment of Chronic Illness Therapy.

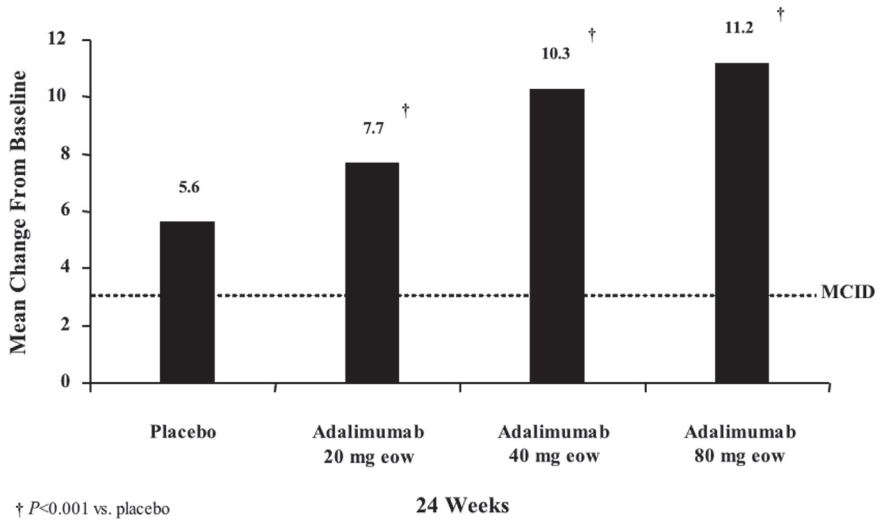

Fig. 2. ARMADA Trial: improvement of fatigue as measured by mean change in FACIT fatigue scale scores.
At 24 weeks, adalimumab-treated patients in the ARMADA trial demonstrated statistically significant improvements in FACIT fatigue scale scores *vs*. placebo.
ARMADA: Anti-TNF Research Program of the Monoclonal Antibody D2E7 Adalimumab in Rheumatoid Arthritis; eow: every other week; FACIT: Functional Assessment of Chronic Illness Therapy; MCID: minimum clinically important difference.

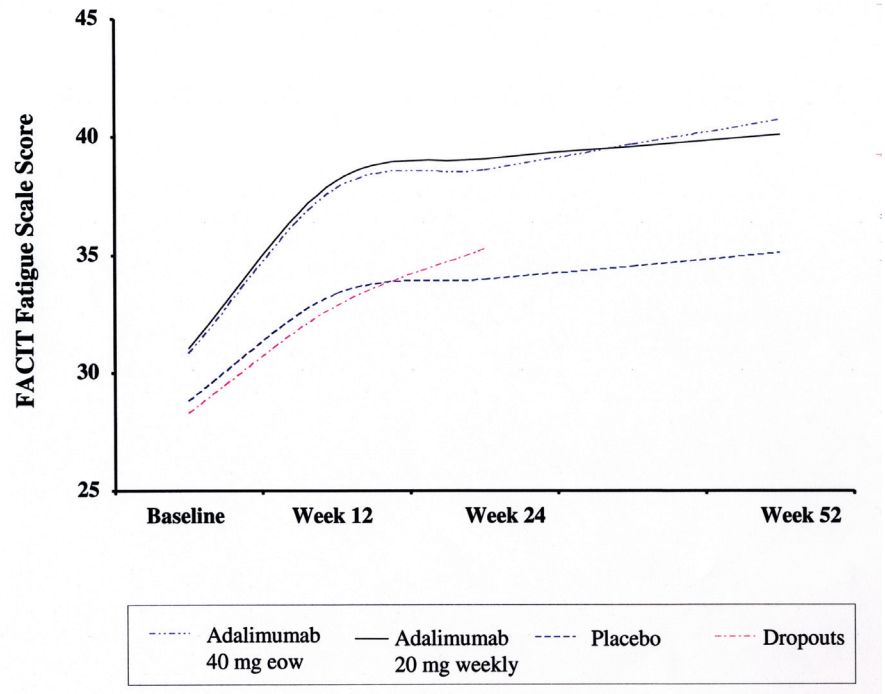

Fig. 3. DE019 Trial: FACIT fatigue scale scores by treatment arms.
Graph lines represent adjusted means of FACIT fatigue scale scores by treatment arm in DE019. Includes estimated means of scores of patients who withdrew from the study up to the point where no further fatigue assessments were collected.
FACIT: Functional Assessment of Chronic Illness Therapy.

nificant improvement in fatigue scores over the course of the study, with the treatment arms improving by 6 points ($p < 0.001$) from baseline to Week 24 and the placebo arm improving an average of 3 points ($p < 0.001$) (Fig. 6).

Sensitivity analyses

To ensure that estimated treatment effects were insensitive to different analytic methods, a sensitivity analysis using ANCOVA models was conducted, with the baseline score as a covariate and treatment group as the main effect. The sensitivity analysis results were similar to the findings shown in the primary analyses, with average "on-treatment" fatigue scores lower in the placebo group than all treatment groups and improvements in fatigue from baseline in the range of 3–5 points in the placebo groups and 6–9 points in all other dosage groups.

Treatment group differences computed using LOCF closely match the results obtained in the above analyses, with placebo groups in all trials showing significantly lower FACIT fatigue scale scores (*i.e.*, more fatigue) at end of study than all treatment groups. Therefore, the results are similar for the 3 different analyses. However, using LOCF, an ANCOVA model, or a mixed-effects model to estimate group means assumes missing data were missing at random. This is unlikely because baseline and follow-up scores of patients who withdrew from the study (and therefore did not enter open-label rescue arms) were lower than scores for those who remained in the study (Figs. 1, 3 and 5). Thus, an analytical model that adjusts group mean estimates for non-random missing data (*e.g.*, maximum likelihood models) tends to enlarge the gap between the placebo and treatment groups in favor of the treatment group for 2 reasons: 1) More people dropped out of the placebo group than the other groups, and 2) Dropouts had lower scores than those who remained in the study. Thus, these analyses used in this study are conservative. Competing models would likely uphold or enlarge statistical significance or estimates of score differences between groups.

The same reassurance, however, may not apply to the estimates of longitudinal changes in these analyses. Since baseline and pre-dropout scores of patients who failed to complete the study were worse than those of the patients who remained, estimates of increases in fatigue scores over time are probably inflated to some degree, resulting in an exaggeration of the degree of fatigue benefit for the entire study population.

Discussion

The results of this study demonstrate that adalimumab provides significant

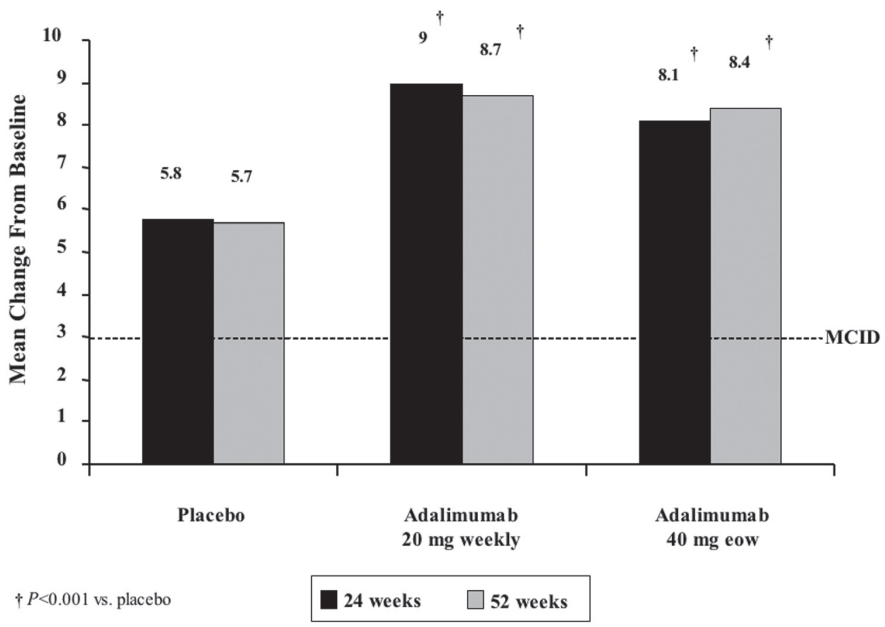

Fig. 4. DE019 Trial: improvement of fatigue as measured by mean change in FACIT fatigue scale scores.
At 24 and 52 weeks, adalimumab-treated patients in the DE019 trial demonstrated statistically significant improvements in FACIT fatigue scale scores *vs.* placebo.
Eow: every other week; FACIT: Functional Assessment of Chronic Illness Therapy; MCID: minimum clinically important difference.

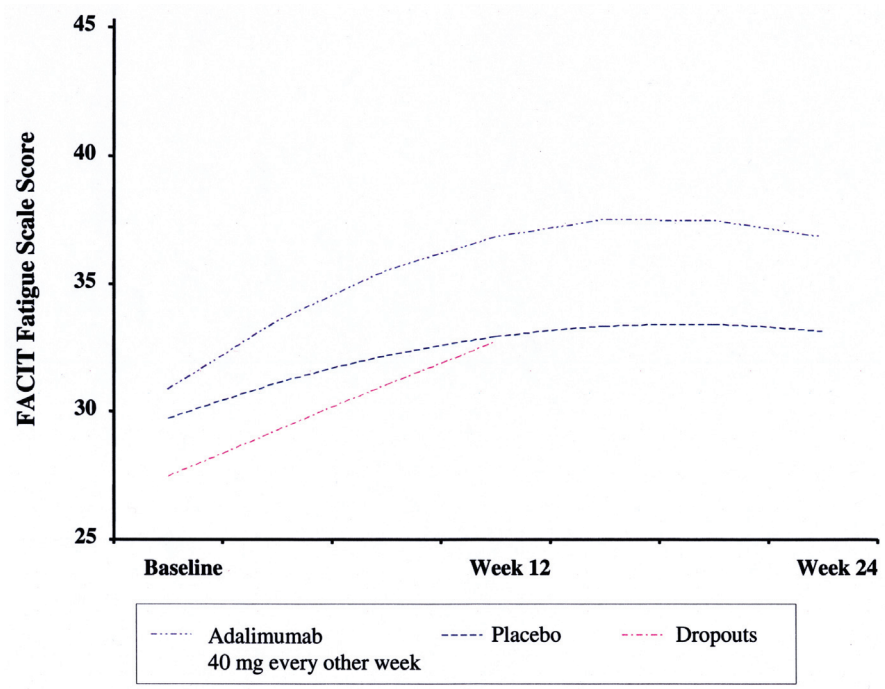

Fig. 5. STAR Trial: FACIT fatigue scale scores by treatment arms. Graph lines represent adjusted means of FACIT fatigue scale scores by treatment arm in STAR. Includes estimated means of scores of patients who withdrew from the study up to the point where no furt\her fatigue assessments were collected.
FACIT: Functional Assessment of Chronic Illness Therapy; STAR: Safety Trial of Adalimumab in Rheumatoid Arthritis.

reductions in patient-reported fatigue, a prominent and disabling feature of RA affecting more than 80% of patients with RA. There appears to be a gender difference for fatigue, with women experiencing greater fatigue than men. Many RA patients have identified fatigue as the most problematic aspect of their disease, yet the symptom of fatigue in RA continues to receive little attention from research and clinical communities.

Fatigue in cancer patients is well-recognized and a prime target for symptom management. This analysis found that the RA patients enrolled in 3 clinical studies had significant fatigue at baseline, and the degree of this fatigue was comparable to fatigue levels experienced by anemic cancer patients (30). Moreover, following treatment with the recommended dosage of adalimumab, 40 mg eow, patients achieved mean fatigue scores close to those observed in the general population. However, fatigue is not among the core set of outcome measures for RA clinical trials recommended by the ACR and OMERACT (19, 20, 31). In fact, to our knowledge, these are the first randomized clinical trials in which patient-reported fatigue has been assessed, making adalimumab the first biologic to be studied for its impact on RA-related fatigue. More-over, fatigue is rarely assessed routinely by rheumatologists in their clinical practices (21). Instead, rheumatologists focus on measures of disease activity (*e.g.*, swollen and tender joint counts, pain ratings, acute-phase reactant values), which although important, may not comprehensively reflect the degree of functional disability and suffering experienced by patients (32).

A strength of this study is that adalimumab demonstrated a reduction in fatigue among RA patients with moderate to severe disease activity despite treatment with MTX or other standard antirheumatic therapies (including other DMARDs, nonsteroidal anti-inflammatory drugs, or corticosteroids) across all 3 clinical trials reported in this paper. Furthermore, patients receiving adalimumab 40 mg eow achieved a 6- to 10-point increase in FACIT scale scores (*i.e.*, improvement in fatigue) from baseline to Week 24 across all trials. These differences were statistically significant versus placebo and are considered clinically important (7, 8). The

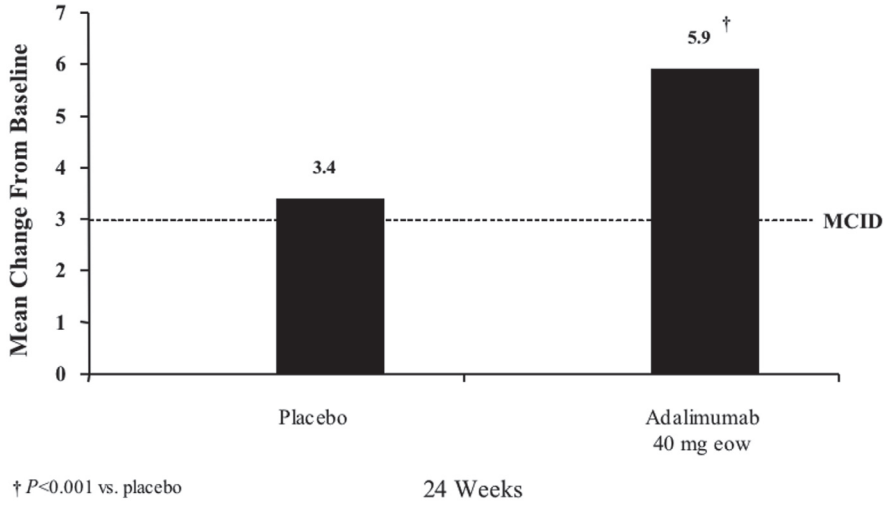

Fig. 6. STAR Trial: improvement of fatigue as measured by mean change in FACIT fatigue scale scores.
At 24 weeks, adalimumab-treated patients in the STAR trial demonstrated statistically significant improvements in FACIT fatigue scale scores *vs*. placebo.
FACIT: Functional Assessment of Chronic Illness Therapy; eow: every other week; MCID: minimum clinically important difference; STAR: Safety Trial of Adalimumab in Rheumatoid Arthritis.

effect on fatigue was seen as early as 4 weeks and was maintained for 1 year. The placebo groups also showed some improvement in fatigue scores, which may reflect some actual treatment effect in that all placebo-treated patients received other RA treatments (MTX or other standard antirheumatic therapies). The protocol-driven (planned) analyses were confirmed by 2 sensitivity analyses: 1 that controlled for baseline differences and another that addressed missing data by carrying forward patients' previous scores.

A limitation of this study is the short duration of treatment. Although the 24-week treatment duration in these trials was comparable to that of other randomized controlled trials of biologics and traditional DMARDs in RA trials, longer term results are needed to verify the durability of the improvement in fatigue observed at 6 months of adalimumab therapy in this analysis. To this end, results from the long-term, open-label extensions of these trials are being assessed. In addition, patients in these trials had moderate to severe RA and at least an inadequate response to MTX and other standard antirheumatic therapies. As some RA patients have milder disease symptoms and are responsive to these therapies, the extent to which these study populations represent typical patients seen in routine clinical practice is unknown. For example, in an analysis of 2 RA patient cohorts from clinical practice in Nashville, Tennessee (146 and 232 patients), in 2001, the majority did not meet inclusion criteria for most clinical trials (33). A study of the effect of adalimumab on fatigue in patients with milder disease and in patients with comorbidities would help determine the generalizability of these findings across the spectrum of RA severity.

Adalimumab therapy represents a significant advance in the treatment of RA-related fatigue. Wolfe and Pincus have argued for the collection of patient-reported data, such as fatigue, to document patient outcomes and the results of care (32, 34). The findings of this analysis underscore the importance of incorporating the routine assessment of patient-reported fatigue into clinical trials and the clinical management of RA patients.

Acknowledgments

The authors wish to thank the following staff members of Abbott Laboratories for their contributions to this article: Mary A. Cifaldi, RPh, MSHA, PhD, and Michael A. Nissen, BS, ELS, for their editorial assistance.

References

1. BELZA B, HENKE C, YELIN E, EPSTEIN W, GILLISS C: Correlates of fatigue in older adults with rheumatoid arthritis. *Nurs Res* 1993; 42: 93-9.
2. PINALS RS, MASI AT, LARSEN RA, and the SUBCOMMITTEE FOR CRITERIA OF REMISSION IN RHEUMATOID ARTHRITIS OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24: 1308-15.
3. BELZA BL: Comparison of self-reported fatigue in rheumatoid arthritis and controls. *J Rheumatol* 1995; 22: 639-43.
4. TACK BB: Self-reported fatigue in rheumatoid arthritis: A pilot study. *Arthritis Care Res* 1990; 3: 154-7.
5. SUURMEIJER TP, WALTZ M, MOUM T *et al*: Quality of life profiles in the first years of rheumatoid arthritis: Results from the EURIDISS longitudinal study. *Arthritis Care Res* 2001; 45: 111-21.
6. HUYSER BA, PARKER JC, THORESON R, SMARR KL, JOHNSON JC, HOFFMAN R: Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 2230-7.
7. CELLA D, ETON DT, LAI JS, PETERMAN AH, MERKEL DE: Combining anchor- and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales. *J Pain Symptom Manage* 2002; 24: 547-61.
8. YELLEN SB, CELLA DF, WEBSTER K, BLENDOWSKI C, KAPLAN E: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) Measurement System. *J Pain Symptom Manage* 1997; 13: 63-74.
9. CELLA D, YOUNT S, SORENSEN M, CHARTASH E, SENGUPTA N, GROBER J: Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale Relative to Other Instrumentation in Patients With Rheumatoid Arthritis. *J Rheumatology* 2005; 32: 811-19.
10. MENDOZA TR, WANG XS, CLEELAND CS *et al*.: The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999; 85: 1186-96.
11. PIPER BF, LINDSEY AM, DODD MJ *et al*.: The development of an instrument to measure the subjective dimensions of fatigue. *In* FUNK SG, TORNQUIST EM, CHAMPAGNE MT *et al*., (Eds.) *Key aspects of comfort management of pain and nausea*. Philadelphia, Springer 1989: 199-208.
12. SMETS EM, GARSSEN B, BONKE B, DE HAES JC: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; 39: 315-25.
13. HANN DM, JACOBSEN PB, AZZARELLO LM *et al*.: Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res* 1998; 7: 301-10.
14. GLASPY J, BUKOWSKI R, STEINBERG D, TAYLOR C, TCHEKMEDYIAN S, VADHAN-RAJ S: Impact of therapy with epoetin alfa on clinical

outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. *J Clin Oncol* 1997; 15: 1218-34.

15. TACK BB: Dimensions and correlates of fatigue in older adults with rheumatoid arthritis. [Unpublished doctoral dissertation] San Francisco, California, University of California, 1991.
16. DEMETRI GD, KRIS M, WADE J, DEGOS L, CELLA D: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol* 1998; 16: 3412-25.
17. GABRILOVE JL, CLEELAND CS, LIVINGSTON RB, SAROKHAN B, WINER E, EINHORN LH: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001; 19: 2875-82.
18. LITTLEWOOD TJ, BAJETTA E, NORTIER JW, VERCAMMEN E, RAPOPORT B: Epoetin Alfa Study Group: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001; 19: 2865-74.
19. FELSON DT, ANDERSON JJ, BOERS M *et al.*: American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
20. TUGWELL P, BOERS M, for the OMERACT COMMITTEE: Developing consensus on preliminary core efficacy endpoints for rheumatoid arthritis clinical trials. *J Rheumatol* 1993; 20: 555-6.
21. FLOWERS N, WOLFE F: What do rheumatologists do in their practices? *Arthritis Rheum* 1998; 41(Suppl. 9): S337.
22. WEINBLATT ME, KEYSTONE EC *et al.*: Adalimumab, a Fully Human Anti TNF-α Monoclonal Antibody, for the Treatment of Rheumatoid Arthritis Patients Taking Concomitant Methotrexate. The ARMADA Trial. *Arthritis Rheum* 2003; 48: 35-45.
23. KEYSTONE EC, KAVANAUGH AF, SHARP JT *et al.*: Radiographic, Clinical, and Functional Outcomes of Treatment with Adalimumab (a Human Anti-TNF Monoclonal Antibody) in Patients with Active Rheumatoid Arthritis on Concomitant Methotrexate Therapy. *Arthritis Rheum* 2004; 50: 1400-11.
24. FURST DE, SCHIFF LM, FLEISCHMANN RM *et al.*: Adalimumab, a Fully Human Anti–TNF-α Monoclonal Antibody, and Concomitant Standard Antirheumatic Therapy for the Treatment of Rheumatoid Arthritis: Results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003; 30: 2563-71.
25. CELLA D (Ed.): *Manual of the Functional Assessment of Chronic Illness Therapy (FACIT)* Measurement System, Version 4.1. Center on Outcomes, Research and Education (CORE). 2004. Available at: http://www.facit.org. Accessed October 9, 2006.
26. VERBEKE G, MOLENBERGHS G: *Linear Mixed Models for Longitudinal Data*. New York, Springer-Verlag, 2002.
27. FAIRCLOUGH DL: *Design and Analysis of Quality of Life Studies in Clinical Trials*. Boca Raton, Florida, Chapman & Hall/CRC, 2002.
28. MOREHEAD K: Evaluation of the Patient – Laborary Assessment. *In* KLIPPEL JH. CROFFORD LJ, STONE, JH, WEYLAND CM (Eds): *Primer on the Rheumatic Diseases* (12th ed.). New York: Springer and Atlanta, The Arthritis Foundation, 2007: 16.
29. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
30. CELLA D, LAI JS, CHANG CH, PETERMAN A, SLAVIN M: Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002; 94: 528-38.
31. MAKINEN H, HANNONEN P, SOKKA T: Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomized clinical trials for the rate of remission. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S022-S028.
32. WOLFE F, PINCUS T: Listening to the patient: A practical guide to self-report questionnaires in clinical care. *Arthritis Rheum* 1999; 42: 1797-1808.
33. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003; 30: 1138-46.
34. WOLFE F, HAWLEY DJ, WILSON K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-17.