

ETANERCEPT IN CHILDREN WITH POLYARTICULAR JUVENILE RHEUMATOID ARTHRITIS

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ABSTRACT

Background We evaluated the safety and efficacy of etanercept, a soluble tumor necrosis factor receptor (p75):Fc fusion protein, in children with polyarticular juvenile rheumatoid arthritis who did not tolerate or had an inadequate response to methotrexate.

Methods Patients 4 to 17 years old received 0.4 mg of etanercept per kilogram of body weight subcutaneously twice weekly for up to three months in the initial, open-label part of a multicenter trial. Those who responded to treatment then entered a double-blind study and were randomly assigned to receive either placebo or etanercept for four months or until a flare of the disease occurred. A response was defined as an improvement of 30 percent or more in at least three of six indicators of disease activity, with no more than one indicator worsening by more than 30 percent.

Results At the end of the open-label study, 51 of the 69 patients (74 percent) had had responses to etanercept treatment. In the double-blind study, 21 of the 26 patients who received placebo (81 percent) withdrew because of disease flare, as compared with 7 of the 25 patients who received etanercept (28 percent) ($P=0.003$). The median time to disease flare with placebo was 28 days, as compared with more than 116 days with etanercept ($P<0.001$). In the double-blind study, there were no significant differences between the two treatment groups in the frequency of adverse events.

Conclusions Treatment with etanercept leads to significant improvement in patients with active polyarticular juvenile rheumatoid arthritis. Etanercept is well tolerated by pediatric patients. (N Engl J Med 2000;342:763-9.)

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JUVENILE rheumatoid arthritis is the most common rheumatic condition in children.^{1,2} In approximately one third of patients, the disease is controlled with nonsteroidal antiinflammatory drugs and an appropriate program of physical and occupational therapy. The remainder are candidates for more aggressive therapy with antirheumatic drugs.

Methotrexate was shown to have a therapeutic advantage over placebo, with an acceptable safety profile, in a randomized, controlled trial in children with juvenile rheumatoid arthritis who had polyarticular involvement (regardless of the type of onset).³ Long-term studies showed that methotrexate is efficacious

and well tolerated in most children with juvenile rheumatoid arthritis.³⁻⁶ However, some patients do not have an adequate response to methotrexate, even at doses of up to 1 mg per kilogram of body weight per week.^{7,8} The frequency and severity of side effects increase with higher doses of methotrexate, and the consequences of long-term use are not known. Exacerbation of disease during treatment with stable doses of methotrexate and the need to increase the methotrexate dose over time suggest that drug resistance to methotrexate may develop.⁹

Tumor necrosis factor (TNF) is a proinflammatory cytokine that has a complex role in the pathogenesis of rheumatoid arthritis.¹⁰⁻¹⁷ TNF is elevated in both the serum and the synovial fluid of children with juvenile rheumatoid arthritis. Serum levels of soluble TNF receptor are elevated in patients with juvenile rheumatoid arthritis (all subtypes), and the level is correlated with disease activity.¹⁸ In one study, tumor necrosis factor was detected in 45 percent of samples of synovial fluid from 44 children with juvenile rheumatoid arthritis (all subtypes).¹⁹ Further evidence that TNF may amplify local inflammation and lead to joint destruction came from a study in which both TNF and lymphotoxin- α were detected in the majority of synovial-tissue samples from patients with juvenile rheumatoid arthritis.²⁰

Etanercept (Enbrel, Immunex, Seattle), a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of human IgG1, effectively binds TNF and lymphotoxin- α and inhibits their activity.^{21,22} Randomized, double-blind, placebo-controlled trials showed that etanercept treatment had significant clinical benefit with minimal toxicity in adults with active rheumatoid arthritis that did not respond to other disease-modifying drugs.²³⁻²⁵ We conducted a randomized, multicenter, double-blind trial of etanercept for the

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treatment of polyarticular juvenile rheumatoid arthritis in children who did not tolerate or who had an inadequate response to methotrexate.

METHODS

Patients

Eligible patients were 4 to 17 years of age and had active polyarticular juvenile rheumatoid arthritis. During the first six months of the disease, some patients had had pauciarticular arthritis (four or fewer joints involved), some had had polyarticular arthritis (five or more joints involved), and some had had systemic arthritis (associated with spiking fever and rheumatoid rash). "Active" polyarticular disease was defined by the presence of five or more swollen joints and three or more joints with limitation of motion and pain, tenderness, or both. Before enrollment, patients had active disease despite treatment with nonsteroidal antiinflammatory drugs and with methotrexate at doses of at least 10 mg per square meter of body-surface area per week. The patients had normal or nearly normal platelet, white-cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal-function tests. Pregnant and lactating patients were excluded, and girls with childbearing potential were required to use contraception throughout the study. Patients with major concurrent medical conditions were also ineligible.

Study Design

An independent review committee at each study site approved the protocol and amendments, and each patient's parent or legal guardian gave written informed consent before the start of the study. A safety monitoring board reviewed adverse events that occurred during the study. Methotrexate was discontinued 14 days and other disease-modifying antirheumatic drugs 28 days before receipt of etanercept. Intraarticular and soft-tissue corticosteroid injections were not permitted during or for one month before the trial. Stable doses of nonsteroidal antiinflammatory drugs, low doses of corticosteroids (≤ 0.2 mg of prednisone per kilogram per day, with a maximum of 10 mg per day), or both were permitted. Pain medications were allowed except during the 12 hours before a joint assessment.

Vials of study medication contained either 25 mg of lyophilized etanercept (for both parts of the study) or placebo (for the double-blind study). Before injection, study-site staff who were not involved in patient assessments reconstituted the contents with 1 ml of bacteriostatic water containing 0.9 percent benzyl alcohol.

All patients received 0.4 mg of etanercept per kilogram (maximum, 25 mg) subcutaneously twice weekly for up to three months in the open-label part of the trial. At the end of the third month, patients whose condition had improved according to the definition of Giannini et al.²⁶ were randomly assigned to receive either placebo or 0.4 mg of etanercept per kilogram subcutaneously twice weekly in the double-blind study (months 4 through 7) until disease flare occurred or four months elapsed, whichever was earlier. Efficacy was assessed according to the number of patients with disease flare after receipt of placebo or etanercept.

Physical examinations, measures of disease activity, and laboratory tests (hematologic analysis, serum chemical analysis, and urinalysis) were performed at screening and repeated on day 1 (before the administration of etanercept or placebo) and day 15 and at the end of each month during the study. Final safety assessments were made 30 days after the discontinuation of the study drug for patients who withdrew from the study or did not continue to the double-blind study, or at the patient's next scheduled visit if the patient withdrew from the study because of disease flare. Serum was obtained at screening and at the end of months 3 and 7 for testing for autoantibodies (antinuclear antibodies, antibodies to double-stranded DNA, IgG and IgM anticardiolipin antibodies, and antibodies to extractable nuclear antigens), and on day 1 before the administration of the study drug and at the end of months 3 and 7 for testing for antibodies to etanercept.

Definition of Improvement

The definition of improvement used to assess disease response employs a core set of six response variables: global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent, number of "active" joints (joints with swelling not due to deformity or joints with limitation of motion and with pain, tenderness, or both), number of joints with limitation of motion, functional ability, and erythrocyte sedimentation rate.^{26,27} In this study, the fourth measure was modified to the "number of joints with limitation of motion and with pain, tenderness, or both" so as to eliminate counting joints with contractures that might not have improved during the short course of treatment.

To meet the definition of improvement at a scheduled visit or at the end of month 3, patients had to have a 30 percent improvement from base line in at least three of the six response variables. They could also have worsening of 30 percent or more in no more than one of the six response variables. Additional assessments of disease activity included the articular severity score,²⁸ duration of morning stiffness, degree of pain (on a visual-analogue scale), and C-reactive protein levels. Patients were also evaluated for 50 percent and 70 percent improvement (50 percent and 70 percent improvement in at least three of the six response variables and a worsening of 30 percent or more in no more than one of the six response variables).

The primary efficacy end point, which was evaluated in the double-blind study, was the number of patients with disease flare. The definition of disease flare created specifically for this pediatric trial was based on the change in the core set of response variables from the beginning of the double-blind study. Patients who met the criteria for disease flare had worsening of 30 percent or more in three of the six response variables and a minimum of two active joints. They also could have improvement of 30 percent or more in no more than one of the six response variables. Global assessments, if used to define flare, had to change by at least 2 units on a scale from 0 to 10.

Statistical Analysis

A blocked randomization scheme with stratification according to study center and number of active joints (≤ 2 vs. >2) at the end of month 3 (in the open-label study) was used to assign patients to placebo or etanercept in the double-blind study.

In the double-blind study, base-line and demographic characteristics were compared between treatment groups by the Wilcoxon rank-sum test and the likelihood-ratio chi-square test. Laboratory results were summarized separately from adverse events according to a modification of the National Cancer Institute Common Toxicity Criteria and the testing laboratory's normal ranges. Comparisons of shifts in laboratory values (to below normal, normal, or above normal) were made with use of the Stuart-Maxwell chi-square test.²⁹

The percentages of patients with a response to therapy who had disease flare while receiving placebo or etanercept in the double-blind study were compared by Mantel-Haenszel methods.³⁰ Patients who withdrew early without disease flare were counted in the analysis with those who continued to have a response.

To evaluate any bias introduced by the withdrawal assumption in the primary analysis, an analysis of time to flare (by the log-rank test) was undertaken in which data on patients who withdrew without flare were censored at the time of withdrawal. The effect of base-line characteristics on flare rates was assessed by main-effects logistic regression. The percentages of patients with a response who continued to have a response after receiving etanercept or placebo in the double-blind study were compared by Mantel-Haenszel methods. All tests were two-sided, with a significance level of 0.05.

In all summaries of measures of disease activity, a last-observation-carried-forward approach was used for missing data or visits and for patients who withdrew early.

RESULTS

Base-Line Characteristics

The base-line demographic and disease characteristics of the study patients are summarized in Table 1.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND DISEASE HISTORY.*

CHARACTERISTIC	OPEN-LABEL STUDY (N=69)	DOUBLE-BLIND STUDY		
		TOTAL (N=51)	PLACEBO (N=26)	ETANERCEPT (N=25)
Mean age — yr	10.5	10.6	12.2	8.9
Age group — no. (%)				
4–8 yr	25 (36)	18 (35)	5 (19)	13 (52)
9–12 yr	14 (20)	9 (18)	4 (15)	5 (20)
13–17 yr	30 (43)	24 (47)	17 (65)	7 (28)
Sex — no. (%)				
Female	43 (62)	34 (67)	15 (58)	19 (76)
Male	26 (38)	17 (33)	11 (42)	6 (24)
Race or ethnic group — no. (%)				
White	52 (75)	37 (73)	23 (88)	14 (56)
Black	6 (9)	4 (8)	1 (4)	3 (12)
Hispanic	9 (13)	8 (16)	2 (8)	6 (24)
Other	2 (3)	2 (4)	0	2 (8)
Type of onset of JRA — no. (%)				
Pauciarticular	7 (10)	3 (6)	1 (4)	2 (8)
Polyarticular	40 (58)	31 (61)	17 (65)	14 (56)
Systemic	22 (32)	17 (33)	8 (31)	9 (36)
Mean duration of JRA — yr	5.9	5.8	6.4	5.3
Positive for rheumatoid factor — no. (%)	15 (22)	12 (24)	8 (31)	4 (16)
Previous methotrexate therapy — no. (%)	69 (100)	51 (100)	26 (100)	25 (100)
DMARDs at washout — no. (%)	51 (74)	35 (69)	19 (73)	16 (64)
Methotrexate	50 (72)	34 (67)	18 (69)	16 (64)
Hydroxychloroquine	13 (19)	9 (18)	7 (27)	2 (8)
Concomitant therapy at washout — no. (%)				
Corticosteroids	25 (36)	19 (37)	13 (50)	6 (24)
NSAIDs	66 (96)	49 (96)	24 (92)	25 (100)
Mean dose of corticosteroids — mg/day	5.6	5.8	5.5	6.5

*Percentages may not total 100, because of rounding. JRA denotes juvenile rheumatoid arthritis, DMARDs disease-modifying antirheumatic drugs, and NSAIDs nonsteroidal antiinflammatory drugs.

Forty-three female and 26 male patients were enrolled in the open-label study; of these, 34 female and 17 male patients continued to the double-blind study. At enrollment, the mean age was 10.5 years (range, 4 to 17) and the mean duration of juvenile rheumatoid arthritis was 5.9 years. The groups were well balanced in the double-blind study, except for age group and race ($P<0.02$) and corticosteroid use at base line ($P=0.05$). The unequal randomization did not affect the study results.

Sixty-four of the 69 patients enrolled in part 1 (93 percent) completed treatment. Early discontinuations were due to an adverse event in one patient who had urticaria with the first dose of etanercept, refusal of treatment by two patients, and lack of response in two patients. Of the 25 patients in the etanercept group in the double-blind trial, 19 (76 percent) completed treatment and 6 withdrew because of disease flare. Seven of the 26 patients in the placebo group (27 percent) completed the study; 1 withdrew because of parental refusal to allow continuation, and 18 withdrew because of disease flare.

Disease Response (Open-Label Study)

Fifty-one of the 69 patients enrolled in the open-label study (74 percent) met the definition of improvement at the end of that study. Considerable improvements in all measures of disease activity were seen with etanercept, and improvement was noted in patients as early as the first evaluation, two weeks after the beginning of treatment (Table 2). Forty-four of the 69 patients (64 percent) met the definition of 50 percent improvement, and 25 (36 percent) met the definition of 70 percent improvement at the end of the open-label study (Fig. 1).

Efficacy (Double-Blind Study)

Disease Flare

In the double-blind study, significantly more patients who received placebo (21 of 26 [81 percent]) than patients who received etanercept (7 of 25 [28 percent], $P=0.003$) had disease flare. The rates of flare remained consistently and significantly lower in the etanercept group ($P<0.001$) after adjustment for

TABLE 2. MEASURES OF DISEASE ACTIVITY AND IMPROVEMENT FROM BASE LINE.*

MEASURE	OPEN-LABEL STUDY (N=69)					DOUBLE-BLIND STUDY, PLACEBO (N=26)			DOUBLE-BLIND STUDY, ETANERCEPT (N=25)		
	BASE LINE	MO 1	MO 2	MO 3	% IMPROVEMENT†	BASE LINE	MO 3	MO 7	BASE LINE	MO 3	MO 7
Juvenile rheumatoid arthritis core set criteria											
Total no. of active joints‡	28	22	15	13	56	27.0	7.5	13.0	32.0	13.0	7.0
No. of joints with limitation of motion and with pain, tenderness, or both‡	10	4	3	2	79	6.5	1.0	4.5	8.0	2.0	1.0
Physician's global assessment of disease severity§	7	3	3	2	60	6	1	5	7	2	2
Patient's or parent's global assessment of overall well-being§	5	3	3	2	50	5	1	5	5	2	3
Score on Childhood Health Assessment Questionnaire¶	1.4	1.0	0.9	0.9	37	1.3	0.4	1.2	1.6	0.9	0.8
Erythrocyte sedimentation rate	35	18	20	20	50	27	12	30	41	15	18
Additional assessments											
Articular severity score**	88	60	47	45	50	84	36	66	90	35	38
Duration of stiffness (min)	45	15	15	15	75	60	5	38	45	15	5
Pain (on a visual-analogue scale)††	3.6	2.1	1.3	1.4	63	3.5	0.3	3.5	3.5	1.3	1.5
C-reactive protein (mg/dl)‡‡	3.5	0.9	1.1	0.8	60	1.8	0.3	3.0	3.5	0.2	0.4
Other‡											
No. of swollen joints	25	16	11	9	58	22.5	6.0	11.0	27.0	12.0	4.0
No. of joints with limitation of motion	23	20	18	15	23	23	17	22	24	12	9

*All values are medians. A last-observation-carried-forward approach was used for missing data and visits and for early termination.

†The percent improvement between base line and month 3 is shown. Patients who had values of zero at base line were omitted from calculations of percent change. Sixty-three patients were included in the analysis of duration of stiffness; 65 in the analysis of joints with both limitation of motion and pain, tenderness, or both, and pain (on a visual-analogue scale); and 67 in the analysis of patient's or parent's global assessment and the score on the Childhood Health Assessment Questionnaire.

‡Seventy-three joints were evaluated for the total active-joint count; 71 for limitation of motion with pain, tenderness, or both; 66 for swollen joints; and 71 for limitation of motion.

§Scores could range from 0 (best) to 10 (worst).

¶Scores could range from 0 (best) to 3 (worst).

||The normal ranges are 1 to 30 mm per hour for females and 1 to 13 mm per hour for males.

**Scores could range from 0 (best) to 962 (worst).

††Scores could range from 0 cm (best) to 10 cm (worst).

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

the effects of base-line characteristics (Table 3). With the exception of corticosteroid use at base line ($P=0.05$), none of the base-line characteristics were significant predictors of flare rates ($P>0.15$) (Table 3).

The median time to flare was more than 116 days for patients who received etanercept and 28 days for patients who received placebo ($P<0.001$) (Fig. 2). Because 13 of 25 patients were still receiving etanercept at the end of the study (day 116) without disease flare, the median time to flare was greater than 116 days.

Disease Response at End of Study

The definition of improvement was based on changes from base-line values, whereas disease flare was based on changes from values at the time of randomization to either etanercept or placebo in the double-blind study. Depending on the magnitude of a patient's response in the open-label study, response to treatment and presence of disease flare were not mutually exclusive outcomes. For example, if a patient had 28 active joints at base line but only 2 active joints

at the time of randomization, a change to 3 active joints would be considered a flare (at least 30 percent worse than the condition at the time of randomization) but would also still be considered improvement (at least 30 percent improved from base line). At the end of the seven-month study, 20 of the 25 patients who received etanercept in the double-blind study (80 percent) still met the definition of improvement, as compared with 9 of the 26 patients who received placebo (35 percent, $P<0.01$).

At the end of the study, 72 percent of the patients who received etanercept (18 patients) and 23 percent of those who received placebo (6 patients) met the definition of 50 percent improvement. Forty-four percent of the patients who received etanercept (11 patients) and 19 percent of those who received placebo (5 patients) met the definition of 70 percent improvement. Measures of disease activity continued to improve in patients who received etanercept in the double-blind study, whereas disease activity increased in those who received placebo (Table 2).

Scores in the disability domain of the Childhood

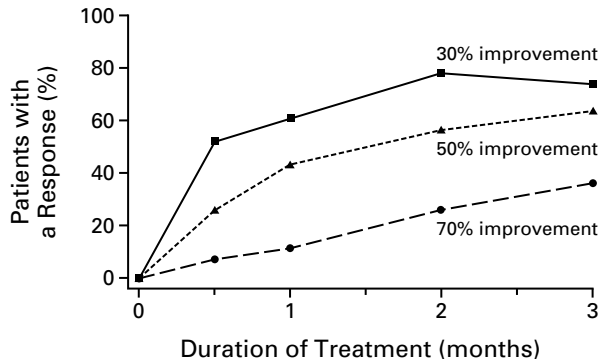


Figure 1. Incidence of 30, 50, and 70 Percent Improvement in the 69 Patients Who Received Etanercept in the Open-Label Study.

At the end of the open-label study, 51 (74 percent) of the patients had a 30 percent improvement, 44 (64 percent) had a 50 percent improvement, and 25 (36 percent) had a 70 percent improvement, as compared with base line.

TABLE 3. INCIDENCE OF DISEASE FLARE IN THE DOUBLE-BLIND STUDY ACCORDING TO THE BASE-LINE CHARACTERISTICS OF THE PATIENTS.

VARIABLE*	PLACEBO	ETANERCEPT
	no./total no. (%)	
Total with disease flare	21/26 (81)	7/25 (28)
Age group		
4–8 yr	4/5 (80)	3/13 (23)
9–12 yr	4/4 (100)	1/5 (20)
13–17 yr	13/17 (76)	3/7 (43)
Sex		
Female	14/15 (93)	5/19 (26)
Male	7/11 (64)	2/6 (33)
Race or ethnic group		
White	18/23 (78)	4/14 (29)
Black	1/1 (100)	1/3 (33)
Hispanic	2/2 (100)	1/6 (17)
Other	0	1/2 (50)
Rheumatoid factor		
Positive	8/8 (100)	0/4 (0)
Negative	13/18 (72)	7/21 (33)
Type of juvenile rheumatoid arthritis at onset		
Pauciarticular	1/1 (100)	0/2 (0)
Polyarticular	13/17 (76)	3/14 (21)
Systemic	7/8 (88)	4/9 (44)
Corticosteroid use at base line†		
Yes	12/13 (92)	3/6 (50)
No	9/13 (69)	4/19 (21)

*For each of the variables in this table, the difference in flare rates between the placebo and etanercept groups continued to be statistically significant ($P < 0.001$) when the effect of the variable was controlled for in a logistic-regression model.

†Corticosteroid use at base line was the only variable found to be predictive of flare rates in the placebo and etanercept groups ($P = 0.05$) in a logistic-regression model. For the other variables, the P value was greater than 0.15.

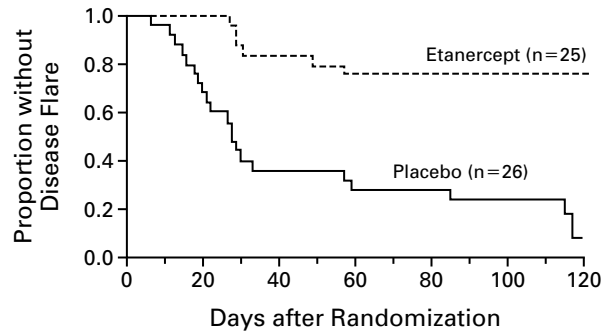


Figure 2. Kaplan–Meier Analysis of the Time to Disease Flare. The median time to disease flare was significantly shorter among the patients who received placebo (28 days) than among those who received etanercept (>116 days, $P < 0.001$) in the double-blind study.

Health Assessment Questionnaire^{31,32} (a measure of the patient’s physical functional ability) began to improve at the first evaluation two weeks after the beginning of etanercept treatment. At the end of the open-label study, a 37 percent median improvement in scores was seen for all patients. In the double-blind study, a 54 percent median improvement in scores from base line was seen in patients who continued to receive etanercept, as compared with no change from base line in patients who received placebo ($P = 0.01$).

In a significant proportion of patients, there were shifts from elevated values at base line to normal values of C-reactive protein, erythrocyte sedimentation rate, and white-cell and platelet counts after treatment with etanercept in the open-label study ($P < 0.03$ for each variable). In the double-blind study as compared with the end of the open-label study, a significant proportion of patients who received placebo had shifts from normal levels of C-reactive protein and erythrocyte sedimentation rates to above-normal values ($P \leq 0.03$ for each variable).

Safety

Etanercept was safe and well tolerated. There were no deaths. One patient withdrew because of urticaria after the first dose of etanercept; the urticaria responded to oral antihistamines. This patient later received commercially available etanercept without recurrence of urticaria. Two patients who received etanercept were hospitalized for serious adverse events (one for depression and a personality disorder and one for gastroenteritis–flu syndrome). All other adverse events were of mild-to-moderate intensity.

In the open-label study, the most common adverse events were injection-site reactions (39 percent of patients), upper respiratory tract infections (35 percent), headache (20 percent), rhinitis (16 percent), abdominal pain (16 percent), vomiting (14 percent), pharyn-

gitis (14 percent), nausea (12 percent), gastrointestinal infection (12 percent), and rash (10 percent).

In the double-blind study, there were no significant differences in the frequencies of adverse events between patients who received etanercept and those who received placebo. Injection-site reactions occurred in one patient in each of the treatment groups in the double-blind study. There were no laboratory abnormalities requiring urgent treatment in the etanercept group. No patient had persistent elevations in autoantibodies or had signs or symptoms of another autoimmune disease. Two patients tested positive for non-neutralizing antibody to etanercept. Fifty-nine of the 68 eligible patients in the study chose to continue treatment in an open-label, extended-treatment study.

DISCUSSION

The choice of a second-line agent for the treatment of juvenile rheumatoid arthritis has become more difficult because placebo-controlled trials and long-term prospective studies in children with juvenile rheumatoid arthritis have shown a lack of efficacy of agents commonly used in adults.³³⁻³⁷ Methotrexate is not efficacious or well tolerated in some patients with juvenile rheumatoid arthritis, and higher doses of methotrexate may be associated with greater toxicity.⁷

The design of this double-blind, placebo-controlled trial was sensitive to the problems of the population of patients with severe juvenile rheumatoid arthritis, for whom few treatment options are available. The study design allowed all patients to try the new treatment; only those who had a response to treatment were enrolled in the randomized portion of the trial. In addition, the definition of disease flare did not require the disease to become as severe as at base line. The protocol allowed patients to discontinue the study immediately after disease flare and be treated with etanercept in an open-label, long-term program. With the definition of disease flare used in this study, we effectively demonstrated differences in flare rates between the treatment groups.

The dose of etanercept used in this study (0.4 mg per kilogram) provided a favorable risk-benefit profile in children with polyarticular juvenile rheumatoid arthritis. Adverse events were of the types and intensity seen in a general pediatric population. There were no life-threatening adverse events, and the events were self-limited. A continued response was documented in patients who received etanercept in the double-blind study. At the end of the study, 80 percent of the patients who received etanercept for seven months met the definition of 30 percent improvement, as compared with 35 percent of the patients who received etanercept for three months and placebo for up to four months.

The results of this study confirm that TNF, lymphotoxin- α , or both have a role in juvenile rheumatoid arthritis, and that inhibition of these substances

is a valid therapeutic intervention. Etanercept was effective in pediatric patients with severe polyarticular juvenile rheumatoid arthritis (regardless of the type of onset) who did not tolerate or have an adequate response to methotrexate. The significant clinical response supports the use of etanercept in children with juvenile rheumatoid arthritis.

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IMAGES IN CLINICAL MEDICINE

The *Journal* has a large backlog of Images in Clinical Medicine that have been accepted for publication. Therefore, we will not consider new submissions in 2000. This decision will be reevaluated in December.
