

# The New England Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

VOLUME 343

NOVEMBER 30, 2000

NUMBER 22



## A COMPARISON OF ETANERCEPT AND METHOTREXATE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

JOAN M. BATHON, M.D., RICHARD W. MARTIN, M.D., ROY M. FLEISCHMANN, M.D., JOHN R. TESSER, M.D.,  
MICHAEL H. SCHIFF, M.D., EDWARD C. KEYSTONE, M.D., MARK C. GENOVESE, M.D., MARY CHESTER WASKO, M.D.,  
LARRY W. MORELAND, M.D., ARTHUR L. WEAVER, M.D., JOSEPH MARKENSON, M.D., AND BARBARA K. FINCK, M.D.

### ABSTRACT

**Background** Etanercept, which blocks the action of tumor necrosis factor, reduces disease activity in patients with long-standing rheumatoid arthritis. Its efficacy in reducing disease activity and preventing joint damage in patients with active early rheumatoid arthritis is unknown.

**Methods** We treated 632 patients with early rheumatoid arthritis with either twice-weekly subcutaneous etanercept (10 or 25 mg) or weekly oral methotrexate (mean, 19 mg per week) for 12 months. Clinical response was defined as the percent improvement in disease activity according to the criteria of the American College of Rheumatology. Bone erosion and joint-space narrowing were measured radiographically and scored with use of the Sharp scale. On this scale, an increase of 1 point represents one new erosion or minimal narrowing.

**Results** As compared with patients who received methotrexate, patients who received the 25-mg dose of etanercept had a more rapid rate of improvement, with significantly more patients having 20 percent, 50 percent, and 70 percent improvement in disease activity during the first six months ( $P < 0.05$ ). The mean increase in the erosion score during the first 6 months was 0.30 in the group assigned to receive 25 mg of etanercept and 0.68 in the methotrexate group ( $P = 0.001$ ), and the respective increases during the first 12 months were 0.47 and 1.03 ( $P = 0.002$ ). Among patients who received the 25-mg dose of etanercept, 72 percent had no increase in the erosion score, as compared with 60 percent of patients in the methotrexate group ( $P = 0.007$ ). This group of patients also had fewer adverse events ( $P = 0.02$ ) and fewer infections ( $P = 0.006$ ) than the group that was treated with methotrexate.

**Conclusions** As compared with oral methotrexate, intravenous etanercept acted more rapidly to decrease symptoms and slow joint damage in patients with early active rheumatoid arthritis. (N Engl J Med 2000; 343:1586-93.)

©2000, Massachusetts Medical Society.

**E**TANERCEPT (Enbrel, Immunex, Seattle) is a soluble tumor necrosis factor (TNF) receptor fusion protein that binds and inactivates TNF, a proinflammatory cytokine that is overproduced in the joints of patients with rheumatoid arthritis.<sup>1</sup> Etanercept reduces disease activity in adults and children with chronic rheumatoid arthritis who have had an inadequate response to other therapies.<sup>2-5</sup>

TNF also stimulates the production of other proinflammatory cytokines, increases cell migration by increasing the production of cellular adhesion molecules, and increases the rate of tissue remodeling by matrix-degrading proteases.<sup>6-8</sup> In addition to reducing symptoms of rheumatoid arthritis, inhibition of the action of TNF may prevent or slow progressive joint destruction.

Over the past decade, methotrexate has been widely used in patients with rheumatoid arthritis because it slows the progression of joint destruction.<sup>9-13</sup> Because it is more effective in preserving function when treatment is initiated before joint damage begins, early intervention with methotrexate is considered essential.<sup>14-16</sup> Although usually well tolerated by patients with rheumatoid arthritis,<sup>17-19</sup> methotrexate has adverse effects that limit its use in some patients.<sup>20</sup> We compared the efficacy and safety of etanercept and methotrexate in patients with early rheumatoid arthritis.

From Johns Hopkins University, Baltimore (J.M.B.); Michigan State University, Grand Rapids (R.W.M.); Metroplex Clinical Research Center, Dallas (R.M.E.); Phoenix Center for Clinical Research, Phoenix, Ariz. (J.R.T.); Denver Arthritis Clinic, Denver (M.H.S.); Mount Sinai Hospital, Toronto (E.C.K.); Stanford University, Stanford, Calif. (M.C.G.); University of Pittsburgh Medical Center, Pittsburgh (M.C.W.); University of Alabama at Birmingham, Birmingham (L.W.M.); Arthritis Center for Nebraska, Lincoln (A.L.W.); Hospital for Special Surgery, New York (J.M.); and Immunex, Seattle (B.K.F.). Address reprint requests to Dr. Bathon at Johns Hopkins Asthma and Allergy Center, Johns Hopkins University, 5501 Hopkins Bayview Cir., Rm. 5A24, Baltimore, MD 21224.

## METHODS

## Patients

The study began in May 1997 and ended in March 1999. We studied 632 patients who were at least 18 years of age, had had rheumatoid arthritis for no more than three years, had no other important concurrent illnesses, and had not been treated with methotrexate. In order to recruit patients who were at high risk for radiographic progression,<sup>21</sup> we required prospective patients to have a positive serum 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 of at least 28 mm per hour, a serum C-reactive protein concentration of at least 2.0 mg per deciliter, or morning stiffness that lasted at least 45 minutes. The institutional review board at each study site approved the protocol, and all patients gave written informed consent.

Disease-modifying antirheumatic drugs, including hydroxychloroquine and sulfasalazine, were discontinued at least four weeks before the study began. Stable doses of nonsteroidal antiinflammatory drugs and prednisone ( $\leq 10$  mg daily) were allowed.

## Study Protocol

Patients were randomly assigned to one of three treatment groups: 10 mg of etanercept twice weekly by subcutaneous injection and three placebo tablets weekly, 25 mg of etanercept twice weekly by subcutaneous injection and three placebo tablets weekly, or three 2.5-mg tablets of methotrexate weekly and twice-weekly subcutaneous injections of placebo. The injections were self-administered. The initial dose of 7.5 mg of methotrexate and its placebo was increased to 15 mg (six tablets) at week 4 and to 20 mg (eight tablets) at week 8. One 5-mg reduction in the dose of methotrexate or its placebo was allowed for patients whose serum aminotransferase concentrations increased to at least 2.5 times the upper limit of the normal range. The dose of etanercept or its placebo was not reduced. All patients also received 1 mg of folic acid per day. Patients who discontinued either study drug received standard care and continued to be evaluated for the duration of the study.

Clinical and laboratory studies were performed at screening, at base line, and after 2 weeks, 1 month, and 6, 8, 10, and 12 months. Disease activity was assessed according to the criteria of the American College of Rheumatology (ACR), which define a response according to its extent: 20 percent (ACR 20), 50 percent (ACR 50), or 70 percent (ACR 70). An ACR 20 response is defined as a reduction of at least 20 percent in the number of tender joints and swollen joints plus an improvement of at least 20 percent in at least three of the following five criteria: patient's assessment of pain, patient's assessment of disease activity, physician's assessment of disease activity, patient's assessment of physical function, and serum C-reactive protein concentration.<sup>2,22,23</sup> Visual-analogue or Likert scales, ranging from 0 to 10, were used for the global assessments. ACR 50 and ACR 70 responses indicate improvement of at least 50 percent and 70 percent, respectively, in the numbers of both tender and swollen joints and in the degree of improvement in at least three of the five criteria. The overall response of each patient (ACR-N) was also determined by calculating the smallest degree of improvement from base line in the following three criteria: the number of tender joints, the number of swollen joints, and the median of the five remaining measures of disease activity. Joint counts were determined by trained assessors who were unaware of the patient's treatment assignment.

Radiographs of the hands, wrists, and feet were obtained at base line, 6 months, and 12 months with the use of high-resolution film (Kodak MIN-R M) and a Lanex single fine intensifying screen. Films were digitized with use of a pixel size of 100  $\mu$ m and a 12-bit gray scale,<sup>24</sup> and the images were scored for erosions and joint-space narrowing by six radiologists or rheumatologists. Each image was scored by two radiologists or rheumatologists, and the interobserver correlation was good ( $r=0.85$ ). The read-

ers were trained in the modified Sharp method<sup>25,26</sup> and were unaware of the patient's treatment assignment and the chronologic order of the images. A total of 46 joints were examined for erosions. Erosions were scored on a 6-point scale on which a score of 0 indicates no new erosions and no worsening of existing erosions and each point increase indicates the occurrence of one new bone erosion or 20 percent worsening of an existing erosion. A total of 42 joint spaces were examined for narrowing. Joint-space narrowing was scored on a 5-point scale on which a score of 0 indicates no narrowing, a score of 1 minimal narrowing, a score of 2 loss of 50 percent of the joint space, a score of 3 loss of 75 percent of the joint space, and a score of 4 complete loss of the joint space. These scores were summed to obtain the total Sharp score.<sup>25,27</sup> The Sharp scoring method, with a range of 0 (no damage) to 398 (severe joint destruction), is a highly sensitive and reproducible measure of progression in early disease.<sup>28</sup> Scores at the higher end of the range are uncommon among patients who have only had rheumatoid arthritis for a short period.

Adverse events and changes in laboratory values were graded on a scale derived from the Common Toxicity Criteria of the National Cancer Institute. Serum samples obtained at base line and at 6 and 12 months were tested for antibodies against etanercept by enzyme-linked immunosorbent assay as previously described,<sup>3</sup> but the plate-coating concentration of etanercept was changed to 250 ng per milliliter to increase the sensitivity.

## Statistical Analysis

An intention-to-treat analysis was performed that included all patients who received at least one dose of the study drug. All statistical tests were two-sided. The primary clinical end point was the overall response during the first six months, as indicated by a comparison of the areas under the curve for ACR-N in the three groups. The area under the curve represents the cumulative response over time. The values were compared with use of analysis of variance. The percentages of patients with ACR 20, ACR 50, and ACR 70 responses were compared with use of chi-square tests.

The primary radiologic end point was the change in Sharp scores over a period of 12 months. A linear extrapolation that considered the first and last observations, adjusted for time, was used for patients who withdrew from the study. We used rank tests stratified according to the duration of disease (the Van Elteren test) to compare the three treatment groups. This analysis allowed us to evaluate change over a 6-month period as well as a 12-month period. At 12 months, 15 patients (2 percent) with no follow-up films were assigned the highest score that had been given to patients who had the same base-line score that they did.

## RESULTS

## Characteristics of the Patients

The base-line characteristics and measures of disease activity were similar in the three treatment groups (Table 1). At base line, 87 percent of patients had erosions and 79 percent had joint-space narrowing.

After the second dose escalation, the mean dose of methotrexate was 19 mg per week. Fifteen percent of the 217 patients in the methotrexate group required reductions in the dose because of adverse events (8 percent) or high serum aminotransferase concentrations (7 percent) (Table 2). Significantly more patients in the methotrexate group than in either etanercept group discontinued treatment because of adverse events.

## Clinical Efficacy

The patients in both etanercept groups had a rapid improvement in their condition. Significant differenc-

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE.\*

CHARACTERISTIC	METHOTREXATE (N=217)	10 mg OF ETANERCEPT (N=208)	25 mg OF ETANERCEPT (N=207)
Age (yr)	49±13	50±13	51±13
Age ≥65 yr (%)	15	14	18
Female sex (%)	75	75	74
White race (%)	88	84	86
Duration of rheumatoid arthritis (mo)	12±11	11±10	12±11
Positive serum test for rheumatoid factor (%)	89	88	87
Serum C-reactive protein (mg/dl)†	3.7±4.4	4.4±6.3	3.3±4.0
Any prior use of DMARDs (%)	46	39	40
Mean no. of DMARDs	0.6±0.7	0.5±0.7	0.5±0.7
Use of any DMARDs at screening (%)	24	25	23
Concomitant therapy at base line (%)			
NSAIDs	80	76	86
Glucocorticoids	41	42	39
Daily glucocorticoid dose (mg)‡	7±4.4	7±2.5	9±8.6
No. of tender joints	30±16.1	31±15.5	31±15.8
No. of swollen joints	24±11.9	24±11.7	24±11.9
Sharp score§			
Total	12.9±13.8	11.2±14.8	2.4±15.8
Erosion	7.5±9.2	6.1±9.0	6.4±9.0
Joint-space narrowing	5.4±6.1	5.0±7.7	6.0±8.2
≥1 Erosions (%)	87	85	88
Estimated rate of progression¶			
Increase in total Sharp score/yr	9	8	9
Increase in erosion score/yr	5	4	5
Increase in narrowing score/yr	4	4	4

\*DMARDs denotes disease-modifying antirheumatic drugs, and NSAIDs nonsteroidal antiinflammatory drugs. Plus-minus values are means ±SD.

†The normal range is 0 to 0.8 mg per deciliter.

‡Only patients who were receiving glucocorticoids were included in the analysis.

§Total scores can range from 0 to 398, scores on the erosion subscale can range from 0 to 230, and scores on the narrowing subscale can range from 0 to 168. Higher scores indicate more radiographically evident damage.

¶Estimates were based on the duration of disease and the base-line Sharp score for each patient.

es between the etanercept and methotrexate groups were apparent at the earliest evaluation at two weeks. The patients in the group assigned to receive 25 mg of etanercept had significantly greater areas under the curve for ACR-N for 3, 6, 9, and 12 months than did the patients in the methotrexate group (Fig. 1). This finding is consistent with etanercept's having a more rapid treatment effect. The percentages of patients in the group assigned to receive 25 mg of etanercept who had ACR 20, ACR 50, and ACR 70 responses were significantly greater than those in the methotrexate group at most evaluations within the first six months but were approximately the same thereafter (Fig. 2). At 12 months, 72 percent of the patients in the group assigned to receive 25 mg of etanercept had an ACR 20 response, as compared with 65 percent of those in the methotrexate group ( $P=0.16$ ).

As previously reported in patients with long-standing rheumatoid arthritis,<sup>4,5</sup> the 25-mg dose of eta-

nercept was more effective than the 10-mg dose. This was true with respect to the area under the curve for ACR-N in the two groups and the ACR 20, ACR 50, and ACR 70 responses at 12 months ( $P<0.03$  for all comparisons).

#### Radiographic Evidence of Progression

In general there was less radiographic evidence of progression in the group assigned to receive 25 mg of etanercept than in the methotrexate group, as evaluated on the basis of Sharp scores, and etanercept had a more immediate effect (Fig. 3). The majority of patients had no new or worsening erosions during the study. Seventy-two percent of patients in the group assigned to receive 25 mg of etanercept had no increase in the erosion score, as compared with 60 percent of patients in the methotrexate group ( $P=0.007$ ). The mean increase in the erosion score at 6 months was 0.30 in the group assigned to receive 25 mg of

TABLE 2. STATUS OF PATIENTS AT 12 MONTHS.

STATUS	METHOTREXATE (N=217)	10 mg OF ETANERCEPT (N=208)	25 mg OF ETANERCEPT (N=207)
Completed 12 mo of evaluation	202 (93)	188 (90)	193 (93)
Completed 12 mo of treatment	172 (79)	166 (80)	176 (85)
Reduction in dose of methotrexate or its placebo because of adverse event	32 (15)	8 (4)*	4 (2)*
Did not complete 12 mo of treatment	45 (21)	42 (20)	31 (15)
Because of adverse event or high serum aminotransferase values	24 (11)	12 (6)	11 (5)†
Because of lack of efficacy	8 (4)	15 (7)	10 (5)
For other reasons‡	13 (6)	15 (7)	10 (5)

\*P<0.001 for the comparison with methotrexate (by Fisher's exact test).

†P=0.04 for the comparison with methotrexate (by Fisher's exact test).

‡Other reasons for not completing 12 months of treatment included protocol violations and a patient's decision to withdraw from the study.

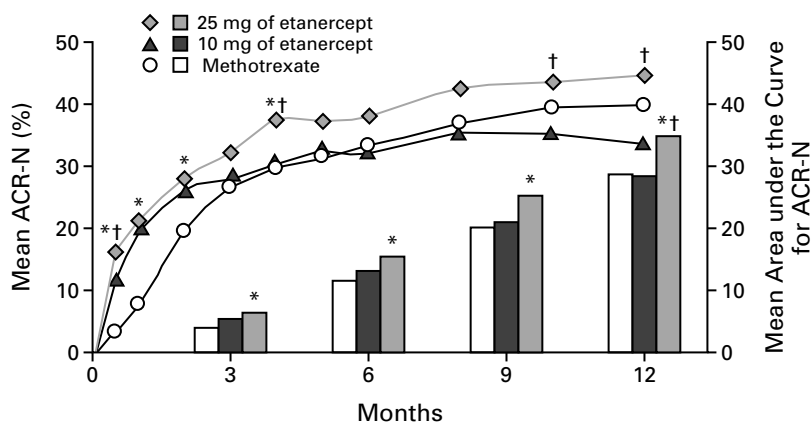


Figure 1. Mean Response of Patients with Rheumatoid Arthritis to Treatment with 10 mg of Etanercept, 25 mg of Etanercept, or Methotrexate, According to the Percent Improvement from Base Line as Measured by the American College of Rheumatology Criteria (ACR-N, Symbols) and by the Area under the Curve for ACR-N (Bars).

Asterisks indicate significant differences (P<0.05) between the methotrexate group and the group assigned to receive 25 mg of etanercept, and daggers indicate significant differences (P<0.05) between the two etanercept groups.

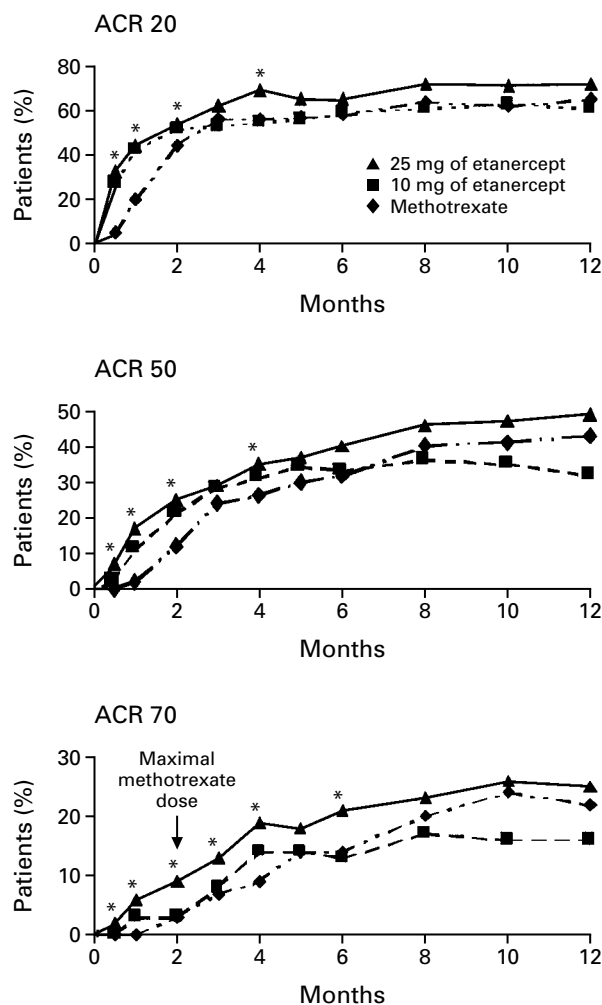
etanercept and 0.68 in the methotrexate group (P=0.001), and the respective changes at 12 months were 0.47 and 1.03 (P=0.002).

In the methotrexate group, the rate of change in erosion, as measured by both the total score and the erosion score on the Sharp scale, was significantly slower during the second six months than during the first six months (P≤0.005 for both scores). During the second six months, the rate of change in erosion scores was similar in the group assigned to receive 25 mg of etanercept and the methotrexate group.

There were no significant differences among the

treatment groups in the changes in scores for joint-space narrowing at either 6 or 12 months. At 6 months, the mean total score on the Sharp scale had increased by 0.57 in the group assigned to receive 25 mg of etanercept and by 1.06 in the methotrexate group (P=0.001), and the respective increases were 1.00 and 1.59 at 12 months (P=0.11). The results in the group assigned to receive 10 mg of etanercept were similar to those in the methotrexate group.

Decreases in clinical evidence of disease activity were correlated with the absence of radiographic evidence of progression. Patients who had the best clinical re-



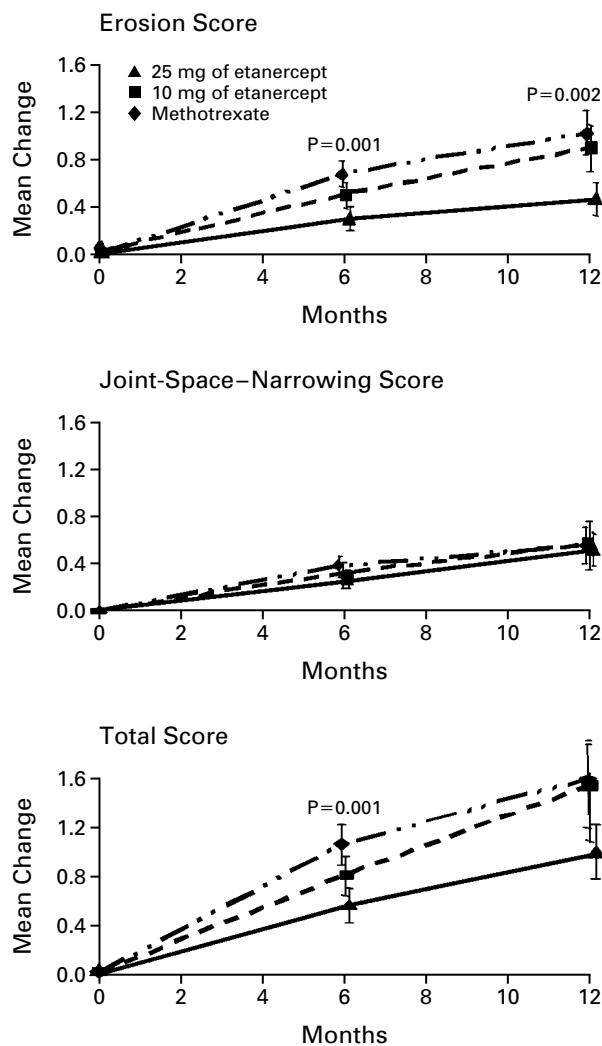
**Figure 2.** Percentages of Patients with Rheumatoid Arthritis Who Had an Improvement, According to the Criteria of the American College of Rheumatology (ACR), of 20 Percent (ACR 20), 50 Percent (ACR 50), and 70 Percent (ACR 70) during Treatment with 25 mg of Etanercept, 10 mg of Etanercept, or Methotrexate.

Asterisks indicate significant differences ( $P < 0.05$ ) between the methotrexate group and the group assigned to receive 25 mg of etanercept.

sponses (in terms of the number of swollen joints, the area under the curve for ACR-N, or the serum C-reactive protein concentration) had the smallest amount of radiographic evidence of progression (data not shown). The strongest correlate of the absence of progression was decreased serum C-reactive protein concentrations in the group assigned to receive 25 mg of etanercept ( $r = 0.45$ ,  $P < 0.001$ ).

#### Adverse Effects

Both methotrexate and etanercept were well tolerated; the severity of most adverse effects was mild or



**Figure 3.** Mean ( $\pm$ SE) Changes from Base Line in Erosion Scores, Joint-Space-Narrowing Scores, and Total Scores on the Sharp Scale at 6 and 12 Months in Patients with Rheumatoid Arthritis Who Received 25 mg of Etanercept, 10 mg of Etanercept, or Methotrexate.

P values indicate significant differences between the methotrexate group and the group assigned to receive 25 mg of etanercept.

moderate. Significantly more patients in the methotrexate group had adverse events than did patients in the group assigned to receive 10 mg of etanercept ( $P = 0.04$ ) or the group assigned to receive 25 mg of etanercept ( $P = 0.02$ ) (Table 3). Some of these adverse effects, including nausea, rash, alopecia, and mouth ulcers, are expected with methotrexate but also occurred in the etanercept groups. Methotrexate-associated pneumonitis was diagnosed in three patients in the methotrexate group (1 percent). As in previous trials, reactions at the injection site were the most common adverse events reported by patients who were re-

**TABLE 3.** ADVERSE EVENTS THAT OCCURRED IN AT LEAST 10 PERCENT OF PATIENTS IN ANY GROUP.

EVENT	METHOTREXATE (N=217)	10 mg OF ETANERCEPT (N=208)	25 mg OF ETANERCEPT (N=207)
Reaction at injection site	16 (7)	63 (30)*	77 (37)*
Upper respiratory tract infection	84 (39)	57 (27)*	72 (35)
Headache	59 (27)	52 (25)	46 (22)
Nausea	62 (29)	29 (14)*	35 (17)*
Rhinitis	30 (14)	36 (17)	31 (15)
Diarrhea	27 (12)	26 (12)	30 (14)
Bleeding at injection site	21 (10)	30 (14)	29 (14)
Skin infection	22 (10)	22 (11)	28 (14)
Asthenia	27 (12)	19 (9)	27 (13)
Influenza-like syndrome	25 (12)	20 (10)	26 (13)
Rash	50 (23)	33 (16)	25 (12)*
Dyspepsia	21 (10)	21 (10)	25 (12)
Dizziness	23 (11)	10 (5)	24 (12)
Back pain	12 (6)	12 (6)	22 (11)
Abdominal pain	22 (10)	23 (11)	20 (10)
Sinusitis	36 (17)	28 (13)	20 (10)
Ecchymosis	22 (10)	17 (8)	18 (9)
Alopecia	25 (12)	14 (7)	12 (6)*
Mouth ulcer	30 (14)	13 (6)*	10 (5)*

\*P&lt;0.05 for the comparison with methotrexate.

ceiving etanercept.<sup>4,5</sup> These occurred in 37 percent of patients in the group assigned to receive 25 mg of etanercept and 7 percent of those in the methotrexate group (who received placebo injections) (P<0.001).

The number of patients with one or more infections was similar in all treatment groups. However, when we analyzed the number of events that occurred per patient-year, the rate of all types of infection was significantly higher among patients who received methotrexate than among those who received either dose of etanercept (1.9 vs. 1.5 events per patient-year, P=0.006). The frequency of upper respiratory tract infections was similar in the methotrexate group and the group assigned to receive 25 mg of etanercept, while the rate of infections at other sites in the respiratory tract was higher in the methotrexate group (1.3 vs. 1.0 events per patient-year, P=0.006). Infections requiring hospitalization or the intravenous administration of antibiotics occurred in less than 3 percent of patients in each group. There were no opportunistic infections, and no deaths from infections.

The frequency of abnormal laboratory results was similar in all three groups. However, approximately twice as many patients in the methotrexate group as in the group assigned to receive 25 mg of etanercept had high serum aspartate aminotransferase concentra-

tions (32 percent vs. 16 percent, P<0.001) or high serum alanine aminotransferase concentrations (44 percent vs. 24 percent, P<0.001). Similarly, patients who were taking methotrexate were more likely to have low peripheral-blood lymphocyte counts ( $\leq 1400$  per cubic millimeter) than were those who were taking the 25-mg dose of etanercept (79 percent vs. 56 percent, P<0.001). Sporadic, nonrecurrent neutropenia was reported more frequently in the group assigned to receive 25 mg of etanercept than in the methotrexate group (16 percent vs. 8 percent of patients, P=0.01). Five patients (two in the methotrexate group, one in the group assigned to receive 10 mg of etanercept, and two in the group assigned to receive 25 mg of etanercept) had transient grade 3 neutropenia (at least 500 but fewer than 1000 neutrophils per cubic millimeter). There were no serious infections associated with transient neutropenia.

During the 12 months of observation, there was no evidence of an increased rate of cancer in any treatment group, as compared with that in the age- and sex-matched general population (Surveillance, Epidemiology, and End Results data base of the National Institutes of Health).<sup>29</sup> There were two cases in the methotrexate group (bladder cancer and colon cancer), two cases in the group assigned to receive 10 mg of etanercept (breast cancer and lung cancer), and three cases in the group assigned to receive 25 mg of etanercept (carcinoid lung cancer, Hodgkin's disease, and prostate cancer). No additional autoimmune diseases developed in any of the patients.

There were two deaths during the 12-month study period. One patient in the group assigned to receive 10 mg of etanercept died of metastatic lung cancer two months after randomization. One patient in the group assigned to receive 25 mg of etanercept died of noninfectious complications resulting from dissection of a preexisting aortic aneurysm.

Less than 3 percent of etanercept-treated patients were positive intermittently on tests for serum non-neutralizing antibodies against etanercept, and the positive tests were not associated with a decrease in the clinical response or adverse effects.

## DISCUSSION

The purpose of our study was to evaluate the effect of etanercept on disease activity and joint damage in patients with active early rheumatoid arthritis. The patients in this study were at risk for rapidly progressive joint damage, and their disease was predicted to progress without treatment at an estimated rate of 4 to 5 points per year on the Sharp erosion subscale and 4 points per year on the Sharp joint-space-narrowing subscale (Table 1). These changes are equivalent to the occurrence of five new erosions per year or the erosion of 80 to 100 percent of a single joint per year and complete loss of the joint space in a single joint per year.

The rates of joint-space narrowing were low. Both etanercept and methotrexate prevented joint-space narrowing. The overall rates of erosion were also low, equivalent to the occurrence of one new erosion or the erosion of 20 percent of one joint every year in the methotrexate group and every two years in the group assigned to receive 25 mg of etanercept. The effects of this dose of etanercept were evident sooner than the effects of methotrexate, and the rates of change were similar in the two groups during the latter half of the study. Over a one-year period, treatment with etanercept halted erosions in 72 percent of patients, whereas treatment with methotrexate halted erosions in 60 percent of patients. These results underscore the importance of early intervention in slowing or arresting damage evident on radiography and support the use of the current treatment algorithm for early, aggressive treatment of active disease.<sup>14,30,31</sup> Preventing the damage that occurs early in the course of the disease may be the key to better long-term functional outcomes.

TNF has a central role in causing synovitis in patients with rheumatoid arthritis, and treatments that inhibit TNF are effective in patients with established rheumatoid arthritis.<sup>3-5</sup> Our findings demonstrate that etanercept monotherapy ameliorates symptoms and prevents progression in patients with early rheumatoid arthritis by inhibiting TNF.

Both the clinical benefits and the decrease in the rate of radiographic evidence of progression occurred more rapidly in the group assigned to receive 25 mg of etanercept than in the methotrexate group, even though the dose of methotrexate was quickly increased during the first weeks of the study. The difference in the percentage of patients with clinical improvement in these two groups, as measured by ACR 20, ACR 50, and ACR 70 responses and by the cumulative response (the area under the curve for ACR-N), was greater during the first six months of therapy. This rapid onset of action is consistent with the timing of responses in previous trials of etanercept in patients with long-standing rheumatoid arthritis.

The decrease in disease activity was correlated with the absence of radiographic evidence of progression. Patients with the most clinical improvement had the least evidence of progression. This correlation is consistent with the findings of other studies<sup>15,32</sup> and supports the view that both clinical and radiographic manifestations of the disease involve TNF-dependent processes.

Etanercept can be safely administered with methotrexate.<sup>4</sup> Further studies are necessary to assess whether the combination of etanercept and methotrexate has additive or synergistic effects on clinical and radiographic outcomes. Combination therapy may be especially important early in the disease, given the fact that etanercept acts more rapidly to decrease disease activity and prevent structural damage.

The excellent tolerability and safety profiles of etanercept in our patients with early rheumatoid arthritis were similar to those in patients with long-standing disease.<sup>2-5</sup> Our findings indicate that etanercept represents an important new therapeutic option to decrease disease activity and slow joint damage in patients with active rheumatoid arthritis.

Supported by Immunex. Drs. Bathon, Martin, Fleischmann, Tesser, Schiff, Keystone, Moreland, Weaver, and Markenson have received grants from or served as consultants to Immunex and other companies that make products for use in patients with rheumatoid arthritis.

## APPENDIX

The following persons also participated in the study: *Investigators* — H.S. Baraf, Wheaton, Md.; S.W. Baumgartner, Spokane, Wash.; G.E. Bayliss, Salem, Va.; A. Bohan, Newport Beach, Calif.; A. Brodsky, Dallas; K. Bulpitt, Los Angeles; F.X. Burch, San Antonio, Tex.; J.R. Caldwell, Gainesville, Fla.; G.W. Cannon, Salt Lake City; J.S. Carlin, Seattle; N.L. Carteron, San Francisco; M.A. Cima, Garden City, N.Y.; M. Cohen, Albuquerque, N.M.; W.E. Davis, New Orleans; F.J. Dega, Boise, Idaho; W.R. Eider, Yakima, Wash.; H.W. Emori, Medford, Oreg.; R.S. Fife, Indianapolis; C.M. Franklin, Willow Grove, Pa.; A.L. Goldman, Milwaukee; T.A. Goodman, Boston; M. Greenwald, Rancho Mirage, Calif.; B. Gruber, Stony Brook, N.Y.; B. Haraoui, Montreal; R. Harris, Whittier, Calif.; S. Harris, Las Vegas; S.S. Hartman, Decatur, Ga.; R.F. Hynd, Oklahoma City; J.L. Kaine, Sarasota, Fla.; A.J. Kivitz, Altoona, Pa.; M.R. Liebling, Torrance, Calif.; C.L. Ludivico, Bethlehem, Pa.; H.W. Marker, Memphis, Tenn.; S.D. Mathews, Daytona Beach, Fla.; R. McKendry, Ottawa, Ont.; P. Mease, Seattle; M. Miller, Portland, Oreg.; E. Morris, Pikesville, Md.; R.A. Neiman, Kirkland, Wash.; K.S. O'Rourke, Winston-Salem, N.C.; P.W. Pratt, Dothan, Ala.; P.J. Riccardi, Syracuse, N.Y.; C. Ritchlin, Rochester, N.Y.; E. Ruderman, Chicago; J. Rutstein, San Antonio, Tex.; B. Samuels, Dover, N.H.; Y. Sherrer, Fort Lauderdale, Fla.; B. Smith, Philadelphia; T. Spiegel, Santa Barbara, Calif.; S.H. Stern, Louisville, Ky.; J. Taborn, Kalamazoo, Mich.; G. Thomson, Winnipeg, Man.; R.G. Trapp, Springfield, Ill.; D.J. Wallace, Los Angeles; N. Wei, Frederick, Md.; G. Williams, La Jolla, Calif.; C. Wise, Richmond, Va.; and D. Wofsy, San Francisco: *Contributors* — M. Dalinka, Philadelphia; P. Ory, Seattle; J.D. Rubenstein, North York, Ont.; D. Salonen, Toronto; J.T. Sharp, Bainbridge Island, Wash.; B.N. Weissman, Boston; A. Barattelle and S. Einstein, Newtown, Pa.; and G. Spencer-Green, L. Garrison, D.J. Burge, P. Grimmer, T. Newcomb, J. Whitmore, and M.L. Lange, Seattle.

## REFERENCES

1. Saxne T, Palladino MA Jr, Heinegard D, Talal N, Wollheim FA. Detection of tumor necrosis factor  $\alpha$  but not tumor necrosis factor  $\beta$  in rheumatoid arthritis synovial fluid and serum. *Arthritis Rheum* 1988;31:1041-5.
2. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000;342:763-9.
3. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-7.
4. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253-9.
5. Moreland L, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
6. Braunstein J, Allendorf J, Reister M, et al. How are soluble forms of ICAM-1 (sCD54) and LFA-3 (sCD58) generated? *Immunobiology* 1994; 191:193. abstract.
7. Paleolog EM, Hunt M, Elliott MJ, Feldmann M, Maini RN, Woody JN. Deactivation of vascular endothelium by monoclonal anti-tumor necrosis factor  $\alpha$  antibody in rheumatoid arthritis. *Arthritis Rheum* 1996;39:1082-91.
8. Tak PP, Taylor PC, Breedveld FC, et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor  $\alpha$  monoclonal antibody treatment in patients with rheumatoid arthritis. *Arthritis Rheum* 1996;39:1077-81.
9. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986;29: 822-31.

10. Weinblatt ME, Trentham DE, Fraser PA, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988;31:167-75.
11. Lopez-Mendez A, Daniel WW, Reading JC, Ward JR, Alarcon GS. Radiographic assessment of disease progression in rheumatoid arthritis patients enrolled in the cooperative systematic studies of the rheumatic diseases program randomized clinical trial of methotrexate, auranofin, or a combination of the two. *Arthritis Rheum* 1993;36:1364-9.
12. Weinblatt ME, Polisson R, Blotner SD, et al. The effects of drug therapy on radiographic progression of rheumatoid arthritis: results of a 36-week randomized trial comparing methotrexate and auranofin. *Arthritis Rheum* 1993;36:613-9. [Erratum, *Arthritis Rheum* 1993;36:1028.]
13. Jeurissen ME, Boerbooms AM, van de Putte LB, et al. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis: a forty-eight-week randomized, double-blind trial. *Arthritis Rheum* 1991;34:961-72.
14. Pincus T, Callahan LE. Remodeling the pyramid or remodeling the paradigms concerning rheumatoid arthritis — lessons from Hodgkin's disease and coronary artery disease. *J Rheumatol* 1990;17:1582-5.
15. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998;41:1571-82.
16. Rich E, Moreland LW, Alarcon GS. Paucity of radiographic progression in rheumatoid arthritis treated with methotrexate as the first disease modifying antirheumatic drug. *J Rheumatol* 1999;26:259-61.
17. Sany J, Anaya JM, Lussiez V, Couret M, Combe B, Daures J-P. Treatment of rheumatoid arthritis with methotrexate: a prospective open long-term study of 191 cases. *J Rheumatol* 1991;18:1323-7.
18. Weinblatt ME, Weissman BN, Holdsworth DE, et al. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis: 84-month update. *Arthritis Rheum* 1992;35:129-37.
19. McKendry RJR, Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. *J Rheumatol* 1993;20:1850-6.
20. Madhok R, Capell HA. Outstanding issues in use of disease-modifying agents in rheumatoid arthritis. *Lancet* 1999;353:257-8.
21. Kim JM, Weisman MH. When does rheumatoid arthritis begin and why do we need to know? *Arthritis Rheum* 2000;43:473-84.
22. Felson DT, Anderson JJ, Boers M, et al. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
23. Felson DT, Anderson JJ, Lange MLM, Wells G, LaValley MP. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum* 1998;41:1564-70.
24. Finck BK, Weissman BNW, Rubenstein JD, Salonen D, Einstein SG, Lange M. 100 Micron digitization resolution is optimal for x-rays for a large multicenter trial in rheumatoid arthritis (RA). *Arthritis Rheum* 1997;40:Suppl:S288. abstract.
25. Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis: correlation of radiologic, clinical and laboratory abnormalities. *Arthritis Rheum* 1971;14:706-20.
26. van der Heijde DMFM, van Leeuwen MA, van Riel PLCM, et al. Bi-annual radiographic assessments of hands and feet in the three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1991;35:26-34.
27. Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum* 1985;28:1326-35.
28. Plant MJ, Saklatvala J, Borg AA, Jones PW, Dawes PT. Measurement and prediction of radiological progression in early rheumatoid arthritis. *J Rheumatol* 1994;21:1808-13.
29. Parker SL, Tong T, Bolden S, Wingo P. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5-27. [Erratum, *CA Cancer J Clin* 1997;47:68.]
30. Wikske KR, Healey LA. Remodeling the pyramid — a concept whose time has come. *J Rheumatol* 1989;16:565-7.
31. Bensen WG, Bensen W, Adachi JD, Tugwell PX. Remodelling the pyramid: the therapeutic target of rheumatoid arthritis. *J Rheumatol* 1990;17:987-9.
32. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis: towards development of a decision support system. *J Rheumatol* 1997;24:20-7.

ELECTRONIC ACCESS TO THE *JOURNAL'S* CUMULATIVE INDEX

At the *Journal's* site on the World Wide Web (<http://www.nejm.org>) you can search an index of all articles published since January 1990. You can search by author, subject, title, type of article, or date. The results will include the citations for the articles plus links to the abstracts of articles published since 1993. Single articles and past issues of the *Journal* can also be ordered for a fee through the Internet (<http://www.nejm.org/customer/>).

**CORRECTION**

**A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis**

A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis . On page 1586 of the print version of this article, in the Abstract, the Conclusions should have referred to "*subcutaneous* etanercept," not "*intravenous* etanercept," as printed. Also, on page 1588, in Table 1, the total Sharp score in the 25-mg group should have read, " $12.4 \pm 15.8$ ," not " $2.4 \pm 15.8$ ," as printed. We regret the errors.

**CORRECTION**

**A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis**

A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis . On page 1592, on lines 15 and 16 of the Appendix, it should have been stated that M. Miller is from Portland, *Maine*, not Portland, *Oregon*, as printed.