

The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 346

MAY 2, 2002

NUMBER 18



TREATMENT OF ANKYLOSING SPONDYLITIS BY INHIBITION OF TUMOR NECROSIS FACTOR α

JENNIFER D. GORMAN, M.D., KENNETH E. SACK, M.D., AND JOHN C. DAVIS, JR., M.D., M.P.H.

ABSTRACT

Background There are few effective treatments for ankylosing spondylitis, which causes substantial morbidity. Because of the central role of tumor necrosis factor α in the spondyloarthritides, we performed a randomized, double-blind, placebo-controlled trial of etanercept, a recombinant human tumor necrosis factor receptor (p75):Fc fusion protein, in patients with ankylosing spondylitis.

Methods Forty patients with active, inflammatory ankylosing spondylitis were randomly assigned to receive twice-weekly subcutaneous injections of etanercept (25 mg) or placebo for four months. The primary end point was a composite of improvements in measures of morning stiffness, spinal pain, functioning, the patient's global assessment of disease activity, and joint swelling. Patients were allowed to continue taking nonsteroidal antiinflammatory drugs, oral corticosteroids (≤ 10 mg per day), and disease-modifying antirheumatic drugs at stable doses during the trial.

Results Treatment with etanercept resulted in significant and sustained improvement. At four months, 80 percent of the patients in the etanercept group had a treatment response, as compared with 30 percent of those in the placebo group ($P=0.004$). Improvements over base-line values for various measures of disease activity, including morning stiffness, spinal pain, functioning, quality of life, enthesitis, chest expansion, erythrocyte sedimentation rate, and C-reactive protein, were significantly greater in the etanercept group. Longitudinal analysis showed that the treatment response was rapid and did not diminish over time. Etanercept was well tolerated, with no significant differences in rates of adverse events between the two groups.

Conclusions Treatment with etanercept for four months resulted in rapid, significant, and sustained improvement in patients with ankylosing spondylitis. (N Engl J Med 2002;346:1349-56.)

Copyright © 2002 Massachusetts Medical Society.

A NKYLOSING spondylitis is a chronic inflammatory disease characterized by axial skeletal ankylosis, inflammation at the insertions of tendons (enthesitis), and occasionally, peripheral arthritis. Although ankylosing spondylitis has been considered a relatively benign form of arthritis,¹ a recent study showed that the rates of pain and disability among patients with ankylosing spondylitis were similar to the rates among those with rheumatoid arthritis.² Moreover, many patients have severe inflammatory symptoms even decades after diagnosis of the disease.³⁻⁸ No therapy has been shown to slow the progression of axial disease in patients with ankylosing spondylitis.⁹

Tumor necrosis factor α (TNF- α) may play a part in the pathogenesis of ankylosing spondylitis and other forms of spondyloarthritis. Increased expression of TNF- α has been reported in the serum,^{10,11} synovium,^{12,13} and sacroiliac joints¹⁴ in affected patients. In addition, axial ankylosis and enthesopathies resembling human ankylosing spondylitis develop in transgenic mice with increased expression of TNF- α .¹⁵ Studies have demonstrated the efficacy of anti-TNF- α agents for the treatment of other inflammatory arthritides.¹⁶⁻¹⁹ We performed a study to evaluate the efficacy of etanercept, a dimeric fusion protein of the human 75-kD (p75) tumor necrosis factor receptor linked to the Fc portion of human IgG₁ (Enbrel, Immunex, Seattle), for the treatment of ankylosing spondylitis.

METHODS

Patients

The study was conducted from July 1999 to December 2001. Patients were recruited from rheumatology practices in northern California. To be eligible for enrollment, patients had to meet the

From the Division of Rheumatology, University of California, San Francisco. Address reprint requests to Dr. Davis at the Division of Rheumatology, University of California, 533 Parnassus Ave., San Francisco, CA 94143, or at jdavis@medicine.ucsf.edu.

modified New York clinical criteria for definite ankylosing spondylitis,²⁰ have evidence of active spondylitis despite accepted treatments, and be at least 18 years old. Active spondylitis was defined as the presence of inflammatory back pain (stiffness and pain that worsened with rest and improved with exercise), morning stiffness for at least 45 minutes, and at least moderate disease activity as assessed by the patient and the physician. The patient's global assessment of disease activity was based on a five-point scale (1, none; 2, mild; 3, moderate; 4, severe; and 5, very severe). The physician's assessment was measured with the use of a visual-analogue scale (a 100-mm horizontal line with 0 mm representing the absence of disease activity and 100 mm very severe activity); a moderate or higher level of disease activity was defined by the placement of a vertical line at 40 mm or higher.

Patients continued to take drugs that had already been prescribed for ankylosing spondylitis if the doses had not been changed for at least four weeks before randomization and if they remained unchanged throughout the trial. Acceptable medications included nonsteroidal antiinflammatory drugs (NSAIDs), oral corticosteroids (≤ 10 mg per day), gold injections (≤ 50 mg per month), methotrexate (≤ 20 mg per week), and sulfasalazine (≤ 3 g per day).

Patients were excluded if they had a spondylitis other than ankylosing spondylitis, clinical or radiographic evidence of complete spinal ankylosis, a history of recurrent infections or cancer, or a serious liver, renal, hematologic, or neurologic disorder.

The study was approved by the committee on human research at the University of California, San Francisco, and by the Food and Drug Administration. All patients provided written informed consent. The majority of funding for the study was provided by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Immunex, the pharmaceutical funding source, supplied etanercept and placebo and provided partial funding. Immunex was not involved in the study design, data collection, statistical analysis, or manuscript preparation; these tasks were performed by the authors.

Protocol

We randomly assigned patients to receive twice-weekly subcutaneous injections of placebo or etanercept (25 mg) for four months. Clinical and laboratory assessments were performed at the time of screening and on study days 1, 28, 56, 84, and 112. The assessments included a physical examination, evaluation of disease activity, and laboratory tests (complete blood count; measurements of electrolytes, blood urea nitrogen, and creatinine; liver-function tests; and urinalysis). Laboratory tests and physical examination were also performed on day 14 to assess the safety of the treatment. Serum was tested for antinuclear antibodies, antibodies to double-stranded DNA, and rheumatoid factor at the time of screening and at four months.

On completion of the study, patients were given the opportunity to enroll in a six-month, open-label extension study in which all patients received etanercept. Clinical and laboratory assessments were conducted at base line (the last day of the placebo-controlled study) and on days 140, 196, and 280 during the extension study.

On the basis of the recommendations issued by the Assessments in Ankylosing Spondylitis Working Group,²¹ we used questionnaires, physical examination, and laboratory tests to evaluate disease activity. Questionnaires were used to determine the duration of morning stiffness (in minutes), the degree of spinal pain at night (as represented on a 100-mm visual-analogue scale, with 0 mm indicating the absence of pain and 100 mm the most severe pain), and the patient's and physician's global assessments of disease activity. Functioning was evaluated with the Bath Ankylosing Spondylitis Functional Index (10 questions about the ability to perform specific tasks, with the use of a visual-analogue scale labeled "easy" at one end and "impossible" at the other)²² and the Dougados Functional Index (20 questions about the ability to

perform specific tasks on a three-point scale, with 0 indicating no difficulty performing the task; 1, able to perform it but with difficulty; and 2, unable to perform the task).²³ Fatigue was evaluated with the Fatigue Severity Scale (nine questions, with 0 indicating no fatigue and 7 the most fatigue),²⁴ and the Medical Outcomes Study Short-Form Health Survey²⁵ (SF-36) was used to measure the quality of life (on a 100-point scale, with 100 indicating the best quality of life).

Physical examination included an assessment of tenderness at 17 tendon-insertion sites according to the modified Newcastle Enthesis Index (with a score of 0 indicating no pain; 1, mild tenderness; 2, moderate tenderness; and 3, tenderness severe enough to elicit a wince or withdrawal)^{26,27}; assessment of 66 joints for pain and 64 joints for swelling, both on a four-point scale (with 0 indicating none; 1, mild; 2, moderate; and 3, severe)²⁸; measurement of chest expansion (the circumferential difference, in centimeters, between full inspiration and expiration)²⁹; measurement of lumbar flexion, in centimeters, according to the modified Schober's Index²¹; and measurement, in centimeters, of the distance from the back of the head to the wall while the patient was standing with back and heels against the wall.³⁰

The laboratory evaluation consisted of measurements of the Westergren erythrocyte sedimentation rate and C-reactive protein. The latter was measured only at base line and on day 112.

A statistician not otherwise involved with the study randomly assigned patients to the study groups, using computer-generated, random blocks of two and four. Cards with the group assignments were placed in sequentially numbered envelopes that were opened by the study pharmacist as each patient was enrolled. The patients and study investigators were unaware of the group assignments.

Adverse Events

At each visit, the study nurse asked the patients about reactions at the injection site; this information was not reported to the investigators responsible for obtaining measurements. Before examination, all patients covered the last two injection sites with bandages, regardless of the presence or absence of a reaction at the site. Side effects were monitored at each clinic visit by means of open-ended questions about any problems that had occurred since the previous visit. Adverse events and changes in laboratory values were graded on a scale derived from the Common Toxicity Criteria of the National Cancer Institute.³¹

Outcome Measures

The primary outcome measure was a prespecified, composite treatment response, defined as 20 percent or greater improvement in at least three of five measures of disease activity, as recommended by the Assessments in Ankylosing Spondylitis Working Group²¹ (duration of morning stiffness, degree of nocturnal spinal pain, the Bath Ankylosing Spondylitis Functional Index, the patient's global assessment of disease activity, and the score for joint swelling), one of which was required to be duration of morning stiffness or degree of nocturnal spinal pain, with no worsening in any of the measures. If the swollen-joint score was zero throughout the study, improvement was required in at least two of the four other outcome measures, with the aforementioned restrictions. Secondary outcome measures included the physician's global assessment of disease activity, measures of spinal mobility, the scores for enthesitis and peripheral-joint tenderness, the erythrocyte sedimentation rate, and the C-reactive protein level.

Statistical Analysis

The study was designed with 80 percent power to detect a response rate of 27 percent in the placebo group as compared with a response rate of 71 percent in the etanercept group. The target sample was 40 patients, in order to allow for the withdrawal of up to 2 patients per treatment group.

The main analysis, based on the intention-to-treat principle, consisted of a comparison of data from the last visit of each randomized patient with data from the base-line visit. For continuous measures, we calculated the change from base line in each patient and compared the mean changes in the two study groups using the Mann-Whitney test for two independent groups.³² For categorical and ordinal data, we compared the two groups at the last visit with the use of Fisher's exact test (two-tailed).³² A second analysis, which included only patients who completed the study, paralleled the intention-to-treat analysis. The analysis of adverse events, performed with Fisher's exact test (two-tailed), was a comparison of the number of patients in each group who had a specific sign or symptom.

All statistical tests were two-sided, with a P value of 0.05 or less considered to indicate statistical significance. Analyses were performed with the use of SAS software, version 8.2.

RESULTS

Patients

The base-line characteristics of the patients are shown in Table 1. Thirty-one men and nine women were enrolled. The mean age was 39 years (range, 20 to 66), and the mean duration of disease was 13 years (range, 1 to 40). Approximately three quarters of the patients were white, and 92 percent were positive for HLA-B27. There were two statistically significant differences between the study groups that may have indicated the presence of more severe disease in the etanercept group: a lower mean SF-36 score for physical functioning (41.8 in the etanercept group vs. 61.0 in the placebo group, $P=0.01$) and a lower mean hemoglobin level (12.6 vs. 13.6 units, $P=0.04$).

Patients in the etanercept group were more likely than those in the placebo group to be receiving corticosteroids, disease-modifying antirheumatic drugs, or both and were more likely to be receiving more than one medication (two or more of the following: NSAIDs, sulfasalazine, methotrexate, gold, and prednisone). Despite the use of these agents, however, there was a trend toward a higher erythrocyte sedimentation rate and a higher score on the Bath Ankylosing Spondylitis Functional Index in the group treated with etanercept than in the placebo group ($P=0.07$ and $P=0.06$, respectively). Eight patients in each group (40 percent) had a swollen-joint score of zero throughout the study.

Three patients withdrew from the study. One of the 20 patients randomly assigned to receive etanercept withdrew for personal reasons unrelated to the study (on day 84), and 2 of the 20 patients assigned to receive placebo withdrew because of lack of efficacy (both on day 28).

Efficacy

On the basis of the prespecified definition of a treatment response and the intention-to-treat principle, the response rate at four months was 80 percent in the etanercept group and 30 percent in the placebo group ($P=0.004$). Patients treated with etanercept had sig-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ETANERCEPT (N=20)	PLACEBO (N=20)
Male sex (%)	65	90
White race (%)	75	70
Positive for HLA-B27 (%)	95	90
Age (yr)	38±10	39±10
Duration of disease (yr)	15±10	12±9
Peripheral-joint involvement (%)†	60	60
Concomitant medications (%)		
Nonsteroidal antiinflammatory drugs	80	95
Corticosteroids	25	10
Disease-modifying antirheumatic drugs	40	35
Combination therapy‡	45	35

*Plus-minus values are medians ±SD. There were no statistically significant differences between the two groups.

†Peripheral-joint involvement was defined as at least one swollen joint.

‡Combination therapy was defined as the receipt of more than one medication for the treatment of ankylosing spondylitis.

nificantly greater improvement in four of the five primary outcome measures that were combined to determine the treatment response than did patients in the placebo group (Table 2). The response to etanercept therapy was rapid and sustained; a significantly greater proportion of patients in the etanercept group had a predefined treatment response at one, three, and four months (Fig. 1).

The etanercept group also had significantly greater improvement in many of the secondary outcome measures than did the placebo group (Table 2). None of the changes from base line in joint counts (data not shown) or joint scores differed significantly between the two groups at four months, although there was a trend toward a benefit of etanercept in reducing joint tenderness. Of the mobility measures, only the change from base line in chest expansion differed significantly between the two groups, with an improvement in the etanercept-treated patients at the end of the study. The etanercept group also had significantly greater improvement in quality-of-life measures, particularly those related to physical functioning and health (Fig. 2).

Thirty-seven patients (18 in the placebo group and 19 in the etanercept group) completed the randomized, double-blind, placebo-controlled study and were treated with etanercept in an open-label extension study for six months. The response to etanercept was rapid in the group that had previously received placebo and paralleled the response of patients treated with etanercept throughout the entire 10-month study period (Fig. 1).

TABLE 2. OUTCOMES AT FOUR MONTHS.*

OUTCOME	ETANERCEPT (N=20)	PLACEBO (N=20)	P VALUE†
Primary			
Treatment response — no. (%)‡	16 (80)	6 (30)	0.004
Duration of morning stiffness — min			
Base line	90.0±50.6	60.0±70.7	0.12
Month 4	25.0±78.9	60.0±65.0	<0.001
Score for nocturnal spinal pain§			
Base line	65.0±23.9	46.5±25.3	0.32
Month 4	15.0±24.3	38.0±27.8	<0.001
Mean swollen-joint score¶			
Base line	3.7±8.1	3.2±5.3	0.53
Month 4	1.6±3.8	3.7±7.6	0.17
Patient's global assessment of disease activity			
Base line	3.0±0.7	3.0±0.7	0.33
Month 4	2.0±0.6	3.0±0.9	<0.001
Bath Ankylosing Spondylitis Functional Index**			
Base line	4.5±2.1	3.2±2.5	0.06
Month 4	2.2±2.1	3.1±3.0	<0.001
Secondary			
Physician's global assessment of disease activity††			
Base line	54.5±19.6	48.0±16.4	0.29
Month 4	23.0±10.6	55.5±22.7	<0.001
Spinal mobility			
Chest expansion — cm			
Base line	2.6±1.6	3.1±1.7	1.00
Month 4	3.5±1.9	2.9±1.7	0.006
Modified Schober's Index — lumbar flexion — cm			
Base line	12.5±1.5	13.5±1.5	0.13
Month 4	13.4±1.6	13.4±1.5	0.26
Mean occiput-to-wall measurement — cm			
Base line	5.7±7.9	2.0±1.5	0.26
Month 4	4.7±7.6	2.7±4.4	0.11
Modified Newcastle Enthesis Index‡‡			
Base line	4.5±8.4	3.0±7.9	0.72
Month 4	0.0±3.0	1.5±8.0	0.001
Score for peripheral-joint tenderness§§			
Base line	3.5±10.5	2.5±11.8	0.40
Month 4	1.0±2.5	2.5±23.1	0.07
Erythrocyte sedimentation rate — mm/hr			
Base line	34.5±23.1	20.0±16.3	0.07
Month 4	8.5±12.8	16.5±18.7	<0.001
C-reactive protein — mg/dl			
Base line	2.0±1.8	1.5±1.2	0.44
Month 4	0.7±1.1	2.0±2.8	0.003

*Plus-minus values are medians ±SD unless otherwise noted; mean values are means ±SD.

†Base-line P values are for the difference between the two groups, and P values at month 4 are for the difference in the change from base line between the two groups; in both cases, P values were calculated with the two-tailed Mann-Whitney test. The comparison of the treatment response in the two groups was calculated with Fisher's exact test.

‡A treatment response was defined as 20 percent or greater improvement in at least three of five outcome measures (duration of morning stiffness, degree of nocturnal spinal pain, the Bath Ankylosing Spondylitis Functional Index, the patient's global assessment of disease activity, and the score for joint swelling).

§Pain was measured on a 100-mm visual-analogue scale, with 0 denoting none, and 100 the most severe pain.

¶A total of 64 peripheral joints were evaluated for swelling on a four-point scale (0, none; 1, mild; 2, moderate; and 3, severe).

||Disease activity was scored on a scale from 0 (none) to 5 (very severe).

**Functional limitations were scored on a scale from 0 (none) to 10 (severe limitations).

††Disease activity was assessed on a 100-mm visual-analogue scale, with 0 denoting none, and 100 the most severe activity.

‡‡Seventeen entheses were scored on a four-point pain scale (0, none; 1, mild; 2, moderate; and 3, eliciting a wince or withdrawal).

§§Sixty-six peripheral joints were scored on a four-point scale for tenderness (0, none; 1, mild; 2, moderate; and 3, severe).

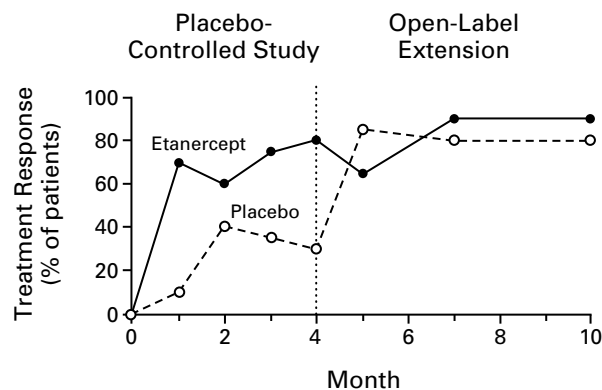


Figure 1. Percentage of Patients in Each Study Group Who Had a Treatment Response.

A treatment response was defined as 20 percent or greater improvement in at least three of five outcome measures (duration of morning stiffness, degree of nocturnal spinal pain, the Bath Ankylosing Spondylitis Functional Index, the patient's global assessment of disease activity, and the score for joint swelling). The patients in the etanercept group received etanercept throughout the 10-month study period; those in the placebo group received placebo for 4 months, followed by etanercept for 6 months. The differences between the groups were statistically significant at month 1 ($P < 0.001$), month 3 ($P = 0.03$), and month 4 ($P = 0.004$). During the open-label portion of the trial, there were no statistically significant differences between the two groups.

Base-line medications were not altered during the randomized, double-blind, placebo-controlled study. During the open-label extension period, however, the dose was decreased or the medication discontinued in 66 percent of the patients receiving corticosteroids, 63 percent of those receiving methotrexate, 63 percent of those receiving sulfasalazine, and 73 percent of those receiving NSAIDs.

Adverse Events

There were no serious adverse events or withdrawals because of adverse events, and the two study groups did not differ significantly with regard to either the overall rate of adverse events or the rates of specific events. The most common adverse events were reactions at the injection site and minor infections. Five patients in the etanercept group and one patient in the placebo group had at least one injection-site reaction. Minor, uncomplicated infections of the upper respiratory tract occurred in 10 etanercept-treated patients and 12 placebo-treated patients. The only other adverse event that occurred in more than 10 percent of either group was diarrhea, which devel-

oped in three patients in the etanercept group and one patient in the placebo group. Two patients treated with etanercept had mild cellulitis that responded to oral antibiotics; in one of the two, it occurred at an injection site.

Two neurologic events occurred in one patient treated with etanercept. The first was tinnitus without obvious cause, which occurred on day 28 and resolved spontaneously after three days. At two months, the same patient noted an increased frequency of preexisting muscle fasciculations involving the left orbicularis oculi and left quadriceps femoris. Neurologic examination and laboratory tests showed no abnormalities. The study medication was withheld pending the results of a neurologic consultation, magnetic resonance imaging of the brain, electromyography, nerve-conduction studies, and repetitive-nerve-stimulation studies. No abnormalities were noted on any of the evaluations, and the neurologic consultant diagnosed benign fasciculations. After 35 days without medication, the frequency of the patient's symptoms returned to base line and remained at this level with the reintroduction of the study medication.

At the end of the randomized, double-blind, placebo-controlled trial, two patients in the placebo group and two in the etanercept group had an antinuclear-antibody titer of 1:80. None of the patients had lupus-like symptoms or antibodies to double-stranded DNA. Tests for rheumatoid factor were negative in all four patients at both the start and the end of the study period.

The most common adverse events during the six-month open-label extension study were similar to those that occurred during the randomized, double-blind, placebo-controlled study, with injection-site reactions in five patients and upper respiratory tract infections in nine. The only other infection during the open-label period was a dental abscess that occurred in one patient after a root canal had been performed. Headache, the only other adverse event that occurred in more than 10 percent of the patients during the open-label period, occurred in four patients. Self-limited episodes of elevated serum creatinine, aminotransferase, and bilirubin levels occurred in one patient each, and one patient had self-limited glycosuria. Hypoalbuminemia and edema of the legs and feet developed in one patient but resolved without treatment.

DISCUSSION

The demonstrated efficacy of etanercept for the treatment of ankylosing spondylitis is a promising development in the treatment of this disease. Until recently, treatment has mainly been supportive, consisting of NSAIDs and physical therapy. Therapeutic options were limited by the paucity of controlled

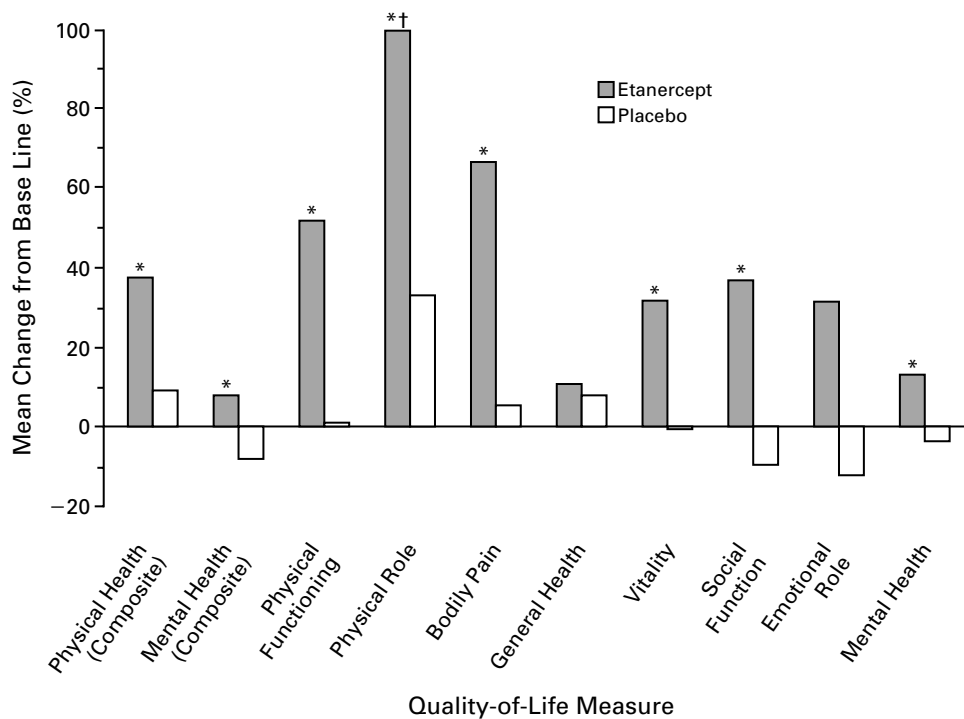


Figure 2. Effect of Treatment on the Quality of Life at Four Months.

The asterisks denote $P < 0.05$, by the two-tailed Mann–Whitney test, for the comparison between the etanercept and placebo groups. The improvement in physical role in the etanercept group (marked with a dagger) was actually 334.8 percent but is shown truncated to 100 percent.

studies of second-line agents in the spondyloarthritis.³³ Sulfasalazine, the most frequently studied disease-modifying antirheumatic drug, has been evaluated in eight randomized, placebo-controlled trials.⁹ A large, recent study, involving 264 patients, demonstrated a small improvement in peripheral joint disease but no improvement in axial symptoms.²⁷ In all the trials of sulfasalazine, efficacy appeared to be restricted to early disease.⁹ The only other disease-modifying antirheumatic drugs that have been evaluated for the treatment of ankylosing spondylitis in randomized, placebo-controlled trials are penicillamine³⁴ and auranofin,⁹ and neither was effective.

In our study, treatment with etanercept resulted in significant improvements in measures of axial and peripheral diseases, with a rapid and sustained response to the drug. The marked reduction in stiffness, pain, and functional limitations with etanercept therapy is particularly promising, since these are the primary problems reported by patients with ankylosing spondylitis⁶ and are among the leading causes of disability.^{3,35} The statistically significant improvements in both the patients' and the physicians' global as-

sessments of disease activity demonstrate the benefit of etanercept with respect to overall health.

These results are particularly notable because of the duration and extent of disease activity in the patients in our study. Despite the use of NSAIDs, disease-modifying antirheumatic drugs, prednisone, or a combination of these drugs, clinical measures at base line indicated the presence of active inflammatory disease. The prolonged duration of the disease is an important factor, because pain and functional disability increase over time^{2,5} and may become increasingly refractory to therapeutic interventions.²⁷

The only measures in our study that did not improve significantly with etanercept therapy were the modified Schober's Index, the occiput-to-wall measurement, the Fatigue Severity Scale (data not shown), and the counts (data not shown) and scores for tenderness in peripheral joints. The lack of significant improvement in two of the three measures of spinal mobility, which is not entirely unexpected, may be due to the presence of areas of spinal ossification resulting from prolonged disease. The lack of significant improvement in the Fatigue Severity Scale is

somewhat surprising in view of the other benefits observed, although this scale has not been validated in studies of ankylosing spondylitis. The failure of peripheral joints to improve significantly with anti-TNF- α therapy is difficult to interpret, since trials with anti-TNF- α agents in patients with other inflammatory arthritides have shown marked reductions in both tenderness and swelling of joints.^{16,18,36}

The measure of enthesitis improved significantly with etanercept therapy. Although the Assessments in Ankylosing Spondylitis Working Group has not recommended a measure of enthesitis for use in clinical trials, the modified Newcastle Enthesis Index^{26,27} is sensitive to change and easy to use, particularly with the reduction in the number of sites evaluated, as implemented by Clegg et al.²⁷ The reliability and validity of this measure may require additional study.

There are only two reports on trials of a TNF- α blocker for the treatment of ankylosing spondylitis; both were open-label studies of infliximab (Remicade), a chimeric (human-mouse) monoclonal antibody to TNF- α .^{37,38} Although the two studies differed with respect to the duration of disease and prior and concurrent exposure to conventional therapies, the results were similar, with statistically significant improvements in disease measures within two to six weeks after the initiation of therapy. Brandt et al. also reported improvement in a controlled trial involving 70 patients with ankylosing spondylitis, substantiating the findings in the open-label studies.³⁹

A randomized, placebo-controlled study of etanercept for the treatment of psoriatic arthritis showed a significant improvement in all clinical end points among the patients who received etanercept.¹⁸ The main criterion for inclusion in the study was the presence of active peripheral-joint disease; the axial response was not evaluated. However, direct application of these results to the treatment of ankylosing spondylitis is difficult because of distinct differences between psoriatic arthritis and ankylosing spondylitis,⁴⁰⁻⁴³ including more erosive peripheral-joint disease and less frequent axial involvement in psoriatic arthritis.

The neurologic symptoms observed in a single patient in our trial deserve consideration in the light of reports of demyelinating disease in patients with rheumatoid arthritis or psoriatic arthritis who were treated with etanercept.⁴⁴ In our patient with neurologic symptoms, no clinical or laboratory abnormalities were identified, and the symptoms were not exacerbated by rechallenge with etanercept. However, our understanding of the effect of anti-TNF- α therapy on the nervous system is limited, and patients receiving this therapy should therefore be closely monitored.

The results of our study show that etanercept al-

leviates many of the disabling symptoms of ankylosing spondylitis and can be used safely in combination with other antiinflammatory and immunosuppressive agents. The paucity of effective therapies for this severe disease underscores the importance of these findings. Long-term studies with larger numbers of patients will be necessary to address the issue of safety further and to determine the effects of etanercept on the progression of spinal ankylosis.

Supported by grants from the National Institutes of Health (N01-AR-9-2244 and NIH AR07304) and by Immunex.

Dr. Davis has served as a consultant to Immunex.

We are indebted to Steve Lund, N.P., Maureen Fitzpatrick, M.P.H., Anne-Marie Dubme, B.S.N., R.N., Allison Webb, B.S., Melanie Vose, B.S., Jeffrey Kishiyama, M.D., Scott Fields, Pharm.D., Désirée van der Heijden, M.D., Ph.D., and David Wofsy, M.D., for their assistance.

REFERENCES

1. Wilkinson M, Bywaters EGL. Clinical features and course of ankylosing spondylitis: as seen in a follow-up of 222 hospital referred cases. *Ann Rheum Dis* 1958;17:209-28.
2. Zink A, Braun J, Listing J, Wollenhaupt J. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis — results from the German rheumatological database. *J Rheumatol* 2000;27:613-22.
3. Gran JT, Skomsvoll JE. The outcome of ankylosing spondylitis: a study of 100 patients. *Br J Rheumatol* 1997;36:766-71.
4. Kennedy LG, Edmunds L, Calin A. The natural history of ankylosing spondylitis: does it burn out? *J Rheumatol* 1993;20:688-92.
5. Ringsdal VS, Andreassen JJ. Ankylosing spondylitis — experience with a self administered questionnaire: an analytical study. *Ann Rheum Dis* 1989;48:924-7.
6. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. *Arthritis Care Res* 1999;12:247-55.
7. Taylor AL, Balakrishnan C, Calin A. Reference centile charts for measures of disease activity, functional impairment, and metrology in ankylosing spondylitis. *Arthritis Rheum* 1998;41:1119-25.
8. Goodacre JA, Mander M, Dick WC. Patients with ankylosing spondylitis show individual patterns of variation in disease activity. *Br J Rheumatol* 1991;30:336-8.
9. Toussiot E, Wendling D. Current guidelines for the drug treatment of ankylosing spondylitis. *Drugs* 1998;56:225-40.
10. Gratacós J, Collado A, Filella X, et al. Serum cytokines (IL-6, TNF- α , IL-1 beta and IFN- γ) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. *Br J Rheumatol* 1994;33:927-31.
11. Toussiot E, Lafforgue P, Boucraut J, et al. Serum levels of interleukin 1-beta, tumor necrosis factor-alpha, soluble interleukin 2 receptor and soluble CD8 in seronegative spondylarthropathies. *Rheumatol Int* 1994;13:175-80.
12. Grom AA, Murray KJ, Luyrink L, et al. Patterns of expression of tumor necrosis factor alpha, tumor necrosis factor beta, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. *Arthritis Rheum* 1996;39:1703-10.
13. Cañete JD, Llena J, Collado A, et al. Comparative cytokine gene expression in synovial tissue of early rheumatoid arthritis and seronegative spondyloarthropathies. *Br J Rheumatol* 1997;36:38-42.
14. Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum* 1995;38:499-505.
15. Crew MD, Effros RB, Walford RL, Zeller E, Cheroutre H, Brahn E. Transgenic mice expressing a truncated *Peromyscus leucopus* TNF-alpha gene manifest an arthritis resembling ankylosing spondylitis. *J Interferon Cytokine Res* 1998;18:219-25.
16. 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.

17. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000;342:763-9.
18. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet* 2000;356:385-90.
19. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
20. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
21. van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis: progress report of the ASAS Working Group. *J Rheumatol* 1999;26:951-4.
22. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281-5.
23. Dougados M, Gueguen A, Nakache JP, Nguyen M, Mery C, Amor B. Evaluation of a functional index and an articular index in ankylosing spondylitis. *J Rheumatol* 1988;15:302-7.
24. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121-3.
25. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
26. Mander M, Simpson JM, McLellan A, Walker D, Goodacre JA, Dick WC. Studies with an enthesitis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987;46:197-202.
27. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis: a Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996;39:2004-12.
28. The Cooperating Clinics Committee of the American Rheumatism Association. A seven-day variability study of 499 patients with peripheral rheumatoid arthritis. *Arthritis Rheum* 1965;8:302-34.
29. Moll JM, Wright V. An objective clinical study of chest expansion. *Ann Rheum Dis* 1972;31:1-8.
30. Viitanen JV, Kokko ML, Heikkilä S, Kautiainen H. Neck mobility assessment in ankylosing spondylitis: a clinical study of nine measurements including new tape methods for cervical rotation and lateral flexion. *Br J Rheumatol* 1998;37:377-81.
31. Arbusk SG, Ivy SP, Setser A, et al. The revised Common Toxicity Criteria: version 2.0. Bethesda, Md.: Cancer Therapy Evaluation Program, 1999. (Accessed March 28, 2002, at <http://ctep.cancer.gov/reporting/ctc.html>.)
32. Conover WJ. Practical nonparametric statistics. New York: John Wiley, 1980:493.
33. Creemers MC, van Riel PL, Franssen MJ, van de Putte LB, Gribnau FW. Second-line treatment in seronegative spondylarthropathies. *Semin Arthritis Rheum* 1994;24:71-81.
34. Steven MM, Morrison M, Sturrock RD. Penicillamine in ankylosing spondylitis: a double blind placebo controlled trial. *J Rheumatol* 1985;12:735-7.
35. Roussou E, Kennedy LG, Garrett S, Calin A. Socioeconomic status in ankylosing spondylitis: relationship between occupation and disease activity. *J Rheumatol* 1997;24:908-11.
36. Lipsky PE, van der Heijde DMFM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-602.
37. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000;43:1346-52.
38. Stone M, Salonen D, Lax M, Payne U, Lapp V, Inman R. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. *J Rheumatol* 2001;28:1605-14.
39. Brandt J, Alten R, Burmester G, et al. Three months results of a double-blind placebo controlled, phase-III clinical trial of infliximab in active ankylosing spondylitis. *Ann Rheum Dis* 2001;60:Suppl 1:61. abstract.
40. McEwen C, DiTata D, Lingg C, Porini A, Good A, Rankin T. Ankylosing spondylitis and spondylitis accompanying ulcerative colitis, regional enteritis, psoriasis and Reiter's disease: a comparative study. *Arthritis Rheum* 1971;14:291-318.
41. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? *Ann Rheum Dis* 1998;57:135-40.
42. Braun J, Sieper J. The sacroiliac joint in the spondyloarthropathies. *Curr Opin Rheumatol* 1996;8:275-87.
43. González S, Martínez-Borra J, López-Larrea C. Immunogenetics, HLA-B27 and spondyloarthropathies. *Curr Opin Rheumatol* 1999;11:257-64.
44. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Siegel JN. Demyelination diagnosed during etanercept (TNF receptor fusion protein) therapy. *Arthritis Rheum* 2000;43:Suppl:S228. abstract.

Copyright © 2002 Massachusetts Medical Society.

CORRECTION

Inhibition of Tumor Necrosis Factor α and Ankylosing Spondylitis

To the Editor: In a recent multicenter trial, Gorman et al. (May 2 issue)¹ found that 80 percent of patients with active ankylosing spondylitis had a favorable response to etanercept. Equivalent results are obtained with infliximab.² Data on uveitis are still lacking. We report a case of severe uveitis in a 45-year-old man that improved with infliximab.

In 1986, the patient was given a diagnosis of HLA-B27–positive ankylosing spondylitis. Since 1993, he had had recurrent bilateral anterior uveitis, leading to functional blindness of the right eye despite the use of antiinflammatory drugs, including corticosteroids. When he was seen in May 1996 because of persistent joint and eye inflammation, he was treated with 60 mg of prednisone per day and 15 mg of methotrexate per week; the dose of prednisone was then tapered. Despite an increase in the dose of methotrexate up to 25 mg per week, bilateral uveitis relapsed. Methotrexate treatment was discontinued in April 2001 because of lack of efficacy and alcoholic hepatitis.

In July 2001, a new relapse led to the initiation of treatment with intravenous cyclophosphamide at a monthly dose of 1000 mg. In January 2002, after six pulses of cyclophosphamide, severe uveitis occurred in the left eye, with a decrease in visual acuity from 10/10 to 5/10 and cystoid macular edema. After three pulses of methylprednisolone, 5 mg of infliximab per kilogram of body weight was administered on day 1, day 8, day 15, and at eight weeks. Cystoid macular edema decreased, visual acuity improved to 10/10, and ocular inflammation disappeared. The dose of oral prednisone was regularly and rapidly reduced to 25 mg per day without relapse. These findings suggest that inhibitors of tumor necrosis factor α (TNF- α) could be effective in the treatment of uveitis associated with ankylosing spondylitis, as they are for uveitis associated with Crohn's disease³ or Behçet's disease.⁴

Bouchra Asli, M.D.

Bertrand Wechsler, M.D.

Claire Lemaître, M.D.

Pitié-Salpêtrière Hospital

75651 Paris, CEDEX 13, France

bertrand.wechsler@psl.ap-hop-paris.fr

References

- Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α . *N Engl J Med* 2002;346:1349-1356.
- Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;359:1187-1193.

- Fries W, Giofre MR, Catanoso M, Lo Gullo R. Treatment of acute uveitis associated with Crohn's disease and sacroileitis with infliximab. *Am J Gastroenterol* 2002;97:499-500.

- Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. *Lancet* 2001;358:295-296.

To the Editor: The role of TNF- α in ankylosing spondylitis is better understood than its role in rheumatoid arthritis. The predominant inflammatory cell at sites of acute enthesitis and osteitis is the macrophage, and a high level of expression of TNF- α has been shown at these sites. Animal models that demonstrate the efficacy of inhibiting tumor necrosis factor (TNF) are arguably better models for the pathogenesis of ankylosing spondylitis than for that of rheumatoid arthritis, and overexpression of TNF leads to a disease reminiscent of ankylosing spondylitis.¹ Evidence in the article by Gorman et al. suggests that up to 80 percent of patients with ankylosing spondylitis have a response to etanercept, as compared with patients with rheumatoid arthritis, who may not have a response — suggesting that TNF- α has a more central role in the pathogenesis of ankylosing spondylitis. We do not believe it is possible to extrapolate observations from peripheral synovial tissue to the enthesitis that characterizes spinal disease in ankylosing spondylitis. In addition, synovitis may be secondary to the release of TNF from these lesions.²

In contrast to the report of Gorman et al., we reported that fatigue improved by 57 percent in patients with ankylosing spondylitis who were treated with etanercept for 24 weeks, and this improvement was mirrored by improvement in spinal inflammatory lesions as determined by magnetic resonance imaging.³ With regard to the many unanswered questions pertaining to the use of biologic agents in patients with ankylosing spondylitis, the pivotal issue is whether suppression of inflammation prevents new bone formation and ankylosis, the chief cause of chronic disability in patients with this disease.

Helena Marzo-Ortega, M.D.

Paul Emery, M.D.

Dennis McGonagle, M.D.

University of Leeds

Leeds LS2 9NZ, United Kingdom

medhmo@leeds.ac.uk

References

- Crew MD, Effros RB, Walford RL, Zeller E, Cheroutre H, Brahn E. Transgenic mice expressing a truncated *Peromyscus leucopus* TNF- α gene manifest an arthritis resembling ankylosing spondylitis. *J Interferon Cytokine Res* 1998;18:219-225.
- McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet* 1998;352:1137-1140.

3. Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept in the treatment of the enthesal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. *Arthritis Rheum* 2001;44:2112-2117.

The authors reply: Regarding the report by Dr. Asli and colleagues of the successful treatment with infliximab of a case of HLA-B27-associated uveitis: although randomized, controlled studies of anti-TNF therapies for this indication are lacking, the use of these agents for the treatment of inflammatory eye disease is being increasingly reported.^{1,2}

In an open-label study of etanercept in the treatment of spondyloarthritis, Dr. Marzo-Ortega and colleagues reported substantial improvement in fatigue. In their study, fatigue was measured by a single question from the Bath Ankylosing Spondylitis Activity Index.³ Responses to this question about fatigue correlate significantly with responses to the eight components of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) that we used,⁴ in six of which there was significant improvement with etanercept therapy in our trial. There may be several suitable measures of fatigue in patients with ankylosing spondylitis,⁴ but at the time our study was initiated, no instrument had been deemed relevant by the Assessments in Ankylosing Spondylitis Working Group.⁵

We would like to make a correction to the response rate among etanercept-treated patients in our trial. One patient in the etanercept group during the randomized portion of the study was inadvertently classified as having had a response at four months. Although the patient had greater than 20 percent improvement in the duration of morning stiffness (33 percent), nocturnal spinal pain (65 percent), patient's global assessment of disease activity (25 percent), and Bath Ankylosing Spondylitis Functional Index (49 percent), the swollen-joint score had increased from 0 to 2 by the end of the study. According to the intention-to-treat principle with the last value carried forward, the percentage of patients in the etanercept group with a response to treatment (reported at the bottom of the left-hand column on page 1351, in Table 2, and in Figure 1 of our article) should be 75 percent instead of 80 percent, with a corrected P value of 0.01 by Fisher's exact test (two-tailed). We regret the error.

Jennifer D. Gorman, M.D.

Kenneth E. Sack, M.D.

John C. Davis, Jr., M.D., M.P.H.

University of California, San Francisco

San Francisco, CA 94143

jdavis@medicine.ucsf.edu

References

1. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis*

Rheum 2001;45:252-257.

2. Reiff A, Takei S, Sadeghi S, et al. Etanercept therapy in children with treatment-resistant uveitis. *Arthritis Rheum* 2001;44:1411-1415.
3. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286-2291.
4. van Tubergen A, Coenen J, Landewe R, et al. Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. *Arthritis Rheum* 2002;47:8-16.
5. van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis: progress report of the ASAS Working Group: Assessments in Ankylosing Spondylitis. *J Rheumatol* 1999;26:951-954.