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Etanercept Versus Methotrexate in Patients With Early Rheumatoid Arthritis

Two-Year Radiographic and Clinical Outcomes

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Objective. **To compare the clinical and radiographic outcomes in patients with rheumatoid arthritis (RA) who received monotherapy with either etanercept or methotrexate (MTX) for 2 years and to assess the safety of this therapy.**

Methods. **In the Enbrel ERA (early rheumatoid arthritis) trial, 632 patients with early, active RA were randomized to receive either twice-weekly subcutaneous etanercept (10 mg or 25 mg) or weekly oral MTX (mean dosage 19 mg per week) for at least 1 year in a double-blind manner. Following the blinded phase of the trial, 512 patients continued to receive the therapy to which they had been randomized for up to 1 additional year, in an open-label manner. Radiograph readers remained blinded to treatment group assignment and the chronologic order of images.**

Results. **At 24 months, more 25-mg etanercept patients than MTX patients met American College of Rheumatology 20% improvement criteria (72% and 59%, respectively; $P = 0.005$), and more had no increase in total score and erosion scores on the Sharp scale ($P = 0.017$ and $P = 0.012$, respectively). The mean changes in total Sharp score and erosion score in the 25-mg etanercept group (1.3 and 0.66 units, respectively) were significantly lower than those in the MTX group (3.2 and 1.86 units, respectively; $P = 0.001$). Significantly more patients in the 25-mg etanercept group (55%) than in the MTX group (37%) had at least 0.5 units of improvement in the Health Assessment Questionnaire disability index ($P < 0.001$). Fewer patients in the etanercept group than in the MTX group experienced adverse events or discontinued treatment because of adverse events.**

Conclusion. **Etanercept as monotherapy was safe and was superior to MTX in reducing disease activity, arresting structural damage, and decreasing disability over 2 years in patients with early, aggressive RA.**

Etanercept is a fully human fusion protein that inhibits tumor necrosis factor (TNF) and the subsequent inflammatory cytokine cascade. Etanercept has been

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shown to be safe and effective in rapidly reducing disease activity in adults with rheumatoid arthritis (RA) and in sustaining that improvement (1–5). It is equally effective in children with polyarticular juvenile RA (6). Etanercept is approved for use as monotherapy, as well as combination therapy with methotrexate (MTX), for the treatment of RA.

Loss of function and radiographic change occur early in the course of disease. These changes can be delayed or prevented with the use of certain disease-modifying antirheumatic drugs (DMARDs). Although several DMARDs are initially clinically effective and well tolerated, many of these drugs become less effective or exhibit increased toxicity over time. Based on its efficacy and tolerability, MTX has become the standard therapy by which other treatments are measured (1,7).

In the first year of the Enbrel ERA (early rheumatoid arthritis) trial, etanercept was shown to be significantly more effective than MTX in improving signs and symptoms of disease and in inhibiting radiographic progression (1). We now report results from the second year of the study, which was designed to compare etanercept alone and MTX alone in terms of safety, sustained efficacy, and prevention of radiographic progression in patients with early, aggressive RA.

PATIENTS AND METHODS

The study design and results of the double-blind portion of this trial have been previously reported (1). Institutional review boards at each study site approved the protocol, and all patients gave written informed consent.

Patients. At study entry, all participants were at least 18 years of age, had had RA for no more than 3 years, and had not been treated with MTX. To ensure that only patients at high risk for radiographic progression of disease were enrolled, subjects were required to have a positive test for rheumatoid factor or at least 3 bone erosions evident on radiographs of the hands, wrists, or feet; at least 10 swollen joints and at least 12 tender or painful joints; and an erythrocyte sedimentation rate $\geq$28 mm/hour, a C-reactive protein concentration $>$2.0 mg/dl, or morning stiffness that lasted at least 45 minutes (1).

Study protocol. Patients were randomly assigned to receive 10 mg of etanercept by subcutaneous injection twice weekly and 3 placebo tablets weekly; 25 mg of etanercept by subcutaneous injection twice weekly and 3 placebo tablets weekly; or three 2.5-mg tablets of MTX weekly and twice-weekly subcutaneous injections of placebo. The initial 7.5-mg dose of MTX and its placebo was rapidly increased, to 8 tablets (20 mg) at week 8 if any joints were actively involved. All patients received folate supplementation (1 mg/day).

After the last patient enrolled had completed 12 months in the study, placebo treatments were discontinued, but no other dosing changes were made. Patients who did not withdraw from the study at this time continued to receive the therapy to which they had originally been assigned for up to 1 additional year. Because the time of entry into the blinded phase of the trial was staggered, a minimum of 13.8 months and a maximum of 23.6 months elapsed from the time patients received a first dose until the study was unblinded (average 18.4 months). The mean dose of MTX was 19 mg/week, and the median dose was 20 mg/week.

Study end points. The American College of Rheumatology (ACR) core set of variables for each patient was collected, and disease activity was assessed according to ACR 20% improvement criteria; ACR 50% and ACR 70% improvement rates were calculated in an analogous manner (8). For the clinical end points, data collected during the blinded phase of the study were pooled with data collected during the open-label phase. Sensitivity analyses showed no significant difference in results when blinded data from the second year were compared with unblinded data from that period.

Radiographs of the hands, wrists, and feet were obtained at baseline and at 6, 12, and 24 months (or at the time of study termination for patients who discontinued prematurely). The films were digitized (9) and scored for erosions and joint space narrowing by 2 of 6 radiologists or rheumatologists using the Sharp scoring method. One pair of readers scored each patient's set of images, and the average score was used in the analysis. The baseline, 6-month, and 12-month films were scored at the end of the first year (1). At the end of the second year, these images, along with the 24-month film, were scored again by the same pair of readers. The readers remained blinded to treatment group assignment and chronologic order of the images, even after unblinding of the study to patients and investigators. Results from the reading that included the 24-month films were used for the present analyses.

During the second year of the study, patients were evaluated every 3 months for safety and efficacy, including use of the disability index of the Health Assessment Questionnaire (HAQ) (10). Serum samples obtained at baseline and at months 6, 12, 18, and 24 were tested for anti-etanercept antibodies by an enzyme-linked immunosorbent assay (ELISA) as previously described (1,2). Cumulative safety data for the entire 2-year study are included. Tests for autoantibodies, including antinuclear antibodies, anti–double-stranded DNA antibodies, and anticardiolipin IgM and IgG antibody titers, were performed at screening and every 6 months thereafter.

Statistical analysis. For the ACR20, ACR50, and ACR70 responses, last observation carried forward (LOCF) analyses were performed, using the last observation recorded while patients were receiving the study drug to which they had been randomized. Although there are sometimes difficulties with the LOCF method (11), its use was considered appropriate in these analyses because the ACR responses were fairly stable in all treatment groups. LOCF analyses were also used for HAQ disability index scoring. The binary end points (ACR20, ACR50, and ACR70 responses) were compared among treatment groups using a chi-square test.

For the radiologic end points, changes in Sharp scores over 24 months were compared. For radiographic scores, linear extrapolations or interpolations, adjusted over time, were used for patients whose final-month radiograph deviated from the planned 24-month time point. Fifteen patients who had only 1 film (at baseline) were excluded from the analyses; inclusion of

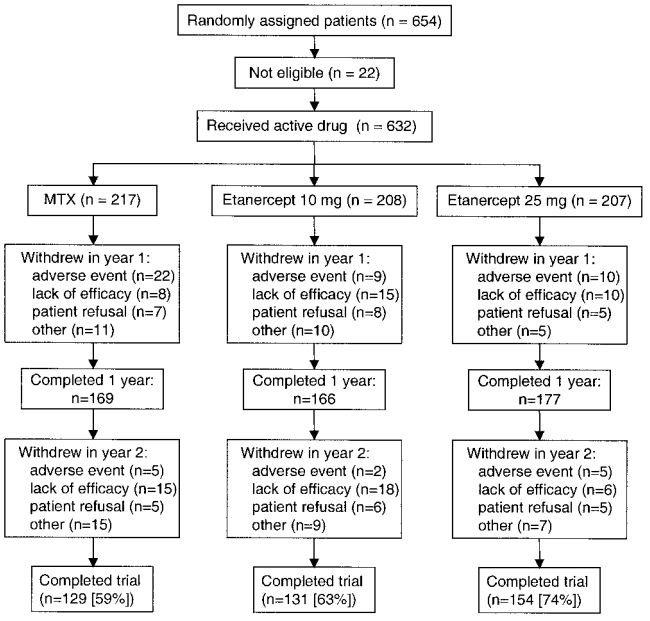

Figure 1. Schematic diagram showing number of study participants in each group who withdrew and the number who completed the trial. MTX = methotrexate.

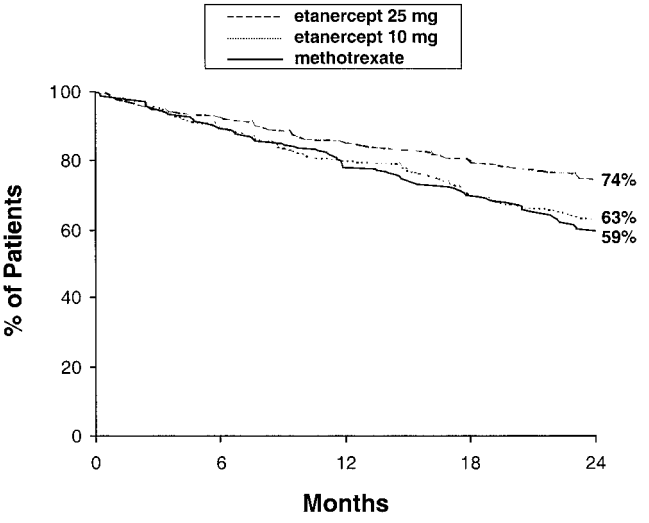

Figure 2. Percentage of patients with rheumatoid arthritis who discontinued use of the study drugs during the 2-year trial. Values shown are the percentage of patients who completed the trial.

these patients did not change the results. Rank tests (van Elteren tests [12]) were used to compare the 3 treatment groups. Predicted yearly progression rates were calculated

Table 1. Characteristics of patients at baseline and at year 2*

	Baseline			Year 2		
		Etanercept			Etanercept	
	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX (n = 169)	10 mg (n = 166)	25 mg (n = 177)
Mean age, years	49	50	51	49	50	50
Age range	21–80	19–84	21–82	21–79	19–84	21–82
% age ≥65 years	15	14	18	14	14	15
% female	75	75	74	75	75	74
% Caucasian	88	84	86	88	86	86
Mean duration of RA, months	12	11	12	12	11	12
% rheumatoid factor–positive	89	88	87	90	89	88
Mean C-reactive protein level, mg/dl†	3.7	4.4	3.3	4.0	4.5	3.6
% who previously took DMARDs	46	39	40	47	39	41
Mean no. of DMARDs taken	0.6	0.5	0.5	0.6	0.4	0.5
% receiving any DMARD at screening	24	25	23	25	25	24
% receiving concomitant therapy at baseline						
NSAIDs	80	76	86	79	77	88
Corticosteroids	41	42	39	46	37	36
Mean daily dosage, mg	7	7	9	7	7	9
Mean ± SD no. of tender joints	30 ± 16	31 ± 16	31 ± 16	30 ± 16	31 ± 16	31 ± 16
Mean ± SD no. of swollen joints	24 ± 12	24 ± 12	24 ± 12	24 ± 12	24 ± 12	24 ± 12
Mean ± SD total Sharp score	12.9 ± 13.8	11.2 ± 14.8	12.4 ± 15.8	11.3 ± 13	9.7 ± 13.8	10.8 ± 14.8
Mean ± SD erosion score	7.5 ± 9.2	6.1 ± 9.0	6.4 ± 9.0	6.9 ± 8.5	5.7 ± 8.6	5.7 ± 8.5
Mean ± SD joint space narrowing score	5.4 ± 6.1	5.0 ± 7.7	6.0 ± 8.2	4.4 ± 5.8	4.0 ± 6.9	5.1 ± 7.6
% with erosions	87	85	88	86	80	84
Estimated rate of progression, units/year						
Total Sharp score	9	8	9	11	10	11
Erosion score	5	4	5	7	6	6
Joint space narrowing score	4	4	4	4	4	5

* MTX = methotrexate; RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs.
† Normal range 0–0.8 mg/dl.

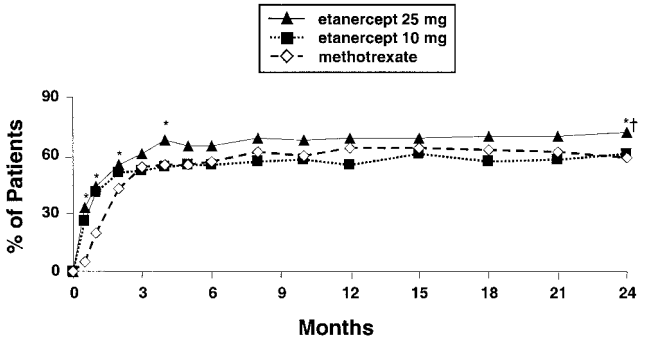

Figure 3. American College of Rheumatology 20% response rates of study patients over 2 years. Data were evaluated using a last observation (on study drug) carried forward analysis to include patients who discontinued use of the study drug prematurely. * = $P < 0.05$ versus 10 mg etanercept. † = $P < 0.05$ versus methotrexate.

using the baseline film and duration of disease. The proportions of patients who had no progression in total Sharp score, erosion score, and joint space narrowing score were calculated. No progression was defined as <0.5 units of change from baseline. This definition was chosen because readers scored using whole numbers only, and scores from 2 readers were averaged for each patient. To maintain the Type I error at 5%, pairwise comparisons at the 0.05 level were considered significant only if the overall comparison (3 groups) was significant at $P < 0.05$.

RESULTS

Patients and study completion. Of the 632 patients enrolled at baseline, 512 patients entered the second year of the study (Figure 1). In the 25-mg etanercept group, 74% of patients received the study drug for 2 years, compared with 59% of patients in the MTX group (Figure 2). The demographic characteristics of the patients who entered year 2 of the study were similar among groups (Table 1), and the cohort continuing in the second year was similar to the entire population of the original study at baseline (1).

Significantly more patients in the MTX group than in the combined etanercept groups discontinued use of the study drug because of adverse events ($P = 0.01$, MTX versus all etanercept). Over the entire 2-year period, 12% of patients in the MTX group discontinued due to adverse events, compared with 5% in the 10-mg etanercept group and 7% in the 25-mg etanercept group. During the 2-year study, 11% of patients in the MTX group withdrew due to lack of efficacy, compared with 16% of patients in the 10-mg etanercept group and 8% in the 25-mg etanercept group.

ACR responses. The improvement in arthritis (as measured by ACR criteria) seen during the first year of the study was sustained through the second year. Although etanercept was numerically superior to MTX, both agents continued to be effective in reducing disease activity (Figure 3). At month 24, significantly more patients in the 25-mg etanercept group than in the MTX group had an ACR20 response (72% versus 59%, $P = 0.005$). ACR50 response rates were 49% and 42%, respectively, in the 25-mg etanercept and MTX groups, and ACR70 rates were 29% and 24%, respectively (P not significant [NS]).

Consistent with results reported during the first year of the study, the 25-mg etanercept dose was more effective than the 10-mg etanercept dose at month 24, with respect to the ACR20 (61%), ACR50 (35%), and ACR70 (19%) ($P < 0.02$ for all comparisons) (1).

Radiographic results. There was significantly less radiographic progression in the 25-mg etanercept group compared with the MTX group (Figure 4). At 2 years, the mean change from baseline in total Sharp score was

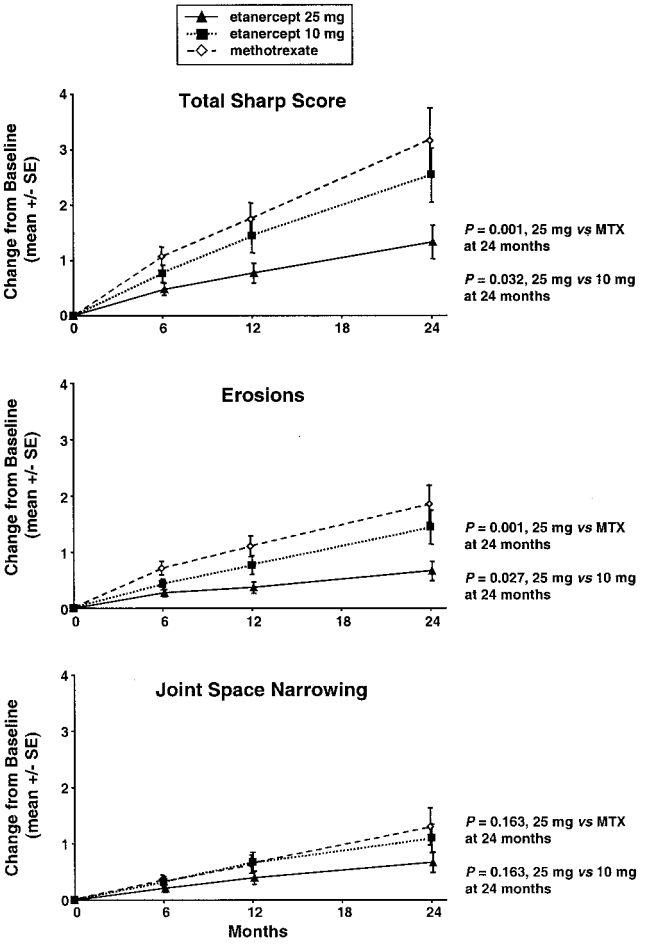

Figure 4. Mean changes in Sharp scale total scores, erosion scores, and joint space narrowing scores over 2 years. MTX = methotrexate.

1.3 units in the 25-mg group versus 3.2 units in the MTX group ($P = 0.001$). Mean changes in erosion score were 0.7 and 1.9 units in the 25-mg etanercept and MTX groups, respectively ($P = 0.001$). In the 25-mg etanercept group, the median change from baseline at 2 years was 0 for total Sharp score, erosion score, and joint space narrowing score (Figure 5).

The 25-mg dose of etanercept was significantly better than MTX in preventing radiographic progression. Sixty-three percent of 25-mg etanercept patients had no increase in total Sharp score, compared with 51% of MTX patients ($P = 0.017$), and 70% versus 58% had no increase in erosions ($P = 0.012$) (Figure 6). More patients in the 25-mg etanercept group than in the MTX group had no increase in the joint space narrowing score (78% versus 69%), but the difference was not significant (overall 3-group comparison $P = 0.1165$).

For the radiographic end points, the 25-mg dose was significantly more effective than the 10-mg dose with respect to the change in total Sharp ($P = 0.032$) and erosion scores ($P = 0.027$, Figure 4). The change in the joint space narrowing score was low in all 3 groups ($P =$ NS). Of interest, of the subgroup of patients whose total Sharp scores were 0 at baseline (17 patients in the MTX group, 21 in the 10-mg etanercept group, and 19 in the 25-mg group), a substantial number had no radiographic progression over 24 months. At month 24, 65% of the MTX patients still had a total Sharp score of 0, compared with 86% of patients in the 10-mg etanercept group and 79% of patients in the 25-mg group.

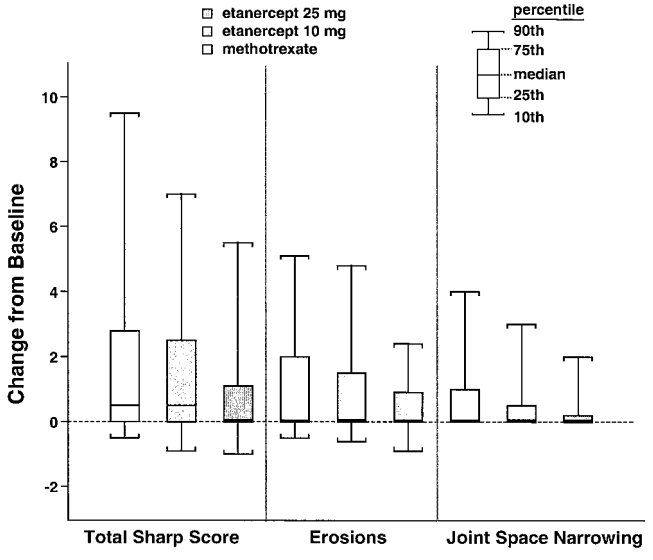

Figure 5. Median changes (percentiles) in Sharp scale total scores, erosion scores, and joint space narrowing scores over 2 years.

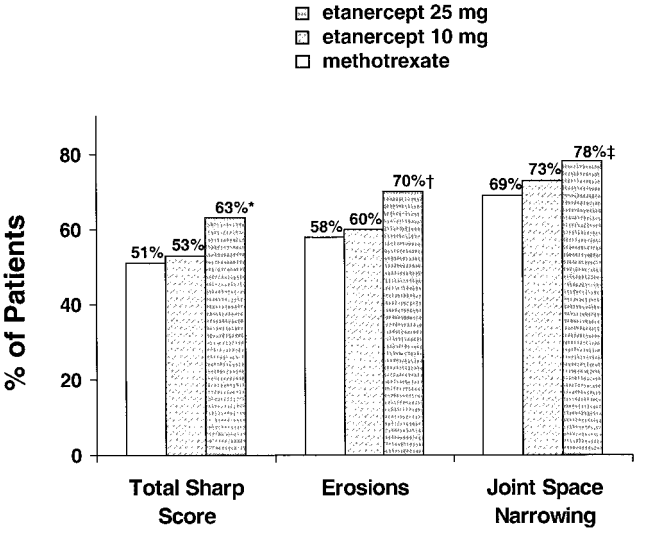

Figure 6. Percentage of rheumatoid arthritis patients in each treatment group who had no radiographic progression, as measured by total score, erosion score, and joint space narrowing score based on the Sharp scale. $* = P = 0.017$ versus methotrexate (MTX) and $P = 0.55$ versus 10 mg etanercept. $† = P = 0.012$ versus MTX and $P = 0.040$ versus 10 mg etanercept. $‡ = P = 0.038$ versus MTX and P not significant versus 10 mg etanercept.

Function and disability. The HAQ disability index is the arthritis-specific quality of life instrument used most commonly to assess functional status. It is scored on a scale of 0–3 units, with higher numbers indicating increasing disability (10). A 0.25-unit change in HAQ score is generally considered to be a clinically significant change in the level of disability (13).

At baseline, patients in this study had a moderate degree of disability, with mean HAQ disability index scores of 1.4–1.5 units. By month 12, ~55% of patients in both the MTX and 25-mg etanercept treatment groups had at least a 0.5-unit improvement in HAQ score (Figure 7). At 24 months, the same proportion (55%) of patients in the 25-mg etanercept group had at least a 0.5-unit improvement in HAQ score, but the percent of MTX patients maintaining this level of improvement declined to 37% ($P < 0.001$). Thus, the 25-mg dose of etanercept was significantly more effective than MTX in improving quality of life over 2 years.

Safety. As in previous studies with etanercept, the most common adverse event in both etanercept groups over the 2-year study period was injection-site reaction (Table 2) (1,2,4). Of the other noninfectious adverse events that occurred in ≥10% of patients in any treatment group, nausea, alopecia, and mouth ulcers were significantly more common in the MTX group.

Four patients (2%) had pneumonitis as a result of MTX use during this study (14).

Serious infections were rare and did not increase in frequency during the second year of the study. Over the 2-year period of study, 21 patients had infections that required hospitalization or use of intravenous antibiotics, including 9 patients in the MTX group, 5 patients in the 10-mg etanercept group, and 7 patients in the 25-mg group. The types of serious infection observed in the second year were similar to those reported in the first year (1) and included cellulitis (1 patient each in all 3 treatment groups), bronchitis (1 patient in the 10-mg group), pneumonia (1 patient in the 10-mg group), and cystitis (2 patients in the 25-mg group). No cases of tuberculosis and no opportunistic infections were seen.

There were 2 deaths during the first year of the study (1), no deaths during the second year, and no deaths due to infection. Ten patients developed cancer during the entire study period (3 in the MTX group, 3 in the 10-mg group, and 4 in the 25-mg group); these rates are similar to those in the age- and sex-matched general population, using the Surveillance, Epidemiology and End Results data base (15). No predominant cancer type was observed.

Etanercept was not demonstrated to be immunogenic in this trial. Over the 2-year study period, 14 etanercept patients (3.5%), including 8 in the 25-mg group and 6 in the 10-mg group, had at least 1 positive anti-etanercept antibody test, using the ELISA described previously (1,2). None of the antibodies had neutralizing activity, and there was no relationship between safety or efficacy and the presence or absence of these antibodies. There was no consistent difference in the number of patients testing positive for autoantibodies between any of the 3 treatment groups. No new autoimmune features and no adverse events suggestive of systemic lupus erythematosus, demyelinating diseases, or other autoimmune diseases were reported.

Table 2. Noninfectious adverse events occurring in ≥10% of patients in any group*

Event	Methotrexate (n = 217)	Etanercept 10 mg (n = 208)	Etanercept 25 mg (n = 207)
Injection site reaction	19 (9)	66 (32)†	81 (39)†
Headache	61 (28)	56 (27)	51 (25)
Nausea	67 (31)	30 (14)†	42 (20)†
Rash	54 (25)	40 (19)	37 (18)
Rhinitis	32 (15)	41 (20)	37 (18)
Diarrhea	32 (15)	28 (14)	35 (17)
Asthenia	37 (17)	25 (12)	33 (16)
Bleeding at injection site	22 (10)	31 (15)	32 (16)
Dyspepsia	27 (12)	33 (16)	31 (15)
Dizziness	26 (12)	15 (7)	30 (15)‡
Abdominal pain	32 (15)	26 (13)	26 (13)
Back pain	15 (7)	17 (8)	25 (12)
Accidental injury	20 (9)	24 (12)	23 (11)
Pain	24 (11)	17 (8)	22 (11)
Ecchymosis	23 (11)	19 (9)	23 (11)
Vomiting	20 (9)	7 (3)†	20 (10)‡
Hypertension	12 (6)	23 (11)	18 (9)
Peripheral edema	9 (4)	23 (11)	14 (7)
Myalgia	21 (10)	19 (9)	12 (6)
Alopecia	27 (12)	14 (7)†	12 (6)†
Mouth ulcer	37 (17)	14 (7)†	10 (5)†

* Values are the number (%) and are not adjusted for time receiving study drug. Patients may have had more than 1 event within a specific category, but each patient was counted only once for each type of event.
† $P \leq 0.05$ versus methotrexate.
‡ $P < 0.05$ versus 10 mg etanercept.

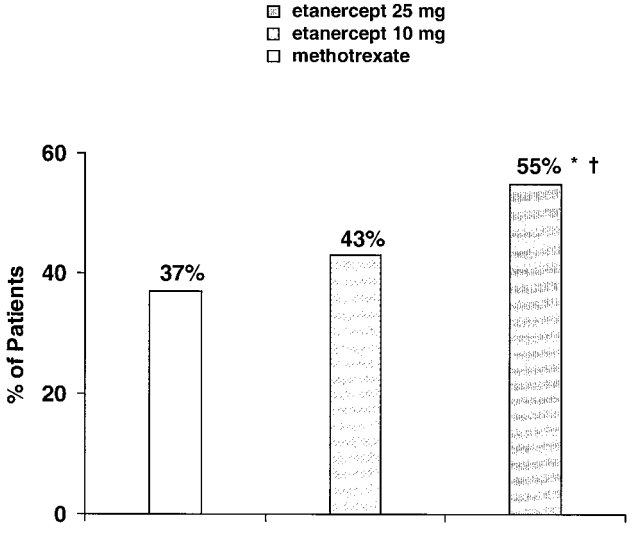

Figure 7. Percentage of rheumatoid arthritis patients who had ≥0.5 units of improvement in the Health Assessment Questionnaire disability index score at the end of the study. Data were evaluated using a last observation carried forward analysis that defined the final score for patients who discontinued prematurely to be the last on-treatment evaluation. * = $P < 0.001$ versus methotrexate. † = $P = 0.021$ versus 10 mg etanercept.

DISCUSSION

Recent studies have examined radiographic progression in patients with late-stage RA who have taken leflunomide, MTX, or placebo (16) as well as patients who have taken infliximab plus MTX or placebo plus MTX following a partial response to MTX (17,18). This is the first study to compare the safety and efficacy of MTX monotherapy with those of a biologic response

modifier. Differences in study population (early versus late RA, MTX naive versus MTX partial responder, baseline demographics, number of prior DMARDs used, baseline radiographic scores) make comparisons among studies difficult. This study represents the largest and longest effort to collect safety, efficacy, and radiologic data while comparing 2 continuous monotherapies in patients with early RA.

Attrition from this study was relatively small over the 2-year time frame. This fact is important, because duration of therapy has become an important surrogate end point for evaluating RA treatment (19,20). Almost three-quarters of the patients who were randomized to receive the 25-mg dose of etanercept completed 2 years of therapy. Fewer patients (59%) remained on MTX at 2 years, and this proportion may be somewhat lower than that reported in earlier studies (21). The fact that patients now have a wider choice of therapies and the high dose of MTX used in this study may have influenced the discontinuations in the MTX group. Both loss of efficacy over time and cumulative toxicity contributed to the higher discontinuation rate for MTX.

The current study demonstrates that both etanercept and aggressively dosed MTX are effective as monotherapy for the treatment of early RA. The clinical response and inhibition of structural damage observed with etanercept or MTX as monotherapy are sustained for at least 2 years in patients with early, active RA. Over the 2-year period of the study, some relative advantages of etanercept became apparent. Within the first few months of the study, a difference in clinical response between patients receiving MTX and those receiving etanercept was observed. This difference was thought to be associated with the more rapid onset of action of etanercept compared with MTX. Aggressively dosed MTX did result in a considerable clinical response by month 3 of this study, and although the clinical response at 2 years remained substantial, it was less than that seen with etanercept. Compared with MTX, patients receiving 25 mg of etanercept had a significantly greater clinical response at 2 years as measured by ACR20. Because the analysis of the data was performed using the LOCF, the ACR20 response rate or efficacy of MTX was not lessened based on withdrawal due to side effects or an inability to tolerate the aggressive dose of MTX.

Again, although both agents were effective for inhibiting radiographic progression, the 25-mg dose of etanercept was significantly more effective than MTX as measured by change in total Sharp score and erosion score, as well as the proportion of patients with no progression in total Sharp score, erosion score, and joint space narrowing score.

The radiographic findings of this study and others are impressive and suggest the unequivocal need for the use of DMARDs early in the course of RA. However, differences in study populations, and in design, duration, and end points measured make comparisons among studies difficult if not impossible. Limitations in the sensitivity of the radiographs as well as in the scoring systems themselves make it difficult to comment on healing or reversal of radiographic damage.

A substantial portion of the second year of this study was conducted in an open-label manner, and all patients were required to remain in the originally assigned treatment groups. Because of the staggered nature of the enrollment period, the mean time that patients remained blinded to treatment was 18.4 months. It is possible that for some patients, the period of unblinded therapy influenced clinical assessment. However, the rate of clinical response did not differ before and after unblinding in the second year of the study, suggesting no marked change in perception of outcome or benefit.

Additionally, the open-label nature of a substantial portion of the second year of the study could also have affected the radiographic results. It is possible that the low progression rates in year 1 created an expectation among the readers that the year 2 progression rates would also be low. This might have biased the scoring to minimize change. However, the readers remained blinded to the treatment group and the chronologic order of the images. Therefore, no obvious mechanism exists that would bias in favor of less progression in the 25-mg etanercept group.

Over the 2 years, monotherapy with etanercept or MTX had acceptable side effect profiles, although patients treated with etanercept had fewer noninfectious adverse events and lower rates of discontinuation due to adverse events compared with patients treated with MTX. There was no evidence of an increase in adverse events or cumulative toxicity in the etanercept groups during the second year of the study. These results corroborate those of a recent long-term followup study of 628 adult patients with long-standing RA who were treated with etanercept for up to 43 months, which demonstrated no cumulative safety issues with sustained etanercept therapy (5).

Results of the current trial support the utility of early aggressive therapy, because the significant impact on disease progression may reduce the functional decline that occurs over many years. This impact can be

demonstrated already at 2 years by the significant improvement in function and reduction in disability as measured by the HAQ disability index.

In summary, etanercept and MTX had excellent profiles for initial treatment of patients with active, erosive RA. The benefits of 25-mg etanercept as monotherapy were shown to be superior to those of MTX at 2 years, and improvements in clinical, radiographic, and disability end points were maintained with sustained therapy.

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