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A TRIAL OF ETANERCEPT, A RECOMBINANT TUMOR NECROSIS FACTOR RECEPTOR:Fc FUSION PROTEIN, IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE

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ABSTRACT

Background Patients treated with methotrexate for rheumatoid arthritis often improve but continue to have active disease. This study was undertaken to determine whether the addition of etanercept, a soluble tumor necrosis factor receptor (p75):Fc fusion protein (TNFR:Fc), to methotrexate therapy would provide additional benefit to patients who had persistent rheumatoid arthritis despite receiving methotrexate.

Methods In a 24-week, double-blind trial, we randomly assigned 89 patients with persistently active rheumatoid arthritis despite at least 6 months of methotrexate therapy at a stable dose of 15 to 25 mg per week (or as low as 10 mg per week for patients unable to tolerate higher doses) to receive either etanercept (25 mg) or placebo subcutaneously twice weekly while continuing to receive methotrexate. The primary measure of clinical response was the American College of Rheumatology criteria for a 20 percent improvement in measures of disease activity (ACR 20) at 24 weeks.

Results The addition of etanercept to methotrexate therapy resulted in rapid and sustained improvement. At 24 weeks, 71 percent of the patients receiving etanercept plus methotrexate and 27 percent of those receiving placebo plus methotrexate met the ACR 20 criteria ($P < 0.001$); 39 percent of the patients receiving etanercept plus methotrexate and 3 percent of those receiving placebo plus methotrexate met the ACR 50 criteria (for a 50 percent improvement) ($P < 0.001$). Patients receiving etanercept plus methotrexate had significantly better outcomes according to all measures of disease activity. The only adverse events associated with etanercept were mild injection-site reactions, and no patient withdrew from the study because of adverse events associated with etanercept.

Conclusions In patients with persistently active rheumatoid arthritis, the combination of etanercept and methotrexate was safe and well tolerated and provided significantly greater clinical benefit than methotrexate alone. (N Engl J Med 1999;340:253-9.)

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AMONG the disease-modifying drugs used to treat rheumatoid arthritis, methotrexate is increasingly regarded as the agent of first choice, because of its early onset of action and superior efficacy and tolerability.¹ Clinical benefit with methotrexate may be seen as early as three weeks after initiating treatment,² and the maximal improvement is generally achieved by six months.³ Although methotrexate can have toxic effects, making careful monitoring of patients necessary, most rheumatologists believe the benefits outweigh the risks. Methotrexate can diminish the activity of rheumatoid arthritis, but many patients have persistent disease even when treated with methotrexate. When this occurs, rheumatologists usually add another disease-modifying drug.

Tumor necrosis factor (TNF) is a proinflammatory cytokine that has a complex role in the pathogenesis of rheumatoid arthritis.⁴⁻¹¹ Etanercept (Enbrel, Immunex, Seattle), a genetically engineered fusion protein consisting of two identical chains of the recombinant human TNF-receptor p75 monomer fused with the Fc domain of human IgG1, binds and inactivates TNF. Two previous randomized, double-blind, placebo-controlled trials showed that etanercept treatment yielded significant clinical benefit, with minimal toxicity, in patients with rheumatoid arthritis who had inadequate responses to other disease-modifying drugs.^{12,13} We undertook the present study to determine whether etanercept combined

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with methotrexate could further diminish disease activity in patients who still had active rheumatoid arthritis despite long-term methotrexate treatment.

METHODS

Patients

Eligible patients were at least 18 years of age and fulfilled the 1987 criteria for rheumatoid arthritis of the American Rheumatism Association¹⁴; were in functional class I, II, or III according to the revised criteria of the American College of Rheumatology (ACR)¹⁵; and had active disease, as manifested by at least six joints that were swollen and six that were tender at the time of enrollment. Before receiving the study drugs, all the patients had been taking methotrexate for at least six months, and at a stable dose of 15 to 25 mg per week for the last four weeks (weekly doses as low as 10 mg were acceptable for patients who could not tolerate higher doses). All patients received folic acid or folinic acid to mitigate the toxic effects of methotrexate.

In addition, eligible patients had platelet counts of at least 125,000 per cubic millimeter, serum creatinine levels of no more than 2 mg per deciliter (177 μ mol per liter), white-cell counts of at least 3500 per cubic millimeter, serum aspartate and alanine aminotransferase levels no more than 1.2 times the laboratory's upper limit of normal, hemoglobin levels of at least 8.5 g per deciliter, stable hemoglobin levels for at least six months in patients with levels of less than 10 g per deciliter, and negative serologic results on tests for hepatitis B surface antigen and hepatitis C antibody.

The study patients discontinued therapy with sulfasalazine and hydroxychloroquine at least two weeks before starting to take the study drug and disease-modifying antirheumatic drugs other than methotrexate at least four weeks before. Patients who were receiving nonsteroidal antiinflammatory drugs, prednisone (at 10 mg daily or less), or both were eligible if the doses had been stable for at least four weeks before the study period and continued to be stable during the study period.

Protocol

The protocol was approved by the human research committee at each study site, and all patients gave written informed consent before undergoing a screening evaluation to determine their eligibility. Clinical and laboratory assessments were conducted at screening and on study days 1, 8, and 15; during weeks 4, 8, 12, 16, 20, and 24; and 15 and 30 days after the last dose of study drug for patients who withdrew from the study. The measurements consisted of a physical examination, measures of disease activity, and laboratory tests (hematologic values, serum chemical values, and urinalysis with microscopical evaluation). In addition, serum was obtained for testing for autoantibodies (antibodies to double-stranded DNA, antinuclear antibodies, and IgG and IgM anticardiolipin antibodies) at screening, on day 1, at the end-of-study evaluation (week 24 or on discontinuation of the study drug), and at the 30-day follow-up (if the patient withdrew prematurely). Serum for testing for antibodies to etanercept was collected on day 1 and at the end-of-study evaluation.

The measures of disease activity consisted of evaluations of 71 joints for tenderness and 68 joints for swelling, physician's and patient's global assessment of disease status, patient's assessment of pain according to a visual-analogue scale,¹⁶ patient's assessment of disability as indicated by responses to the Health Assessment Questionnaire,¹⁷ the erythrocyte sedimentation rate (as measured by the Westergren method), and the C-reactive protein level.¹⁶

Adverse events and changes in laboratory values were graded on a scale derived from the Common Toxicity Criteria of the National Cancer Institute. The reasons for withdrawal were prespecified as lack of efficacy, pregnancy, withdrawal of consent, non-compliance, a decision by an investigator, serious systemic toxic effects that were unresponsive to treatment or that recurred on

rechallenge, serious infection or hypotension suggestive of impending sepsis syndrome, and interruption of scheduled therapy for more than two weeks.

Treatment

A 2:1 randomization scheme was used to increase exposure to the combination of etanercept and methotrexate. Patients were assigned to receive etanercept plus methotrexate or to receive placebo plus methotrexate. Etanercept was supplied in single-dose vials containing a lyophilized powder consisting of 25 mg of etanercept, 40 mg of mannitol, 10 mg of sucrose, and 1.2 mg of tromethamine. The placebo had the same ingredients except for the omission of etanercept. The study drug was reconstituted with 1.0 ml of bacteriostatic water and injected subcutaneously twice weekly for 24 weeks. The patients received stable doses of oral or subcutaneous methotrexate.

Testing for Antibodies

Testing for antibodies to etanercept has been described previously.¹² Rheumatoid factor was measured by nephelometry (Beckman, Fullerton, Calif.). Antinuclear antibodies were measured by indirect fluorescent antibody with HEp-2 cell substrate (Kallestad, Chaska, Minn.); a titer of 1:160 or higher was considered positive. Antibodies to double-stranded DNA were measured with use of a ¹²⁵I radiobinding assay kit (Dupont Medical Products, Boston); a value of 3.6 IU per milliliter or higher was considered positive. IgG and IgM anticardiolipin antibodies were detected by indirect enzyme-linked immunosorbent assay (Readds Medical Products, Westminster, Colo.); values of 23 IgG phospholipid units or higher and 11 IgM phospholipid units or higher were considered positive.

Statistical Analysis

The primary end point with respect to efficacy was the proportion of patients meeting the ACR preliminary criteria for improvement in rheumatoid arthritis (ACR 20) at 24 weeks.¹⁶ Patients who met these criteria had a reduction of at least 20 percent in the number of both swollen and tender joints and an improvement of at least 20 percent in at least three of the following: the patient's assessment of pain, the physician's global assessment of disease status, the patient's global assessment of disease status, the patient's assessment of disability (a domain of the Health Assessment Questionnaire¹⁷), and values for acute-phase reactants (either the erythrocyte sedimentation rate or the level of C-reactive protein).¹⁶ Safety was evaluated according to the frequency of adverse events, laboratory abnormalities, and antibody formation.

The other efficacy end points were the proportion of patients who reached the ACR 20 at 12 weeks and the proportions who met the ACR 50 and ACR 70 (defined in the same manner as ACR 20, but with improvements of 50 percent and 70 percent, respectively, in the various scores) at 12 and 24 weeks. Individual measures of disease activity, such as numbers of swollen and tender joints and physician's assessment, were evaluated at 12 and 24 weeks.

The power of the study with respect to the primary efficacy end point (based on the ACR 20) was estimated to be approximately 80 percent, on the assumption that the response rates would be 25 percent in the placebo-plus-methotrexate group and 55 percent in the etanercept-plus-methotrexate group. At the planned sample size of 75 patients, if the underlying rate of adverse events was 5 percent, the probability of observing at least one adverse event was 92 percent in the etanercept-plus-methotrexate group (50 subjects) and 72 percent in the placebo-plus-methotrexate group (25 subjects).

Response rates measured by the ACR 20 and ACR 50 were compared with use of the chi-square test. Fisher's exact test (two-tailed) was used for response rates according to the ACR 70 and for data on safety. With regard to the ACR response measures,

patients who withdrew from the study were considered not to have had a response at all points after withdrawal, irrespective of the clinical response. For individual measures (tender and swollen joints and global assessments), the last observation was used in analysis if the patient withdrew. Patients who received intraarticular injections of corticosteroids during the study were counted as having or not having a response according to their overall evaluation, but the joint or joints injected were counted as tender and swollen for the remainder of the study. Patients who received increased doses of oral corticosteroids were considered not to have had a response at all time points after the increase.

RESULTS

The base-line demographic and clinical characteristics of the patients are summarized in Table 1. Fourteen men and 75 women were enrolled. The mean age was 50 years (range, 26 to 71), and the mean duration of rheumatoid arthritis was 13 years. The treatment groups were generally well matched. The mean weekly dose of methotrexate per patient was 18 mg in the placebo-plus-methotrexate group and 19 mg in the etanercept-plus-methotrexate group. Despite long-term methotrexate therapy, the patients had a median of 28 tender and 18 swollen joints at base line.

Of the 59 patients randomly assigned to receive etanercept plus methotrexate, 57 (97 percent) completed the 24-week study and 2 withdrew because of adverse events unrelated to etanercept (abdominal pain due to an incisional hernia from prior surgery in 1 patient, and traumatic fractures of the shoulder and calcaneus in the other). Of the 30 patients randomly assigned to receive placebo plus methotrexate, 24 (80 percent) completed the study, 4 withdrew because of lack of efficacy, 1 had a myocardial infarction, and 1 was lost to follow-up. All the patients received at least one dose of study drug and could be included in the evaluation of the safety and efficacy of the treatment. The mean number of doses of study drug received was 47 in the etanercept-plus-methotrexate group and 43 in the placebo-plus-methotrexate group.

Efficacy

The etanercept-plus-methotrexate group had significantly superior outcomes for all end points according to the ACR response criteria (Table 2). The primary efficacy end point, the proportion of patients who reached the ACR 20 at 24 weeks, was achieved in 71 percent in the etanercept-plus-methotrexate group, as compared with 27 percent in the placebo-plus-methotrexate group ($P < 0.001$). The response in the etanercept-plus-methotrexate group was rapid and sustained; at all evaluations, beginning at week 1, a significantly greater proportion of patients in the etanercept-plus-methotrexate group achieved the ACR 20. Significantly greater proportions of patients in the etanercept-plus-methotrexate group achieved the ACR 50 at one month and at each subsequent evaluation and reached the ACR 70

TABLE 1. BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC*	PLACEBO PLUS METHOTREXATE (N=30)	ETANERCEPT PLUS METHOTREXATE (N=59)
Mean age (yr)	53	48
Female sex (%)	73	90
White race (%)	83	76
Mean duration of disease (yr)	13	13
Positive test for rheumatoid factor (%)	90	84
Mean no. of prior DMARDs	2.8	2.7
Receiving DMARDs other than methotrexate at screening (%)	20	8
Receiving NSAIDs (%)	80	75
Receiving corticosteroids (%)	70	53
Mean duration of methotrexate therapy (mo)	35	58
Methotrexate dose (%)		
12.5 mg/wk	3	3
15–19 mg/wk	60	58
20–25 mg/wk	36	40

*DMARDs denotes disease-modifying antirheumatic drugs, and NSAIDs nonsteroidal antiinflammatory drugs.

TABLE 2. PATIENTS WITH 20, 50, AND 70 PERCENT IMPROVEMENT ACCORDING TO THE CRITERIA OF THE AMERICAN COLLEGE OF RHEUMATOLOGY (ACR).*

AMOUNT OF IMPROVEMENT AND DURATION OF TREATMENT	PLACEBO PLUS METHOTREXATE (N=30)	ETANERCEPT PLUS METHOTREXATE (N=59)	P VALUE
20% (ACR 20)			
12 wk	33	66	0.003†
24 wk	27	71	<0.001†
50% (ACR 50)			
12 wk	0	42	<0.001†
24 wk	3	39	<0.001†
70% (ACR 70)			
12 wk	0	15	0.03‡
24 wk	0	15	0.03‡

*Patients who withdrew from the study were considered not to have had a response at all points after withdrawal, irrespective of the actual clinical response.

†The P value was calculated by the chi-square test.

‡The P value was calculated by Fisher's exact test.

at three months and at each subsequent evaluation. At base line the patients had a median of 28 tender joints and 18 swollen joints. At 24 weeks the median number of tender joints was 7 in the etanercept-plus-methotrexate group and 17 in the placebo-plus-methotrexate group (an improvement from base line of 75 percent and 39 percent, respectively); the median number of swollen joints was 6 in the etaner-

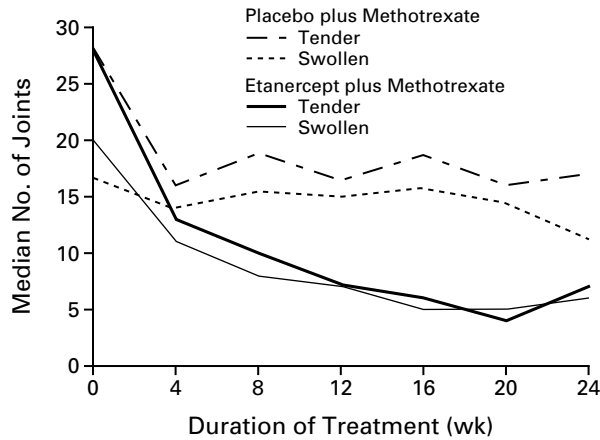


Figure 1. Median Number of Tender and Swollen Joints during the Study.

cept-plus-methotrexate group and 11 in the placebo-plus-methotrexate group (an improvement from base line of 78 percent and 33 percent, respectively) (Fig. 1). In addition, patients receiving etanercept plus methotrexate had significantly greater improvement in all other individual measures of disease activity at 12 and 24 weeks (Table 3).

The median disability-index score from the Health Assessment Questionnaire improved from 1.5 to 0.8 in the etanercept-plus-methotrexate group, an improvement of 47 percent. The score in the placebo-plus-methotrexate group did not change significantly (the median base-line value was 1.5, and the end-of-study value was 1.1, an improvement of 27 percent).

Acute-phase reactants also improved significantly more in the patients in the etanercept-plus-metho-

TABLE 3. MEDIAN VALUES FOR MEASURES OF DISEASE AND QUALITY OF LIFE AT BASE LINE AND AT 12 AND 24 WEEKS.

MEASURE AND TREATMENT*	At BASE LINE	At 12 WK	P VALUE†	At 24 WK	P VALUE†
No. of tender joints‡					
Placebo	28	17	<0.001	17	<0.001
Etanercept	28	7		7	
No. of swollen joints‡					
Placebo	17	15	<0.001	11	<0.001
Etanercept	20	7		6	
Physician's assessment§					
Placebo	6.5	5.0	0.003	4.0	0.003
Etanercept	6.0	2.0		2.0	
Patient's assessment§					
Placebo	6.0	4.5	0.009	4.0	0.008
Etanercept	6.0	2.0		2.0	
Pain (on visual-analogue scale)¶					
Placebo	5.6	4.0	0.004	4.4	0.001
Etanercept	5.0	2.0		1.8	
Morning stiffness (min)					
Placebo	120	60	<0.001	75	<0.001
Etanercept	90	10		10	
Disability index					
Placebo	1.5	1.1	0.006	1.1	<0.001
Etanercept	1.5	0.9		0.8	
Erythrocyte sedimentation rate (mm/hr)**					
Placebo	36	38	0.004	30	0.004
Etanercept	25	12		15	
C-reactive protein (mg/dl)††					
Placebo	2.6	1.8	<0.001	1.6	<0.001
Etanercept	2.2	0.3		0.5	

*All patients received methotrexate in addition to placebo or etanercept.

†P values were calculated by analysis of variance, except for P values for morning stiffness and C-reactive protein, which were calculated by the Kruskal-Wallis test.

‡The tender-joint count evaluated 71 joints; the swollen-joint count evaluated 68, omitting the hips and cervical spine.

§On this scale, 0 indicates no symptoms and 10 severe symptoms.

¶On this scale, 0 indicates no pain and 10 severe pain.

||The disability index is a section of the Health Assessment Questionnaire; on this scale, 0 is best and 3 is worst.

**The normal ranges are 1 to 13 mm per hour for men and 1 to 30 mm per hour for women. The base-line value was missing for one patient in the placebo-plus-methotrexate group.

††The normal range is 0 to 0.79 mg per deciliter.

trexate group. Among patients with abnormal erythrocyte sedimentation rates at base line, 62 percent of those treated with etanercept plus methotrexate and 30 percent of those treated with placebo plus methotrexate had normal erythrocyte sedimentation rates at their last visits. Among patients with abnormal C-reactive protein levels at base line, 44 percent of those treated with etanercept plus methotrexate and 13 percent of those treated with placebo plus methotrexate had normal values at their last visits.

Intraarticular corticosteroids and increasing doses of oral corticosteroids were used in a small number of patients and might have affected the study results. However, only one of the four patients who received an increased dose of oral corticosteroids (a patient receiving placebo plus methotrexate) would have been classified as having a response on the basis of observation. Only one of the four patients who received intraarticular corticosteroids (a patient receiving etanercept plus methotrexate) would have been classified as having a response on the basis of observation. Reclassification of these two patients did not alter the conclusion regarding the primary end point (P=0.001).

The combination of etanercept and methotrexate was superior to the combination of placebo and methotrexate regardless of the dose of methotrexate, the duration of methotrexate therapy, or background use of corticosteroids or nonsteroidal antiinflammatory drugs.

Safety

Etanercept was well tolerated (Table 4). Reactions at the injection site were the only events that occurred significantly more often in the etanercept-plus-methotrexate group (42 percent vs. 7 percent, P<0.001). All injection-site reactions were mild (erythema with or without itching, pain, or swelling), most resolved without treatment (median duration, three days), and none required suspension of the study drug. Most patients had five or fewer injection-site reactions during the 24-week trial. The difference between the treatment groups in the percentage of patients with injection-site reactions does not appear to have affected the outcome of the study, because the response rates of patients treated with etanercept who had injection-site reactions were no different from those of patients treated with etanercept who did not have reactions (72 percent and 71 percent, respectively, met the ACR 20 criteria at 24 weeks). Infection was the most common adverse event overall, but there were no significant intergroup differences in the incidence or types of infection. Approximately one third of the infections in both groups were upper respiratory infections (colds) or sinusitis.

No patients died during the study or within 30 days after receiving the last dose of study drug. Two

TABLE 4. ADVERSE EVENTS OBSERVED IN AT LEAST 5 PERCENT OF PATIENTS.

ADVERSE EVENT	PLACEBO PLUS METHOTREXATE (N=30)	ETANERCEPT PLUS METHOTREXATE (N=59)	P VALUE*
	% of patients		
Infection	63	51	0.37
Injection-site reaction	7	42	<0.001
Headache	17	20	0.78
Rhinitis	3	14	0.26
Diarrhea	20	12	0.35
Nausea	23	10	0.12
Dizziness	13	10	0.73
Asthenia	3	8	0.66
Hypertension	0	7	0.30
Abdominal pain	3	5	1.00
Dyspepsia	3	5	1.00
Vomiting	0	5	0.55
Increased cough	10	3	0.33
Trauma	7	3	0.60
Mouth ulcer	7	3	0.60
Pharyngitis	7	2	0.26
Bone pain	7	0	0.11

*P values were calculated by Fisher's exact test.

patients in each treatment group were hospitalized during the study. In the placebo-plus-methotrexate group, one patient had a myocardial infarction and discontinued the study, and one patient was hospitalized for gastrointestinal bleeding due to a gastric ulcer. In the etanercept-plus-methotrexate group, one patient withdrew from the study before undergoing surgery to relieve abdominal pain (due to an incisional hernia from prior surgery) and intertrigo (due to a large abdominal panniculus). After surgery the patient was readmitted to the hospital twice because of infection at the incision site. Another patient who was receiving etanercept and methotrexate was admitted to the hospital for idiopathic pancreatitis that was treated symptomatically and resolved spontaneously, without interruption of etanercept-and-methotrexate therapy.

Most laboratory abnormalities in both groups were mild; more serious laboratory abnormalities included lymphocytopenia (fewer than 500 cells per cubic millimeter) in two patients from each group, hyponatremia (116 to 124 mmol of sodium per liter) in one patient receiving placebo plus methotrexate, and anemia (less than 6.5 g of hemoglobin per deciliter) secondary to gastrointestinal bleeding in another patient receiving placebo plus methotrexate. No other serious laboratory abnormalities were noted in the etanercept-plus-methotrexate group.

Non-neutralizing antibodies to etanercept were detected in only one patient during the study, at the

24-week evaluation of a patient in the etanercept-plus-methotrexate group. This patient had a rapid and sustained response to therapy, with an 84 percent reduction in the number of tender joints and a 100 percent reduction in the number of swollen joints by week 24. This patient had no injection-site reactions or other adverse events.

Before receiving the study drugs, 1 of the 30 patients assigned to placebo plus methotrexate (3 percent) and 4 of the 59 patients assigned to etanercept plus methotrexate (7 percent) had positive results on assays for antibodies to double-stranded DNA. At 24 weeks or at the last visit before discontinuation, one additional patient assigned to placebo plus methotrexate and four additional patients assigned to etanercept plus methotrexate had positive tests for antibodies to double-stranded DNA. Of the patients who had positive tests for antibodies to double-stranded DNA at any time, half in each group had negative results for antinuclear antibodies at the time of the positive results for anti-double-stranded DNA antibodies, and only one patient in each group had a positive antinuclear antibody titer at the end of the study. With regard to the levels of antinuclear antibodies and anticardiolipin antibodies, a small number of patients in each group shifted from positive to negative or from negative to positive test results. There were no significant differences between the groups in the proportions of patients undergoing these shifts. Moreover, no patients had new connective-tissue disorders, thrombotic events, or thrombocytopenia.

DISCUSSION

Over the past decade, methotrexate has emerged as the main treatment for rheumatoid arthritis. However, in many patients methotrexate alone does not result in satisfactory control of the disease, and therefore methotrexate in combination with other drugs has been tested. After six months of therapy, 48 percent of patients receiving cyclosporine plus methotrexate and 16 percent of those receiving placebo plus methotrexate met the ACR 20 criteria.¹⁸ Also among these patients, 1 percent of those receiving the combination and none receiving only methotrexate met the ACR 70 criteria. The ACR 70 criteria are important because they have been proposed by the Food and Drug Administration (FDA) as the preliminary criteria for a major clinical response.¹⁹ According to modified Paulus response criteria, triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine was superior to methotrexate alone or the combination of sulfasalazine and hydroxychloroquine.²⁰ However, even with these combinations, patients continue to have active rheumatoid arthritis.

Two previous trials showed that etanercept was effective against rheumatoid arthritis and had no seri-

ous toxic effects. In one trial, 75 percent of patients receiving 16 mg of etanercept per square meter of body-surface area twice weekly had at least an ACR 20 response, as compared with only 14 percent of those receiving placebo.¹² A fixed dose of 25 mg of etanercept was used in a second trial, and 62 percent of the etanercept-treated patients had at least an ACR 20 response, as compared with only 23 percent of the patients receiving placebo.¹³

Because of the prominent role of methotrexate in the treatment of rheumatoid arthritis and the efficacy of etanercept alone, it is important to study the combination of the two. This study was designed to determine whether the combination was safe and whether additional benefit could be achieved in patients who had active disease despite therapeutic doses of methotrexate.

In this six-month study in patients who had persistent disease activity despite methotrexate therapy, the addition of etanercept provided additional benefit without potentiating the toxic effects of methotrexate or inducing dose-limiting toxic effects of its own. At 24 weeks, the ACR 20 criteria were met in 71 percent of patients receiving etanercept and methotrexate and 27 percent of those receiving placebo and methotrexate. The ACR 50 criteria were met in 39 percent and 3 percent of the patients in the two groups, respectively. The ACR 70 criteria (proposed by the FDA as the criteria for a major clinical response) were met by 15 percent of the etanercept-plus-methotrexate group and none of the placebo-plus-methotrexate group.

With the exception of injection-site reactions in the etanercept-plus-methotrexate group, no significant differences were found between the treatment groups in the incidence or types of adverse events reported, including those characteristic of methotrexate therapy. Moreover, the adverse events seen in this trial were similar to those seen with methotrexate alone in patients with rheumatoid arthritis.^{21,22} Specifically, gastrointestinal side effects, hematologic effects, and headaches were not increased by the addition of etanercept.

The combination of methotrexate plus etanercept is a novel therapy for rheumatoid arthritis. A long-term study²³ has demonstrated the efficacy and safety of etanercept therapy continued for more than 18 months. We are continuing to follow the patients in this study in order to evaluate the safety and efficacy of the etanercept-plus-methotrexate combination. Another trial is currently comparing etanercept with methotrexate, and on the basis of these results, an additional study comparing etanercept with etanercept plus methotrexate would be valuable. The combination of etanercept and methotrexate offers a promising new alternative for patients who have persistently active rheumatoid arthritis despite treatment with methotrexate.

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REFERENCES

- Lipsky PE. Rheumatoid arthritis. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., eds. Harrison's principles of internal medicine. 14th ed. New York: McGraw-Hill, 1994:1880-8.
- Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985;312:818-22.
- 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.
- Thornton SC, Por SB, Penny R, Richter M, Shelley L, Breit SN. Identification of the major fibroblast growth factors released spontaneously in inflammatory arthritis as platelet derived growth factor and tumor necrosis factor-alpha. *Clin Exp Immunol* 1991;86:79-86.
- Dayer JM, Beutler B, Cerami A. Cachectin/tumor necrosis factor stimulates collagenase and prostaglandin E₂ production by human synovial cells and dermal fibroblasts. *J Exp Med* 1985;162:2163-8.
- Bertolini DR, Nedwin GE, Bringman TS, Smith DD, Mundy GR. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986;319:516-8.
- Saklatvala J. Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature* 1986;322:547-9.
- von Asmuth EJU, van der Linden CJ, Leeuwenberg JFM, Buurman WA. Involvement of the CD11b/CD18 integrin, but not of the endothelial cell adhesion molecules ELAM-1 and ICAM-1 in tumor necrosis factor-alpha-induced neutrophil toxicity. *J Immunol* 1991;147:3869-75.
- Beckham JC, Caldwell DS, Peterson BL, et al. Disease severity in rheumatoid arthritis: relationships of plasma tumor necrosis factor-alpha, soluble interleukin 2-receptor, soluble CD4/CD8 ratio, neopterin, and fibrin D-dimer to traditional severity and functional measures. *J Clin Immunol* 1992;12:353-61.
- Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF α antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 1989;2:244-7.
- Saez-Llorens X, Jafari HS, Olsen KD, Nariuchi H, Hansen EJ, McCracken GH Jr. Induction of suppurative arthritis in rabbits by Haemophilus endotoxin, tumor necrosis factor- α , and interleukin-1 β . *J Infect Dis* 1991;163:1267-72.
- 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.
- Moreland LW, Schiff MH, Baumgartner SW, et al. Phase III trial of DMARD failing rheumatoid arthritis patients with TNF receptor p75 Fc fusion protein (TNFR:Fc, ENBREL). *J Investig Med* 1998;46:228A. abstract.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992;35:498-502.
- Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.
- Fries JE, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, Disability and Pain Scale. *J Rheumatol* 1982;9:789-93.
- Tugwell P, Pincus T, Yocum D, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995;333:137-41.
- Guidance for industry: clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA): draft guidance. Washington, D.C.: Food and Drug Administration, March 1998. (See <http://www.fda.gov/cder/guidance/index.htm>.) (Also available from NAPS [document no. 05498 for 52 pages], c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513.)
- O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287-91.
- Alarcón GS. Methotrexate: its use for the treatment of rheumatoid arthritis and other rheumatic disorders. In: Koopman WJ, ed. *Arthritis and allied conditions: a textbook of rheumatology*. 13th ed. Vol. 1. Baltimore: Williams & Wilkins, 1997:679-98.
- Weinblatt ME. Methotrexate. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. *Textbook of rheumatology*. 5th ed. Vol. 1. Philadelphia: W.B. Saunders, 1997:771-86.
- Moreland LW, Baumgartner SW, Tindall EA, et al. Longterm treatment of DMARD failing rheumatoid arthritis patients with TNF receptor p75 Fc fusion protein (TNFR:Fc, ENBREL). *J Investig Med* 1998;46:229A. abstract.