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Long-Term Efficacy and Safety of Etanercept in Children With Polyarticular-Course Juvenile Rheumatoid Arthritis

Interim Results From an Ongoing Multicenter, Open-Label, Extended-Treatment Trial

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Objective. **To evaluate the long-term efficacy and safety of etanercept in children with juvenile rheumatoid arthritis (JRA) participating in an ongoing multicenter, open-label, extended-treatment trial. All patients had been participants in an initial randomized efficacy and safety trial of etanercept.**

Methods. **Etanercept was administered at a dosage of 0.4 mg/kg (maximum 25 mg) subcutaneously twice each week. Safety and efficacy evaluations were performed every 3–4 months. The JRA 30% definition of improvement (DOI) was defined as improvement of ≥30% in at least 3 of 6 response variables used to assess disease activity, with no more than 1 variable worsening by more than 30%.**

Results. **At the time of analysis, 48 of the 58 patients (83%) were still enrolled in the study; 43 of them (74%) had completed 2 years of treatment. Of these 43 patients, 81% met the JRA 30% DOI, 79% met the JRA 50% DOI, and 67% met the JRA 70% DOI. Ten children started low-dose methotrexate after year 1. Of the 32 children taking prednisone, the dosage was decreased to <5 mg/day in 26 (81%). Two children had serious infections (varicella with aseptic meningitis in one and complicated sepsis in the other). In general, adverse events were of the types seen in a general pediatric patient population.**

Conclusion. **Children with severe, longstanding, methotrexate-resistant polyarticular JRA demonstrated sustained clinical improvement with >2 years of continuous etanercept treatment. Etanercept was generally well-tolerated. There were no increases in the rates of adverse events over time. However, children taking etanercept should be monitored closely for infections.**

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in children (1,2). The proin-

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flammatory cytokine tumor necrosis factor (TNF) has been shown to play a central regulatory role in the pathogenesis of rheumatoid arthritis (3–10), and TNF levels have been shown to be elevated in both serum and synovial fluid from children with JRA (11). Treatment with etanercept (Enbrel; Immunex, Seattle, WA), a fully human fusion protein that inhibits excess TNF and the subsequent inflammatory cytokine cascade, has proved to be beneficial in adults with rheumatoid arthritis and in children with JRA (12).

In a previous 7-month study of etanercept, we evaluated 69 pediatric patients with severe polyarticular-course JRA who did not tolerate, or had an inadequate response to, methotrexate treatment (12). The study was designed with an initial open-label phase followed by a randomized double-blind phase. Seventy-four percent of the patients experienced significant clinical benefit with minimal toxicity after 3 months of open-label etanercept therapy. Eighty percent of the patients who received etanercept for 7 months met the JRA 30% definition of improvement (DOI), compared with 35% of the patients who received etanercept for 3 months and then placebo for up to 4 months.

Fifty-eight of the 69 patients who participated in the initial study (84%) chose to continue treatment in an open-label, extended-treatment trial (the extension trial). We report herein the interim results of the extension trial, in which patients have received etanercept for a median of 2.3 years.

PATIENTS AND METHODS

Patient population. The 58 patients in this extension trial were previously enrolled in the initial trial described above. At the time of enrollment in the initial trial, patients were 4–17 years of age and had active, polyarticular-course JRA. The JRA onset type could have been pauciarticular, polyarticular, or systemic. There were no pregnant or lactating patients, and patients of childbearing potential were required to use contraception throughout the study. Patients were not eligible if they had significant concurrent medical conditions.

Study design. This study is an ongoing multicenter, open-label, extended-treatment trial. The institutional 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.

The end-of-study evaluations obtained for the initial study were used as screening evaluations for the extension trial, provided that the patients enrolled directly from the blinded portion of the initial study. If patients discontinued from, or were nonresponders in, the double-blind portion of the initial study, screening evaluations were done within 2 weeks before entry into the extension trial.

Vials of study medication contained 25 mg of lyophilized etanercept. Before injection, the contents of the vial were reconstituted with 1 ml of bacteriostatic water containing 0.9% benzyl alcohol. All patients received 0.4 mg/kg of etanercept (maximum 25 mg) subcutaneously twice weekly.

Use of methotrexate was not permitted during the first year of study. Intraarticular and soft-tissue injections of corticosteroids were allowed after a patient had received etanercept for 12 continuous weeks. (Treatment time in the initial study was included if treatment was continuous upon enrollment in the extension study.) A joint injected within 24 hours before a complete joint examination was performed was not included in the examination. Stable doses of nonsteroidal antiinflammatory drugs (NSAIDs) and low doses of corticosteroids ($\leq$0.2 mg/kg/day of prednisone; maximum 10 mg/day) were permitted. Pain medications were allowed except during the 12–18 hours before joint assessment. After the first year, investigators were allowed to adjust the use and dosages of corticosteroids, NSAIDs, and pain medications without restriction, and methotrexate could be added to the treatment regimen.

Physical examinations, laboratory tests (hematology, serum chemistry, and urinalysis), and evaluations of disease activity measures and response were performed at the end of months 1, 2, and 3 and every 3 months thereafter during the first year. For patients whose treatment was interrupted between the initial and extension studies, these evaluations also were done on day 1 (before administration of etanercept).

At the 6-month visit, blood was drawn for testing serum levels of rheumatoid factor, antibodies to etanercept, and autoantibodies (antinuclear antibodies [ANA], anti–double-stranded DNA [anti-dsDNA] antibodies, IgG and IgM anticardiolipin antibodies, and antibodies to extractable nuclear antigens).

After 1 year of treatment was completed, physical examinations, laboratory tests, and evaluations of disease activity measures and response were performed every 4 months. Significant adverse events, including malignancies, hospitalizations, and new signs or symptoms of other connective tissue diseases, also were recorded. Tanner scores were obtained yearly for patients who had not reached sexual maturity. Final safety assessments were made 30 days after discontinuation of the study drug if patients withdrew from the study.

The same assay methods for the erythrocyte sedimentation rate (ESR; Westergren) and rheumatoid factor (latex fixation) were used throughout the study period.

Definition of improvement. The outcome measures used to assess disease response consisted of the following set of 6 response variables (the JRA core criteria) (13,14): 1) global assessment of disease severity by the physician, 2) global assessment of overall well-being by the patient or the patient's parent or guardian, 3) number of joints with active disease (joints with swelling not due to deformity or joints with limitation of motion and with pain, tenderness, or both), 4) number of joints with limitation of motion, 5) functional ability, assessed in this study by the Childhood Health Assessment Questionnaire (C-HAQ) (15,16), and 6) a laboratory marker of inflammation, defined in this study as the ESR during the first year and as the C-reactive protein (CRP) level thereafter. The fourth criterion was modified to "number of joints with limitation of motion and with pain, tenderness, or

both" to eliminate counting joints with contractures that might not have improved during the course of treatment.

To meet the JRA 30% DOI at a scheduled visit, patients had to have 30% improvement from baseline in at least 3 of the 6 response variables, with no more than 1 variable worsening by more than 30% (13). (Responses were compared with patients' baseline values from the initial study.) This same definition of response has been officially adopted by the American College of Rheumatology (ACR) and is known as the ACR Pediatric 30 (17).

Additional activity assessments. Additional assessments of disease activity included an articular severity score (18), the duration of morning stiffness, an assessment of pain (Likert scale), and an evaluation of CRP levels. Patients also were evaluated for JRA 50% and 70% DOI. To meet the JRA 50% and 70% DOI, patients had to have 50% or 70% improvement, respectively, in at least 3 of the 6 response variables, with no more than 1 variable worsening by more than 30%.

Statistical analysis. Demographic and background characteristics at enrollment into the initial trial were listed and summarized. Adverse events were classified using the COSTART dictionary (19). Infections were reported separately from other adverse events. Laboratory results also were summarized separately from adverse events, using modified common toxicity criteria of the National Cancer Institute and the testing laboratory's normal ranges.

After completion of the first 12 months of the extension study, only significant adverse events were described. These included any hospitalizations, occurrences of malignancies, and new signs or symptoms of other connective tissue diseases.

Responses were evaluated according to the JRA 30% DOI and were compared with patients' baseline values from the initial study. Response data were analyzed for both a per protocol and a modified intent-to-treat group. The per protocol group included 43 subjects who had received etanercept for 2 years at the time of the analysis. The modified intent-to-treat group (n = 51) included the 43 subjects from the per protocol group and 8 of 10 subjects who had prematurely discontinued the study (7 subjects with suboptimal clinical response and 1 subject who discontinued because of an adverse event). These 8 subjects were counted as nonresponders in the analysis. Not included in the modified intent-to-treat analysis are 1 patient who was lost to followup and 1 patient who discontinued treatment because of disease remission.

RESULTS

Baseline characteristics. Baseline demographic and disease characteristics at the time of enrollment in the initial trial are summarized in Table 1 for the 58 patients in this extension study. Thirty-nine girls and 19 boys were enrolled. Their mean age was 10 years (range 4–17 years), and their mean duration of JRA was 5.9 years.

Table 1. Demographic characteristics and disease history of the patients with JRA at enrollment into the initial trial*

Characteristic	Etanercept (n = 58)
Mean age, years	10
Sex, no. (%)	
Female	39 (67)
Male	19 (33)
Race, no. (%)	
White	43 (74)
Black	4 (7)
Hispanic	9 (16)
Other	2 (3)
JRA onset type, no. (%)	
Pauciarticular	5 (9)
Polyarticular	34 (59)
Systemic	19 (33)
Mean duration of JRA, years	5.9
RF positive, no. (%)	13 (22)
Previous methotrexate, no. (%)	58 (100)
DMARDs (any) at washout, no. (%)	43 (74)
Methotrexate	42 (72)
Hydroxychloroquine	12 (21)
Concomitant therapy at enrollment, no. (%)	
NSAIDs	56 (97)
Corticosteroids	22 (38)
Mean steroid dose, mg/day	5.7

* JRA = juvenile rheumatoid arthritis; RF = rheumatoid factor; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs.

Disposition of the patients. At the time of this interim analysis, 48 of the 58 patients (83%) were still enrolled in the study; 43 of them (74%) had completed at least 2 years of treatment. Ten patients discontinued the extension study for the following reasons: suboptimal clinical response (n = 7), lost to followup (n = 1), adverse event (n = 1), and disease remission (n = 1). (A discontinuation due to an adverse event that was reported after the database was analyzed is discussed in the safety section below.) Table 2 shows the disease onset type for the 10 patients who withdrew from the

Table 2. Disease onset type for the 10 patients with juvenile rheumatoid arthritis (JRA) who withdrew from the study as of the interim analysis

Reason for discontinuation	JRA onset type		
	Systemic	Polyarticular	Pauciarticular
Suboptimal clinical response (n = 7)	4	2	1
Lost to followup (n = 1)	0	1	0
Adverse event (n = 1)	1	0	0
Disease remission (n = 1)	0	0	1
Total withdrawals	5	3	2

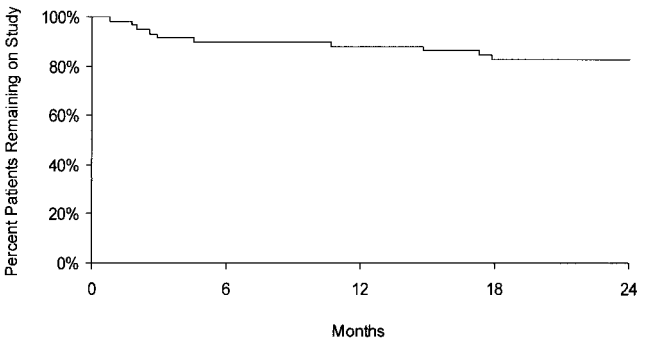

Figure 1. Patient discontinuations during the first 2 years of the etanercept extension trial. Kaplan-Meier curve showing the discontinuation curve for patients during the first 2 years of the study. At the end of 2 years, 83% of the patients continued in the study.

study. Figure 1 shows the discontinuation curve during the first 2 years of this extension trial.

Concomitant medications. After the first year of treatment, methotrexate could be added to the treatment regimen. Ten patients started methotrexate after 12 months in the extension study. At the time of this interim analysis, 8 patients were still receiving methotrexate (mean 0.56 mg/kg/week; median 0.51 mg/kg/week) and a stable dosage of etanercept.

Twenty-three patients were taking systemic corticosteroids when they started the extension study. During the extension study, 9 of the 23 patients discontinued prednisone treatment, and an additional 9 patients decreased their daily prednisone dosage to ≤3 mg. Another 9 patients started prednisone therapy during the extension study; 4 of these 9 patients were able to discontinue prednisone treatment during the study, and 2 others were taking dosages of <5 mg/day. Overall, 26 of the 32 patients (81%) who received prednisone during the extension study were able to decrease the dosage to <5 mg/day. At the time of this interim analysis, 16 patients were receiving corticosteroids (mean dosage 0.13 mg/kg/day; median dosage 0.09 mg/kg/day).

Nine patients received steroid joint injections

Table 3. Disease activity measures at baseline and over time and percentage improvement from baseline at the end of year 2*

	Initial trial		Extension trial									
Parameter	Baseline	Month 3	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 16	Month 20	Month 24	% improvement
JRA core criteria												
Total no. of active joints†	29	10.5	10.0	6.5	4.0	2.0	3.0	2.5	2.5	3.0	3.0	88
No. of joints with LOM and P/T†	9	1.0	1.0	1.0	0	0	1.0	0	0.5	0	0	98
Physician's global assessment‡	7	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	2.0	70
Patient's/parent's global assessment‡	5	2.0	2.0	2.0	2.0	2.0	1.5	2.0	1.0	1.0	1.0	67
C-HAQ score§	1.4	0.75	0.8	0.8	0.6	0.8	0.6	0.5	0.6	0.7	0.4	58
ESR¶	35	18	15.0	15.0	14.5	15.0	13.5	15.5	NA	NA	NA	NA
Additional assessments												
No. of swollen joints†	26	8.0	8.0	6.0	4.0	2.0	1.0	1.5	1.0	2.0	2.0	93
No. of joints with LOM†	24	15.0	15.0	13.5	12.0	14.0	12.0	12.5	12.0	13.0	12.0	43
Articular severity score#	88	41	51.0	38.0	27.0	31.0	29.5	24.5	29.0	24.5	42.0	65
Duration of morning stiffness (minutes)**	53	15	10.0	5.0	3.0	2.0	3.0	5.0	NA	NA	NA	NA
Pain‡	3.6	1.0	1.3	0.9	0.6	1.0	0.8	0.3	0.7	0.9	0.8	75
CRP††	3.4	0.7	0.5	0.6	0.2	0.3	0.2	0.4	0.3	0.2	0.1	90

* Only data for patients with juvenile rheumatoid arthritis (JRA) who underwent assessment at the respective visits are included. Patients who had values of zero at baseline were omitted from calculations of the percentage of improvement from baseline. Values are the median. NA = not assessed.

† The total numbers of joints evaluated were as follows: 73 joints for the total active joint count, 71 joints for the limitation of motion (LOM) with pain and/or tenderness (P/T) count, 66 joints for the swollen joint count, and 71 joints for the LOM joint count. For this study, the JRA core set parameter "number of joints with loss of motion" was modified to "number of joints with limitation of motion and with pain, tenderness, or both."

‡ A Likert scale was used for the global assessments and the assessment of pain (0 = best; 10 = worst).

§ The range of scores for the Childhood Health Assessment Questionnaire (C-HAQ) is 0–3 (0 = best; 3 = worst).

¶ The range of normal values for the erythrocyte sedimentation rate (ESR) is 1–30 mm/hour in females and 1–13 mm/hour in males. The ESR was not assessed after year 1.

The range of scores for articular severity was 0–926.

** Duration of morning stiffness was not assessed after year 1.

†† The range of normal values for the C-reactive protein (CRP) level is 0–0.79 mg/dl.

Table 4. Percentages of patients who met the JRA 30%, 50%, and 70% definitions of improvement at the end of year 2*

Group, improvement level	All patients	Patients who received placebo in previous study	JRA onset type		
			Pauciarticular	Polyarticular	Systemic
Per protocol group†					
30% improvement	81 (35/43)	85 (17/20)	100 (3/3)	79 (22/28)	83 (10/12)
50% improvement	79 (34/43)	85 (17/20)	100 (3/3)	79 (22/28)	75 (9/12)
70% improvement	67 (29/43)	75 (15/20)	67 (2/3)	68 (19/28)	67 (8/12)
Modified ITT group‡					
30% improvement	69 (35/51)	77 (17/22)	75 (3/4)	73 (22/30)	59 (10/17)
50% improvement	67 (34/51)	77 (17/22)	75 (3/4)	73 (22/30)	53 (9/17)
70% improvement	57 (29/51)	68 (15/22)	50 (2/4)	63 (19/30)	47 (8/17)

* Values are the percentage of patients with juvenile rheumatoid arthritis (JRA) (number who met the definition of improvement/number evaluated).
† The per protocol group includes 43 patients who received etanercept for 2 years at the time of the interim analysis.
‡ The modified intent-to-treat (ITT) group includes the 43 patients in the per protocol analysis, the 7 patients who discontinued the study because of suboptimal clinical response, and the 1 patient who discontinued because of an adverse event (n = 51). Two patients were not included in the modified ITT group: 1 was lost to followup, and 1 discontinued because of disease remission.

during the extension study. A total of 28 joints were injected in these 9 patients.

Efficacy. Clinical benefits were sustained in the 43 patients who had received etanercept for 2 years (Table 3). Patients who received etanercept in the initial study maintained their improvements in disease activity measures, while patients who received placebo in the initial study reestablished clinical responses once they resumed treatment with etanercept in the extension trial.

Two years into this extension trial, 81% of the 43 patients in the per protocol group met the JRA 30% DOI (compared with baseline), 79% met the JRA 50% DOI, and 67% met the JRA 70% DOI. Efficacy also was apparent in the modified intent-to-treat group; 69% of the 51 patients met the JRA 30% DOI, 67% met the 50% DOI, and 57% met the 70% DOI (Table 4).

The percentage of improvement from baseline also was evaluated in 2 subgroups of patients. The first subgroup included patients who received placebo in the blinded portion of the initial study and then resumed etanercept treatment in this trial. Responses in these patients deteriorated while they were taking placebo during the second part of the initial trial, but the responses were regained and sustained once the patients resumed etanercept treatment in the extension trial (Table 4).

The second subgroup consisted of 8 patients who did not meet the JRA 30% DOI after treatment with etanercept for 3 months during the open-label portion of the initial trial. To examine whether extended treatment with etanercept improved response, these patients stopped etanercept treatment for 1 month and then resumed treatment in this extension trial. The majority of patients achieved clinical response (JRA 30% DOI) with extended treatment: 71% (5 of 7) at 6 months, 57% (4 of 7) at 1 year, and 67% (4 of 6) at 2 years.

Etanercept treatment was effective regardless of the JRA onset type. Table 4 presents the responses at the end of year 2 in all patients, in patients who received placebo in the previous trial, and in patients categorized by JRA onset type.

The percentages of patients in whom JRA disease response measures yielded normal results at 2 years are shown in Table 5. Data are given for both the per protocol group and the modified intent-to-treat group.

For patients who continued to take etanercept, improvement in scores in the disability domain of the C-HAQ (15,16) (a quantitative assessment of a child's or an adolescent's physical functioning) was maintained throughout the trial. At the end of year 2, there was a median of 58% improvement in scores compared with baseline values in all patients. Patients who resumed treatment with etanercept after having taken placebo at the end of the initial trial had a median of 67% improvement in C-HAQ scores compared with baseline values in the initial study.

In addition, a significant proportion of all patients enrolled in the extension study (n = 58) demonstrated shifts toward normal CRP levels (48%; 28 of 58), ESRs (37%; 21 of 57), hemoglobin values (21%; 12 of 58), and platelet counts (35%; 20 of 58) at their last visit in the extension trial compared with their baseline values. These changes were statistically significant ($P < 0.001$ for CRP, ESR, and platelets; $P = 0.017$ for hemoglobin).

Table 5. Patients with normalization of disease response measures at the end of year 2

Arthritis activity measure	No. of patients	% of patients	
		Per protocol group (n = 43)*	Modified ITT group (n = 51)†
Total no. of active joints = 0‡	11	26	22
No. of joints with LOM and P/T = 0‡	22	51	43
No. of joints with LOM = 0‡	7	16	14
Physician's global assessment = 0§	7	16	14
Patient's/parent's global assessment = 0§	10	23	20
C-HAQ score = 0¶	13	30	25
CRP = within normal range#	26	60	51
Pain = 0§	8	19	16

* The per protocol group includes 43 patients who received etanercept for 2 years at the time of the interim analysis.
† The modified intent-to-treat (ITT) group includes the 43 patients in the per protocol analysis, the 7 patients who discontinued the study because of suboptimal clinical response, and the 1 patient who discontinued because of an adverse event (n = 51). Two patients were not included in the modified ITT group: 1 was lost to followup, and 1 discontinued because of disease remission.
‡ The total numbers of joints evaluated were as follows: 73 joints for the total active joint count, 71 joints for the limitation of motion (LOM) with pain and/or tenderness (P/T) count, and 71 joints for the LOM joint count.
§ A Likert scale was used for the global assessments and the assessment of pain (0 = best; 10 = worst).
¶ The range of scores for the Childhood Health Assessment Questionnaire (C-HAQ) is 0–3 (0 = best; 3 = worst).
# The range of normal values for the C-reactive protein (CRP) level is 0–0.79 mg/dl.

Among the subgroup of 10 patients (8 girls, 2 boys) who received methotrexate after 12 months in the study, 6 patients had polyarticular-onset JRA, 3 had systemic-onset JRA, and 1 had pauciarticular-onset JRA. The median number of joints with active disease in these patients was 38.0 and 28.0 at baseline and month 3, respectively, in the initial study. At 1 month in the extension study, the median number of joints with active disease decreased to 24.0. The median number of joints with active disease was 21.0 at month 3, 9.5 at month 6, 23.5 at month 9, and 26.0 at month 12. The patients continued to have stable, active disease with etanercept treatment, and methotrexate was added to the treatment regimen. Elevations in CRP levels and the ESR persisted even after methotrexate was added to the treatment regimen. Two patients discontinued the study after starting methotrexate because of lack of efficacy. One of these patients had polyarticular-onset JRA and discontinued after month 12. The other patient had systemic-onset JRA and discontinued after month 16. At year 2, the 8 patients remaining in this subgroup had a median of 22.5 joints with active disease.

Safety. Most adverse events, including infections, were of mild-to-moderate intensity. No significant increases in the overall rates of adverse events or infections occurred with prolonged exposure to etanercept. The rates of adverse events that were related and unrelated to infections during the first year of this trial were comparable to the rates observed in the initial study.

The most commonly reported adverse events unrelated to infection were headache, abdominal pain, rhinitis, nausea, fever, accidental injury, and rash. The most commonly reported infections were upper respiratory tract infection, pharyngitis, skin infection, flu syndrome, otitis, and conjunctivitis. Table 6 shows the rates of adverse events in all patients during the first year of this extension study, as well as the event rates in the etanercept and placebo treatment groups during the double-blind portion of the initial study.

No treatment-related effects were seen on hematologic or serum chemistry profiles or on urinalysis. No patients demonstrated signs or symptoms of other autoimmune diseases during the extension study. Testing for ANA and anti-dsDNA antibodies was done at baseline and after 6 and 12 months of etanercept therapy. No child who was negative for ANA at baseline became consistently positive during the study, and no child developed anti-dsDNA antibodies or evidence of antibodies to antiphospholipid antigens.

Rheumatoid factor was positive in 17 patients. Nine of the 17 patients were positive for rheumatoid factor at baseline and remained so during the trial. Four of the 17 patients were positive at baseline and became consistently negative during the study. The remaining 4 patients were negative for rheumatoid factor at baseline

Table 6. Rates of adverse events of all intensities that occurred in 5 or more patients in the extension trial*

Adverse event	Double-blind portion of initial trial		Extension trial
	Etanercept (n = 25) (6.8 patient-years)	Placebo (n = 26) (3.7 patient-years)	Etanercept (n = 58) (52.6 patient-years)
Unrelated to infections			
Headache	1.08	1.08	0.84
Abdominal pain	0.48	0.24	0.36
Rhinitis	0.72	0.24	0.17
Nausea	0.48	0	0.15
Fever	0.60	0.24	0.11
Accidental injury	0.48	0.24	0.11
Rash	0	0.84	0.11
Infections			
Upper respiratory tract infection	1.92	1.68	1.31
Pharyngitis	0.48	0	0.21
Skin infection	0.48	0	0.19
Flu syndrome	0.24	0.60	0.17
Otitis	0.12	0.60	0.13
Conjunctivitis	0	0	0.10

* Values are the number of events per patient-year (event rate). Patients may have had more than one event of the same type. All occurrences of each event were counted for each patient. After the first 12 months of the extension study, only significant adverse events were recorded. Events are listed by decreasing rate for the extension trial.

and became positive at least once during the study. In the patients in whom rheumatoid factor status changed, the positive findings were all weakly positive on a very sensitive enzyme-linked immunosorbent assay.

Nine patients were hospitalized for the following serious adverse events during the study: peritonitis/appendicitis, cervical subluxation and aseptic meningitis after infection with varicella-zoster virus (VZV), varicella, soft tissue infection after a cut to the hand, epigastric and abdominal pain, epigastric pain, postoperative wound infection and type 1 diabetes mellitus, sepsis, and dental abscess. The patient with aseptic meningitis and the patient with sepsis withdrew from the study because of the adverse events.

Three children developed VZV infections during this study. All 3 had negative VZV antibody titers before etanercept treatment and developed positive VZV antibody titers (IgM and IgG) after the infections. None of the children received varicella-zoster immune globulin upon exposure.

The cervical subluxation and aseptic meningitis occurred in a 13-year-old boy after an infection with VZV, which occurred 2 months after he started treatment in this extension trial. (The patient received etanercept for 3 months in the initial study.) The patient was not taking methotrexate or prednisone at the time of the VZV infection. Approximately 1 week after the onset of the varicella rash, he was hospitalized because of sore throat, vomiting, a swollen right knee, and bilateral numbness of the face. Treatment with intravenous acyclovir was started at that time. He experienced neurologic deterioration, with numbness in the dorsal aspects of the hands and feet, and urinary and bowel incontinence. Magnetic resonance imaging of the spine showed subluxation of C1–C2, with occlusion of the right vertebral artery. The patient had preexisting bony abnormalities in the spine that were secondary to severe JRA. There was pleocytosis of the cerebrospinal fluid, and serum was positive for antibodies to VZV. The vomiting and cerebrospinal fluid pleocytosis were attributed to aseptic meningitis. The patient was placed in a halo brace, and a spinal fusion (from the posterior occiput to C2) was performed. The patient's condition improved with the splint and surgical fixation procedure.

The second VZV infection occurred in a 10-year-old boy who had been receiving etanercept for ~15 months in this trial, when he developed fever, headache, and a rash with fluid-filled lesions involving his entire body. The patient also was taking 5 mg/day of prednisone. Treatment with etanercept was temporarily suspended, and the patient was hospitalized. A diagnosis of varicella was substantiated by findings of a skin lesion smear and the presence of a more than 4-fold increase in VZV antibody on a quantitative assay. The patient was treated with intravenous acyclovir and prophylactic antibiotics to prevent secondary bacterial infection of the

skin. The varicella resolved. The patient discontinued the study 3 months later to begin treatment with commercial etanercept.

The third patient who had VZV infection was an 8-year-old girl. She received etanercept for 7 months in the initial trial. After receiving etanercept for ~2 months in the present trial, she developed a skin rash and itching. Treatment was temporarily suspended for 2 doses, acyclovir was administered, and the infection resolved. At the time of the VZV infection, the patient was not taking methotrexate or prednisone. One week later, she developed lethargy, headache, nausea, vomiting, and intermittent fever, and 1 dose of study drug was withheld. She did not experience any neurological deficits, and the symptoms resolved after 5 days.

The most serious adverse event in this study was sepsis, which occurred in a 10-year-old girl who had been taking etanercept for ~2 years in the present trial. She also was receiving concomitant low-dose prednisone (~5 mg/day for >2 years) and methotrexate (0.8 mg/kg/week). She was admitted to the hospital because of pain in both legs and was found to have arterial occlusion in the left lower leg. Group A β-hemolytic streptococci were isolated in cultures of her blood. Within 24 hours, she went into shock and developed respiratory distress, disseminated intravascular coagulation, and purpura fulminans. She was intubated because respiratory assistance with a mechanical ventilator was required, and platelets and plasma were administered. She recovered; however, complications of the vascular damage resulted in dry ischemic gangrene of her left foot, and an amputation was subsequently performed.

DISCUSSION

The treatment of JRA continues to evolve, with the introduction of many new pharmacologic interventions. Although methotrexate continues to be the disease-modifying antirheumatic drug used most frequently for the treatment of JRA, it is not efficacious in, or well-tolerated by, some patients. Higher doses of methotrexate may not be more effective and may be associated with greater toxicity (20,21). An exceptional benefit-to-risk profile in children with polyarticular-course JRA was demonstrated with etanercept treatment in the initial study (12) as well as in the extension trial reported herein. Children who received more than 2 years of continuous treatment with etanercept maintained a significant clinical response to treatment.

Nine patients experienced serious adverse events during the extension study, and 2 of them discontinued the trial because of the adverse events. The majority of adverse events in this study were of mild-to-moderate intensity, and there were no significant increases in the rates of adverse events unrelated to infection over time. Overall, the reported adverse events unrelated to infection were of the types and intensities seen in a general pediatric population (22). There were no cases of tuberculosis, demyelination, or pancytopenia in the pediatric patients in this study, and no patients tested positive for new autoantibodies or developed autoimmune illnesses.

Concerns have been raised about an increased risk of infections with immunomodulating agents such as etanercept. In this study, the categorical types and rates of infections were similar to those observed in the placebo group in the initial study. However, there were significant infections in the children in this study. Three patients contracted varicella, and all were treated with acyclovir. In 2 children, the varicella infections were complicated by self-limited central nervous system changes (aseptic meningitis in 1 patient). There was a very serious, complicated case of sepsis in a child who also was receiving other immunosuppressive medications. The contribution of etanercept therapy to the severity of infections is difficult to ascertain given the small number of study subjects and the lack of a comparison population. Therefore, it is important to carefully assess patients for active, chronic, or recurrent infections before initiating, as well as during, etanercept therapy.

Until additional data are available, unvaccinated, susceptible children receiving etanercept who are exposed to varicella should be treated similarly to children receiving other immunomodulatory therapies (e.g., methotrexate and corticosteroids). Treatment with varicella-zoster immune globulin as soon as possible after exposure and acyclovir should be considered at the earliest sign of infection.

At this time, a much larger, long-term safety study comparing etanercept treatment with methotrexate treatment is being conducted in children with JRA. The study will permit a more accurate assessment of the effect of etanercept therapy on the frequency and severity of viral and bacterial infections.

Results of the present study show that long-term treatment with etanercept can provide significant clinical benefit to pediatric patients with severe polyarticular-course JRA, regardless of disease onset type. Etanercept is generally well-tolerated even with prolonged use and has not been associated with increases in the rates of adverse events or infections with longer-term treatment.

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