Comparison of 2 Doses of Etanercept (50 vs 100 mg) in Active Rheumatoid Arthritis: A Randomized Double Blind Study

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ABSTRACT. ***Objective***. To assess the safety and efficacy of etanercept 50 mg administered twice weekly versus 25 mg administered twice weekly as monotherapy in patients with tumor necrosis factor-α (TNF-α) blocker-naïve active rheumatoid arthritis (RA).

Methods. Seventy-seven patients with RA were randomized in an unequal allocation (2:1) in a blinded fashion to receive either 50 mg (51 patients) or 25 mg (26 patients) of etanercept twice a week for 24 weeks.

Results. The primary outcome measure, the ACR-N AUC at 24 weeks, showed no difference between the 2 dose groups. In addition, there was no difference in ACR 20, 50, and 70 responses or in EULAR response criteria by Week 24. There were no statistically significant differences between the 2 groups in the proportion of patients with any non-infectious adverse event. The proportion of patients with upper respiratory tract infections was significantly higher in patients receiving 50 mg etanercept compared with those receiving 25 mg (26% vs 4%, p = 0.027).

Conclusion. Etanercept as a monotherapy at 50 mg twice weekly does not provide increased efficacy when compared to the standard dose of 25 mg twice weekly in TNF-α blocker-naïve patients. (First Release Feb 15, 2006; J Rheumatol 2006;33;659–64)

Key Indexing Terms:
RHEUMATOID ARTHRITIS RANDOMIZED CONTROLLED TRIAL ETANERCEPT DOSAGE

Etanercept therapy has been shown to be effective in active rheumatoid arthritis (RA). The drug is a soluble fusion protein consisting of 2 identical chains of the recombinant human TNFR (p75) monomer attached directly to the Fc portion of human IgG1. Etanercept at a dose of 25 mg twice a week decreases disease activity in patients with RA who have had an inadequate response to disease modifying antirheumatic drugs (DMARD)[1,2]. Both etanercept 10 mg twice weekly and 25 mg twice weekly are superior to placebo in improving symptoms, but the 25 mg dose showed increased efficacy over the 10 mg dose[3]. In patients with early RA, etanercept at a dose of 25 mg subcutaneously twice a week, when compared with oral methotrexate (MTX), acts more rapidly to decrease joint symptoms, and has been shown to decrease the erosion score at 6 months and at one year (although it does not significantly decrease the total Sharp score at one year). The 25 mg dose of etanercept was more effective than the 10 mg dose at Month 12 as measured by the the area under the curve (AUC) of the ordinal American College of Rheumatology (ACR) response (ACR-N AUC), and ACR20, ACR50, and ACR70[4]. In addition, when given to patients taking chronic MTX, etanercept 25 mg twice a week is superior to placebo in improving measures of RA clinical disease activity[5]. Moreover, at this dose, the effect of etanercept when added to MTX is superior to either MTX or etanercept alone in the reduction of disease activity, improvement in functional disability, and retardation of radiographic progression[6]. Initially, the approved dose of etanercept for RA was 25 mg twice weekly as a subcutaneous injection. Currently, etanercept is also approved as two 25 mg injections on one day of the week or as 50 mg in a pre-filled syringe given weekly. Controlled studies of higher doses in patients with RA, however, have not been published. It is therefore not known whether a dose greater than 25 mg twice a week would be more effective in decreasing RA activity in TNF-α blocker-naïve individuals. Recently, a double-blind randomized placebo controlled trial of etanercept in patients with psoriasis showed that it was efficacious and well tolerated at doses of 25 mg weekly, 25 mg twice weekly, and 50 mg twice weekly. There was a significant dose-dependent increase in efficacy observed at each dose increment after 12

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and 24 weeks of therapy, with the 50 mg twice weekly dose being the most effective[7].

The present study was designed to assess the safety and efficacy of etanercept 50 mg versus 25 mg administered twice weekly as monotherapy in patients with active RA. Although eventually the safety and efficacy of higher dose etanercept in combination with MTX will need to be determined, it was appropriate to first establish the outcome with the 50 mg twice weekly dose as monotherapy.

MATERIALS AND METHODS

Patients. Eligible patients were recruited in 1999 and were at least 18 years of age, fulfilled the 1987 American Rheumatism Association criteria for RA, and were functional class I, II, or III[8]. They were required to have active RA at the time of screening as demonstrated by ≥ 10 swollen joints and > 12 tender/painful joints, and either C-reactive protein (CRP) ≥ 2.0 mg/dl or morning stiffness lasting ≥ 45 minutes. Patients were required to have failed at least one DMARD (e.g., hydroxychloroquine, oral or injectable gold, MTX, azathioprine, D-penicillamine, sulfasalazine) during the course of the illness. Failure was defined as discontinuation of therapy because of lack of clinical efficacy. Heterosexually active men and women of childbearing potential agreed to use a medically accepted form of contraception beginning at the screening visit and throughout the study (including the followup period of one month. All patients were required to have aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≤ 2 times the laboratory upper limit of normal; hemoglobin ≥ 8.5 g/dl; platelet count ≥ 125,000/mm^3; white blood cell count ≥ 3500 cells/mm^3; and serum creatinine ≤ 2 mg/dl. This study was approved by each local institutional review board, and patients gave written, voluntary informed consent before the screening evaluation.

Patients were excluded from the study if they had previously received any of the following: etanercept, monoclonal antibodies to TNF-α, or experimental metalloproteinase inhibitors (past use of minocycline and doxycycline was acceptable); investigational drugs or other non-TNF biologics within 4 weeks before the screening visit; anti-CD4 or diphtheria interleukin 2 fusion protein within the previous 6 months with a subsequent abnormal absolute T cell count; intraarticular corticosteroids during the 2 weeks before the screening visit; DMARD (e.g., hydroxychloroquine, oral or injectable gold, MTX, leflunomide, azathioprine, D-penicillamine, cyclosporine, or sulfasalazine) within 2 weeks before screening; or cyclophosphamide treatment within 6 months of the first dose of study drug.

Oral corticosteroid doses were required to be stable for at least 2 weeks before the screening evaluation, and patients were excluded if they were receiving concomitant oral corticosteroids > 10 mg/day (prednisone or its equivalent). No changes in corticosteroids were permitted during the study, and no corticosteroid injections were allowed during the 24-week study period. Patients were excluded if they were receiving a dose of nonsteroidal antiinflammatory drug (NSAID) greater than the maximum recommended dose, and the dose of NSAID was to be stable for at least 2 weeks before the screening evaluation.

In addition, other standard exclusion criteria were utilized, including exclusion of patients receiving concurrent antibiotic treatment, or patients with significant concurrent medical disease, including serious infection or uncompensated congestive heart failure.

Study protocol. Arthritis activity was assessed at baseline before the first dose of etanercept, and at Weeks 4, 8, 12, and 24. Assessment of disease status included a complete tender/painful and swollen joint count (71 joints were assessed, but hips and cervical spine were evaluated only for tenderness, and replaced joints were excluded from evaluation), physician global assessment, patient global assessment, pain as measured by the visual analog scale (VAS), disability as measured by the Health Assessment Questionnaire (HAQ), and CRP. Standard laboratory tests including a complete blood cell count and chemistry profiles were measured at each visit, and serum concentrations of etanercept were obtained at weeks 4 and 12. Rheumatoid factor (RF) testing and a chest radiographs were obtained at screening.

Treatment. This was a 24 week multicenter, randomized, double blind study to evaluate the efficacy and safety of a higher dose (50 mg biw) versus the usual dose (25 mg biw) of etanercept. Patients were randomly assigned to receive in a blinded fashion either 50 mg or 25 mg twice a week of etanercept with a 2:1 allocation of patients per group. Patients in the 50 mg etanercept treatment group received two 25 mg injections of etanercept per dose. Patients in the 25 mg treatment group received one 25 mg injection of etanercept and one placebo injection per dose.

Study endpoints. The primary efficacy endpoint was the AUC of the ordinal ACR response (ACR-N) from baseline to 24 weeks. ACR-N AUC was compared between the 2 treatment groups. ACR-N was calculated as the minimum percentage improvement from baseline in the following disease activity measures: (1) swollen joint count, (2) tender/painful joint count, (3) median percentage improvement of the physician and patient global assessments, patient assessment of pain (VAS), disability index (HAQ), and acute phase reactant (CRP). Disease activity measures were assessed at screening, baseline, Weeks 4, 8, and 12, and at Week 24.

Secondary endpoints included the ACR-N AUC from Weeks 0–12, the ACR 20, ACR50, and ACR70 responses at Weeks 12 and 24, the percentage change from baseline at weeks 12 and 24 in total swollen joint count, total tender/painful joint count, patient assessment of pain (VAS), physician global assessment, patient global assessment of functionality (HAQ), CRP, RF (week 24 only), and duration of morning stiffness. The Disease Activity Score 28 CRP (DAS-28 CRP) was computed post-hoc. European League Against Rheumatism (EULAR) response criteria were also used for comparison of the 2 groups[9].

Statistical analysis. The sample size of 50 patients in the 50 mg etanercept treatment group and 25 patients in the 25 mg etanercept treatment group was chosen based on the results of a Phase 3 trial of 10 mg versus 25 mg etanercept twice weekly, in which the mean ACR-N AUC was 130 units versus 180 units over 6 months. Assuming a similar response in the 25 mg group in this trial, the power for the study is 0.80 if the 50 mg dose increases the mean ACR-N AUC from 180 to 300 units. The study also has a 70% power to detect an increase in the adverse event rate from 5% to 25%, using a 1-sided test at a significance level of 0.10.

Demographic and baseline characteristics were summarized to assess comparability of the treatment groups. Treatment groups were compared with respect to incidence of adverse events using Fisher's exact test. The rate of adverse events over time was calculated using an exact binomial test[10].

The primary efficacy measure, ACR-N AUC, was computed from the ACR-N over the 24-week study period using the trapezoidal rule (i.e., a piecewise linear interpolation was made between sequential pairs of ACR ordinals and the area under this curve was calculated). The ACR-N AUC was calculated in ACR-N-years. This is in contrast to the power calculation, which was calculated in ACR-N-months. Therefore, the experimental results differ from the results of the power calculation by a factor of 12. A patient who had a negative ACR-N or who had missing evaluations due to premature withdrawal from the study (before 24 weeks of treatment) had the ACR-N set to zero for that evaluation. The treatment effect was tested using 2-way analysis of variance (ANOVA). All patients who received at least 1 dose of study medication were included in the efficacy analyses. All testing was done at the 5% (2-sided) level of significance.

The secondary endpoints were assessed as follows: ACR-N AUC from 0-12 weeks was analyzed as described above for the primary endpoint. The 20%, 50%, and 70% ACR response rates at 12 and 24 weeks were analyzed using the Fisher's exact test. For binary endpoints, patients who prematurely withdrew from the study before 24 weeks were considered nonresponders at all time points after premature withdrawal. The treatment groups were compared with respect to the observed values of ACR component variables at 12 and 24 weeks using analysis of covariance. The baseline value was used as a covariate, and the model included terms for the study center and treatment group. ANOVA was used to compare treatment groups with respect to the per-

centage change from baseline using a last-observation-carried-forward imputation method for subjects withdrawing before 24 weeks.

For the post-hoc analysis by the EULAR response criteria, the p value was assessed by the 2-sided Fisher's exact test.

RESULTS

Seventy-seven patients were enrolled (26 in the 25 mg dose group and 51 in the 50 mg dose group). The groups were well matched in baseline demographic characteristics and disease history (Table 1). The patients were predominantly female, with a median age of 50 years in the 25 mg dose group and 55 years in the 50 mg dose group. In the 25 mg dose group the median duration of RA was 12.5 years, and 73% of the patients in this group were RF positive at baseline. Similarly in the 50 mg dose group the median duration of RA was 15 years and 80% of patients were RF positive at baseline. Profiles of prior DMARD use were similar in each group. However, NSAID use was slightly higher in the 50 mg dose group. The arthritis activity at baseline was similar between groups. Twenty-three of 26 (88%) and 43/51 (84%) patients in the 25 and 50 mg dose groups, respectively, completed the study. In the 25 mg dose group, 2 patients discontinued due to lack of efficacy, and one due to subject refusal. In the 50 mg dose group, 4 patients discontinued due to adverse events, 3 due to lack of efficacy, and 1 due to subject refusal.

For the primary outcome in this study, ACR-N AUC at 24 weeks, there was no difference between the 2 groups, with median values of 9.5 and 11.6 in the 25 mg and 50 mg dose group, respectively (p = 0.744). At 4 weeks, however, there was a trend towards improved efficacy in the 50 mg dose group, with median ACR-N AUC values of 0.2 and 0.8 in the 25 mg and 50 mg groups, respectively, (p = 0.083) (Table 2).

ACR 20, 50, and 70 responses were similar in the 2 groups at Week 24. There was, however, a trend towards a higher number achieving an ACR 20 response by Week 4 in the 50 mg etanercept group (Table 2). The ACR component measures of disease activity are shown in Table 3. By Week 24, there was no significant difference in any of these variables between the 2 dose groups. At 4 weeks, there was a difference between the 25 mg versus the 50 mg groups in the median tender joint count (20.8 vs 14.0, p = 0.008), and the CRP (1.0 vs 0.8, p = 0.003). There was no significant difference between 25 mg and 50 mg doses using the EULAR response criteria based on the calculated DAS-28 CRP (Table 2).

To ensure that increased levels of drug were present in the 50 mg group, etanercept serum concentrations were determined at Weeks 4 and 12 and showed higher concentrations with the 50 mg dose group. At Week 4, mean serum concentrations in ng/ml (with standard error) were 2079.6 (367.1) and 4078.5 (405.3) for 25 mg and 50 mg groups, respectively. Similarly at Week 12, the mean serum concentrations in ng/ml were 2187.6 (253.1) and 4925.2 (291.8).

Table 1. Demographic characteristics, disease history, and baseline arthritis activity.

Characteristic	Etanercept 25 mg (n = 26)	Etanercept 50 mg (n = 51)
Median age, yrs	50.5	55.0
Female, No. (%)	23 (88)	43 (84)
Caucasian, No. (%)	20 (77)	46 (90)
Median weight, kg	75.7	66.0
Duration of RA in years, median	12.5	15.0
Positive RF at baseline, n (%)	19 (73)	41 (80)
No. of prior DMARD, median	3.5	3.0
Previous therapies, No. (%)		
Corticosteroids	16 (62)	29 (57)
NSAID	13 (50)	38 (75)
Methotrexate	22 (85)	43 (84)
Baseline arthritis activity, mean (median)		
Tender joint count	32 (31)	32 (29)
Swollen joint count	24 (23)	22 (20)
HAQ disability index	1.6 (1.6)	1.7 (1.8)
DAS28CRP	6.0 (5.8)	6.2 (6.3)

Table 2. Number (%) of patients who achieved 20%, 50%, and 70% ACR responses and EULAR good or moderate responses, and mean ACR-N AUC in ACR-years (SE).

	Etanercept 25 mg (n = 26)	Etanercept 50 mg (n = 51)	p (25 vs 50 mg)
ACR 20			
Week 4	6 (23)	24 (47)	0.050
Week 8	10 (38)	27 (53)	0.335
Week 12	16 (62)	34 (67)	0.801
Week 24	17 (65)	30 (59)	0.628
ACR 50			
Week 4	2 (8)	8 (16)	0.480
Week 8	5 (19)	14 (27)	0.578
Week 12	5 (19)	18 (35)	0.191
Week 24	10 (38)	19 (37)	1.000
ACR 70			
Week 4	0	3 (6)	0.547
Week 8	1 (4)	5 (10)	0.657
Week 12	2 (8)	8 (16)	0.480
Week 24	4 (15)	8 (16)	1.000
ACR-N AUC			
Week 4	0.5 (0.2)	1.0 (0.1)	0.083
Week 8	2.1 (0.5)	3.1 (0.4)	0.189
Week 12	4.3 (0.8)	5.7 (0.7)	0.260
Week 24	11.3 (1.7)	12.7 (1.4)	0.744
EULAR response Week 4			
Good or moderate	13 (50)	36 (71)	0.0862
None	13 (50)	15 (29)	
Week 8			
Good or moderate	17 (65)	38 (75)	0.4329
None	9 (35)	13 (25)	
Week 12			
Good or moderate	22 (85)	39 (76)	0.5556
None	4 (15)	12 (24)	
Week 24			
Good or moderate	23 (88)	43 (84)	0.7410
None	3 (12)	8 (16)	

Table 3. Disease activity measures. Values are the median.

Disease Activity Measure	25 mg Etanercept (n = 26) Baseline	25 mg Etanercept (n = 26) Week 24	50 mg Etanercept (n = 51) Baseline	50 mg Etanercept (n = 51) Week 24	p (25 mg vs 50 mg) Baseline	p (25 mg vs 50 mg) Week 24
Tender joint count	30.9	8.0	28.8	7.0	0.402	0.494
Swollen joint count	23.0	6.5	20.0	8.0	0.328	0.857
Patient pain assessment (VAS)	5.9	2.2	7.0	2.4	0.271	0.812
Physical global assessment	6.5	3.0	7.0	3.0	0.456	0.866
Patient global assessment	7.0	4.0	7.0	4.0	0.626	0.749
Disability index (HAQ)	1.6	1.3	1.8	1.4	0.756	0.916
CRP (mg/dl)	1.3	0.8	1.4	0.8	0.962	0.107

Etanercept was generally well tolerated at both dose levels. There were no statistically significant differences between the 2 groups in the proportion of patients with non-infectious adverse events (data not shown). The serious adverse events and adverse events that resulted in discontinuation are summarized in Table 4. In the 50 mg dose group one patient was hospitalized for a gastrointestinal hemorrhage related to warfarin therapy and a second patient was hospitalized for seizures secondary to a prior ischemic event. Both these patients completed the study. A third patient had hydrocephalus and was discontinued, and the fourth patient had a cerebrovascular accident and refused to continue the study. Three additional patients in the 50 mg group were discontinued due to adverse events; 2 due to rash and one due to delayed healing of cuts and scratches. One of the 2 patients with rash had a mild maculopapular rash on the lower extremities felt by the investigator to be related to the study drug. The other patient had a mild rash on the face, chest, and ears that was not felt by the investigator to be related to the study drug. No patient in the 25 mg dose group was discontinued due to an adverse event. One patient in the 25 mg treatment group was hospitalized for less than 24 hours and received 2 doses of intravenous ceftriaxone for sinusitis 3 weeks after the last dose of study drug. No other infections in either group required intravenous antibiotics or hospitalization.

The proportion of patients with upper respiratory tract infections was significantly higher in the patients who received 50 mg etanercept versus patients who received 25 mg (26% vs 4%, p = 0.027). The proportion of patients with other infectious adverse events, including sinusitis, cystitis, bronchitis, urinary tract infections, flu syndrome, gastroenteritis, and fungal infections (skin), was not significantly different between the 2 groups (Table 5). There were no cases of tuberculosis, opportunistic infections, multiple sclerosis, or systemic lupus erythematosus in this study.

DISCUSSION

The efficacy of etanercept has been demonstrated in placebo-controlled trials of 10-25 mg twice weekly. An initial pilot study comparing doses of 2, 4, 8, and 16 mg/m^2 administered subcutaneously twice weekly after a single initial intravenous loading dose showed a trend toward clinical improvement[1]. These results led to the first large randomized controlled trial of etanercept in which doses of 0.25, 2, or 16 mg/m^2 subcutaneously twice weekly were compared to placebo. Seventy-five percent of the patients assigned to the 16 mg/m^2 group (23–30 mg) achieved an ACR 20 at 3 months compared to 46%, 33%, and 14% in the 2 mg/m^2, 0.25 mg/m^2, and the placebo groups, respectively[2]. Based on these results a Phase III placebo controlled trial was designed to test fixed doses of

Table 4. Serious adverse events and adverse events that resulted in discontinuation.

	Dose, mg	Pt. No.	Day	Details	Discontinuation
Back pain	25	110	72		No
Gastrointestinal hemorrhage	50	121	176	Elevated prothrombin	No
Seizures	50	215	3	Previous ischemic event	No
			66	Subtherapeutic phenytoin, possible silent myocardial infarction	
Cerebrovascular accident	50	301	83	History of cerebrovascular accident	Yes
Hydrocephalus	50	407	51		Yes
Rash	50	214	129	Chest, ears and face	Yes
	50	317	17	Maculopapular on lower extremities	Yes
Delayed healing of cuts and scratches	50	319			Yes

Table 5. Number (%) of patients with infections (infections that occurred in ≥ 5% of patients)

	Etanercept		p
	25 mg (n = 26)	50 mg (n = 51)	(25 vs 50 mg)
Any infection	13 (50)	27 (53)	0.815
Sinusitis	4 (15)	8 (16)	1.000
Cystitis	3 (12)	2 (4)	0.329
Bronchitis	2 (8)	3 (6)	1.000
Urinary tract infection	2 (8)	1 (2)	0.262
Flu syndrome	1 (4)	3 (6)	1.000
Upper respiratory infection	1 (4)	13 (26)	0.027
Fungal infection	0	3 (6)	0.547
Gastroenteritis	0	3 (6)	0.547

25 mg versus 10 mg twice weekly[3]. In that study, at 3 months 62% of the patients receiving 25 mg of etanercept, 45% of the patients receiving 10 mg of etanercept, and 23% of the patients receiving placebo achieved an ACR 20 response. At 6 months, 59% of the 25 mg group, 51% of the 10 mg group, and 11% of the placebo group achieved an ACR 20 response.

Although 10 mg was an effective dose compared to placebo, the number of patients achieving an ACR 20 at 2 weeks, ACR 20 at 3 months, ACR 50 at 3 months, and ACR 50 at 6 months was significantly higher in the 25 mg dose group versus the 10 mg dose group. Subsequently, in patients with early RA, 25 mg was shown to be more effective than 10 mg by the ACR-N AUC and ACR 20, 50, and 70 responses at 12 months[4]. The 25 mg dose twice weekly is the US Food and Drug Administration approved dose for the treatment of adult RA. Etanercept at this dose has been shown to have an additive effect in combination with MTX[5,6]. More recently, etanercept has been approved for use as two 25 mg injections once weekly, or as 50 mg weekly in a pre-filled syringe in RA, psoriatic arthritis, and ankylosing spondylitis.

Although previous studies have clearly shown the 25 mg twice weekly dose to be efficacious, only a small number of patients achieve ACR 70 responses or remission criteria. The question remained whether therapy initiated at a higher dose could provide improved clinical response. Our current study was a randomized double-blind controlled trial comparing a 25 mg dose of etanercept twice weekly with a higher dose of 50 mg twice weekly as monotherapy in TNF-α blocker-naïve patients with RA. No differences in measures of disease activity, including ACR 20, 50, and 70 responses as well as EULAR response criteria, were found between the 2 groups by Week 24. Although at Week 4 there was a trend towards a higher number achieving an ACR 20 response in the 50 mg etanercept group and an improvement in the tender joint count and CRP in the 50 mg versus 25 mg dose group, these differences were not apparent beyond 4 weeks. Therefore, although there may be a trend toward an earlier response with etanercept 50 mg twice weekly when compared to 25 mg twice weekly, no significant improvement was seen with the higher dose at later time points. There were no statistically significant differences in the incidence of any individual non-infectious adverse event. The incidence of upper respiratory tract infections, however, was higher in the 50 mg dose group, and it is unclear if this is merely an incidental finding or whether it will be substantiated by further studies. In addition, one must bear in mind that this study was designed primarily to assess efficacy of the higher dose of etanercept, and was not powered at a level sufficient for safety assessment, as it was only powered to detect 5-fold increases in adverse events. Therefore, further studies to substantiate the safety of this dose are still required. This is the first time a dose higher than 50 mg has been evaluated in a controlled trial in patients with RA. Higher doses may show increased efficacy in other diseases, however, as illustrated by a recent double-blind randomized controlled trial of etanercept in psoriasis[7]. That study compared doses of 25 mg weekly, 25 mg twice weekly, and 50 mg twice weekly and found significant dose-dependent improvements at all doses, with the 50 mg twice weekly dose providing the best response. In the psoriasis patients, etanercept was well tolerated at all doses, and adverse events and infections occurred in similar proportions of patients in each group.

In our study, patients with active RA who had failed prior DMARD therapy showed no enhanced clinical response to etanercept 50 mg twice weekly when compared to the standard dose of 25 mg twice weekly as monotherapy. This study was powered to detect an increase in ACR-N AUC from 180 to 300 units at 6 months, and therefore smaller changes in efficacy would not have been detected. Of note, no major safety signal was seen in this limited number of patients with higher dose therapy. The combination of etanercept and MTX is superior to either drug alone[6], and many patients are currently being treated concurrently with both drugs. It is not known if higher dose etanercept, when administered with MTX, would lead to a better response than standard dose etanercept plus MTX. Our study with higher dose etanercept monotherapy provides the foundation for moving forward with studies of higher dose etanercept in combination with MTX. In addition, we cannot determine based on the results presented here whether patients who have demonstrated a partial response to etanercept at 25 mg twice weekly may experience a further improvement in clinical variables with an increased etanercept dose. Further studies will be required to answer these questions.

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