

Safety and Efficacy of up to Eight Years of Continuous Etanercept Therapy in Patients With Juvenile Rheumatoid Arthritis

Daniel J. Lovell,¹ Andreas Reiff,² Norman T. Ilowite,³ Carol A. Wallace,⁴ Yun Chon,⁵ Shao-Lee Lin,⁵ Scott W. Baumgartner,⁵ and Edward H. Giannini,¹ for the Pediatric Rheumatology Collaborative Study Group

Objective. To evaluate the safety and efficacy of up to 8 years of etanercept treatment in patients with polyarticular-course juvenile rheumatoid arthritis (JRA).

Methods. Patients with JRA who previously participated in a randomized controlled trial (RCT) of etanercept were eligible to receive etanercept in a long-term open-label extension (OLE) trial. Safety end points included the incidences of serious adverse events

(SAEs), medically important infections (MIIs), and death. Efficacy end points included the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), Pedi 50, Pedi 70, Pedi 90, and Pedi 100 criteria for improvement.

Results. Of the 69 patients originally enrolled in the RCT, 58 (84%) participated in the OLE, for a total of 318 patient-years of etanercept exposure. A total of 42 of the 58 patients (72%) entered the fourth year of continuous etanercept treatment, and 26 patients (45%) entered the eighth year. Sixteen patients (23% of those entering the RCT) reported 39 SAEs. The overall rate of SAEs (0.12 per patient-year) did not increase with long-term exposure to etanercept. The rate of MIIs (0.03 per patient-year) remained low; 1 new MII was reported in patients with ≥ 5 years of etanercept exposure. No cases of tuberculosis, opportunistic infections, malignancies, lymphomas, lupus, demyelinating disorders, or deaths were reported. An ACR Pedi 70 response or higher was achieved by 100% of patients with 8 years of data (11 of 11) and by 61% of patients according to the last observation carried forward data (28 of 46).

Conclusion. These data suggest that the acceptable safety profile of etanercept therapy is maintained for up to 8 years in this population of JRA patients. Improvements in the signs and symptoms of JRA were also maintained for up to 8 years.

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in children (1,2). JRA is typified by joint inflammation that can cause joint damage, retard normal growth, and lead to long-term disability and decreased quality of life (3,4). Traditional treatment of children with JRA includes the use of nonsteroidal antiinflammatory drugs (NSAIDs), cortico-

ClinicalTrials.gov identifier: NCT00357903.

Supported by Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth Pharmaceuticals.

¹Daniel J. Lovell, MD, MPH, Edward H. Giannini, MSc, DrPH: Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ²Andreas Reiff, MD: University of Southern California, Los Angeles, and Childrens Hospital Los Angeles, Los Angeles, California; ³Norman T. Ilowite, MD: Albert Einstein College of Medicine, Bronx, New York; ⁴Carol A. Wallace, MD: Children's Hospital and Regional Medical Center, Seattle, Washington; ⁵Yun Chon, PhD, Shao-Lee Lin, MD, PhD, Scott W. Baumgartner, MD: Amgen Inc., Thousand Oaks, California.

Dr. Lovell has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Centocor, Wyeth, Bristol-Myers Squibb, Amgen, Abbott, Pfizer, Regeneron, Novartis, and Hoffmann-La Roche. Dr. Reiff has received consulting fees, speaking fees, and/or honoraria (less than \$10,000) from Amgen, Abbott, Wyeth, Merck, Pfizer, and Novartis and has served as an expert witness on behalf of Pfizer concerning FDA rehearsal. Dr. Ilowite has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Novartis, Bristol-Myers Squibb, and Abbott. Dr. Wallace has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Amgen, Pfizer, Novartis, and Bristol-Myers Squibb and has received research grants (more than \$10,000 each) from Pfizer and Centocor. Drs. Chon, Lin, and Baumgartner hold stock and/or stock options in Amgen. Dr. Giannini has been awarded a research grant (to Children's Hospital Medical Center) from Amgen for clinical trial expenses.

Address correspondence and reprint requests to Daniel J. Lovell, MD, MPH, Children's Hospital Medical Center, Location E, Room 2-129, 3333 Burnet Avenue, Cincinnati, OH 45229. E-mail: Daniel.Lovell@cchmc.org.

Submitted for publication October 23, 2007; accepted in revised form January 28, 2008.

steroids, and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) (5); however, these therapies are effective only in a subset of patients (5,6).

Tumor necrosis factor (TNF) has been found to play an important role in the inflammatory response of a number of inflammatory diseases including JRA (7–9). The advent of TNF antagonists has dramatically improved the treatment options for patients with rheumatic diseases. In addition, anti-TNF therapies have been shown to be highly effective in the treatment of JRA patients whose disease has been unresponsive to traditional therapies (8,10). Specifically, nonrandomized open-label studies of the TNF-blocking agents etanercept and infliximab have shown that these agents safely control active disease when used in combination with traditional therapies (11,12). Moreover, a randomized, double-blind, placebo-controlled trial showed that etanercept was well tolerated and produced significant improvements in disease activity when used in the absence of DMARDs (13).

Data from patients receiving long-term treatment are needed. JRA is a chronic disease, and recent reports indicate that many patients with JRA continue to have active disease 10 years after onset, with persistence into adulthood in many patients (9,14). In addition, a recent longitudinal study by Wallace et al (15) evaluating 437 patients with JIA over a mean followup period of 6.8 years showed that $\leq 35\%$ of patients, regardless of the category of JIA, demonstrated a period of disease inactivity of 12 months or longer while off the medication regimen (15).

Etanercept is a soluble dimeric fusion protein consisting of the human p75 TNF receptor fused to the Fc region of human IgG1, and it was the only biologic agent that had been approved by the Food and Drug Administration for the treatment of children with polyarticular-course JRA until very recently. Adalimumab was approved for JRA in 2008. Etanercept has demonstrated sustained improvement in the signs and symptoms of polyarticular-course JRA with an acceptable safety profile in an open-label extension (OLE) of a randomized controlled trial (RCT) at 2 and 4 years (16,17). Here, we report additional safety and efficacy data from JRA patients who have received up to 8 years of continuous etanercept treatment in this ongoing OLE trial.

PATIENTS AND METHODS

Patients and study design. This study is an ongoing multicenter OLE trial. The double-blind RCT (13), the 2-year

OLE trial (16), and the 4-year OLE trial (17) have been described previously. Briefly, patients ages 4–17 years with active polyarticular-course JRA (onset could be systemic, polyarticular, or pauciarticular) were eligible to enroll in the original RCT. All patients had active disease despite treatment with NSAIDs and MTX at baseline. Active polyarticular-course JRA was defined as the presence of ≥ 5 swollen joints and ≥ 3 joints with limitation of motion and pain, tenderness, or both.

The RCT consisted of an initial 3-month open-label phase in which all patients received etanercept. Patients who responded to treatment then entered a randomized, double-blind, placebo-controlled phase for 4 months or until disease flare. Patients could choose to enroll directly from the double-blind portion of the initial study into the OLE phase. If patients discontinued or were nonresponders during the double-blind portion of the initial study, screening evaluations were performed within 2 weeks to determine eligibility for enrollment in the extension trial. Patients were assessed at 1, 2, and 3 months and at every 3 months thereafter during the first year of the extension phase, and then approximately every 4–6 months during the following years.

The institutional review boards at each study site approved the protocols. Written informed consent was provided by each patient's parent or guardian before the start of the efficacy study and the extension phase.

Treatment with MTX and other DMARDs was discontinued 2 weeks and 4 weeks, respectively, before enrollment in the RCT; use of these agents was prohibited during the RCT. Stable doses of NSAIDs and low doses of corticosteroids (≤ 0.2 mg/kg/day of prednisone; maximum 10 mg/day) were permitted in the RCT and the OLE phase. Intraarticular injections of steroids were not allowed during the treatment period of the RCT, and no injection should have occurred for at least 1 month prior to entry. After 1 year of the OLE trial, the dosages and the use of other medications for JRA, including corticosteroids, intraarticular injections of steroids, and NSAIDs, could be adjusted or added at the discretion of the treating physician, without restriction. MTX could be added to the regimen, but the dosage was limited to 10–20 mg/m²/week.

The Immunex study number is 016.0018 and the ClinicalTrials.gov registration number is NCT00357903.

Study medication. Patients received subcutaneous injections of etanercept at a dosage of either 0.4 mg/kg twice a week (maximum dose 25 mg per injection) or 0.8 mg/kg once a week (maximum dose of 50 mg/week).

Safety analysis. In the OLE study, the safety analyses end points included serious adverse events (SAEs), medically important infections (MIIs), and death. Events of interest were also reported, including opportunistic infections, tuberculosis, lupus, demyelinating disorders, malignancies, and lymphomas. Nonserious adverse events were not collected during the extension study.

SAEs were defined as events that were fatal or life-threatening, required hospitalization or prolonged an existing hospitalization, resulted in a persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect. SAEs were recorded using COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) terminology. MIIs were defined as infections requiring treatment with intravenous antibiotics or hospitalization.

Analyses of safety included all available data from all patients who received at least 1 dose of etanercept in the RCT or the ongoing OLE phase up to 30 days after their last dose. For rates of events (SAEs and MIIs) per patient-year of therapy, the duration of exposure to etanercept was calculated for all patients from the beginning of the original efficacy study and excluded time off etanercept therapy between the efficacy study and the extension study, where applicable.

Efficacy analysis. Efficacy analyses were limited to data from the patients who entered the long-term OLE trial. Efficacy values were compared with the baseline values from the beginning of the RCT because all patients initially received etanercept treatment in the open-label phase before randomization.

Efficacy was assessed using the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), Pedi 50, Pedi 70, Pedi 90, and Pedi 100 criteria for improvement. The criteria required to meet an ACR Pedi 30 response have been previously described (18). The definition of improvement for the ACR Pedi 30 (18) requires both of the following: 1) at least 30% improvement from baseline in at least 3 of the 6 variables in the core set (number of joints with active arthritis, number of joints with limitation of motion, physician's assessment of disease activity, parent's assessment of the patient's overall well-being, a validated measure of physical function, and a laboratory measure of inflammation), and 2) no more than 1 of the remaining variables worsening by >30%. ACR Pedi 50, 70, 90, and 100 criteria are defined as an improvement from baseline of at least 50%, 70%, 90%, or 100%, respectively, in at least 3 of the 6 core set of variables, with no more than 1 of the remaining variables worsening by >30%. Joint assessments were performed as follows: 74 joints were assessed for tenderness and/or pain on motion, 71 joints were assessed for limitation of motion, and 66 joints were assessed for swelling.

Other efficacy assessments included the patient's assessment of pain using a 0–10 visual analog scale (VAS), the physician's global assessment using a 0–10 Likert scale, the patient's/parent's global assessment using a 0–10 Likert scale, the articular severity score (sum of the severity scores for swelling, tenderness, limitation of motion, and pain on motion), the Childhood Health Assessment Questionnaire (C-HAQ), and the C-reactive protein (CRP) level (in mg/dl).

Some patients reached the age of 18 during the course of the study, and therefore the childhood disease activity measures were not applicable (scores on the ACR Pediatric criteria for improvement and the C-HAQ, and joint assessments). Data from patients who reached the age of 18 and discontinued the study and who therefore no longer had valid childhood efficacy measures were not included in efficacy analysis and the summary of the last visit using the last observation carried forward (LOCF) method.

A new high-sensitivity method of analyzing the CRP level became available in December 2004. Data reported for the first 6 years represent only the former method of analyzing CRP levels. Data reported for year 7 represent the average of the results obtained with both the former and the new methods. Data reported for year 8 represent only the new method. The range of normal values for the CRP is 0–0.79 mg/dl for the former method and 0–0.287 mg/dl for the new method. Laboratory results were summarized using the testing laboratory's normal ranges.

Statistical analysis. Demographic and background characteristics at enrollment into the initial RCT were listed and summarized descriptively. Time to discontinuation from the study was summarized using Kaplan-Meier estimates for patient retention in the study. For safety analysis, the exposure-adjusted event rate for SAEs, MIIs, deaths, and other events of interest were summarized yearly as well as overall. Efficacy data were summarized descriptively for all patients with available data at a given time point, without any imputation. Each patient's last visit was summarized according to the LOCF method. All patients who had at least 1 valid measure for a particular efficacy assessment were included in the LOCF analysis.

RESULTS

Patient characteristics. A total of 69 patients with JRA enrolled in the original RCT; 58 of those patients (84%) enrolled in the OLE trial and received weekly etanercept treatment for a total of 318 patient-years of etanercept exposure. Demographic data are shown in Table 1 for all 58 patients who enrolled in the OLE. The mean \pm SD age of the patients at baseline was 10.4 ± 3.8 years. Most patients were female (67%) and white (74%), and all patients had taken MTX prior to enrollment in the RCT. Most patients had polyarticular JRA at disease onset (34 of 58 [59%]), and 13 of 56 patients (23%) were RF positive. The mean duration of disease was 5.9 years at baseline, 56 of the 58 patients (97%) were receiving NSAIDs, and 22 of the 58 patients (38%) were receiving corticosteroids.

Concomitant medications. Patients were not receiving DMARDs at baseline of the OLE trial. At 8 years after initiation of the RCT, 31 of the 58 patients (53%) had received 1 or more DMARDs over the course of the OLE. MTX was the most common DMARD used, with 22 of the 58 patients (38%) having received MTX at some point during the OLE. An examination of MTX use at yearly intervals showed that a range of 0–10 patients (2–55%) were taking MTX; the mean dose of MTX ranged from 12.92 mg/m² to 20.00 mg/m²; and there was no trend indicating that the use or the dosage of MTX increased over time. It could not be determined from these data whether MTX was used to control partial remission or to treat disease flare. Of the 58 patients, 2 (3%) received leflunomide, 2 (3%) received hydroxychloroquine, and 1 (2%) received sulfasalazine at some point during the OLE. At baseline of the efficacy study, 22 of the 58 patients (38%) were receiving corticosteroids. At the baseline of the OLE, 17 of 58 patients (29%) were receiving corticosteroids. A total of 35 of the 58 patients (60%) received cortico-

Table 1. Demographic and clinical features at baseline of the efficacy study in patients who enrolled in the OLE trial and in those who entered the eighth year of treatment*

Characteristic	Patients who enrolled in the OLE (n = 58)	Patients who entered the eighth year of the OLE (n = 26)
Age, years		
Mean \pm SD	10.4 \pm 3.8	10.8 \pm 3.9
Range	4–17	4–17
Sex, no. (%) female	39 (67)	21 (81)
Race, no. (%)		
White	43 (74)	23 (88)
Black	4 (7)	–
Hispanic	9 (16)	3 (12)
Other	2 (3)	–
JRA onset type, no. (%)		
Pauciarticular	5 (9)	2 (8)
Polyarticular	34 (58)	19 (73)
Systemic	19 (33)	5 (19)
Duration of JRA, mean \pm SD years	5.9 \pm 3.2	6.4 \pm 3.4
RF positive, no. (%)†	13 (23)	6 (24)
Previous methotrexate therapy, no. (%)	58 (100)	26 (100)
Concomitant therapy at enrollment, no. (%)		
NSAIDs	56 (97)	25 (96)
Corticosteroids	22 (38)	8 (31)
Corticosteroid dosage, mean \pm SD mg/day	5.7 \pm 3.2	4.1 \pm 2.3

* Patients with juvenile rheumatoid arthritis (JRA) who previously participated in a randomized controlled trial of etanercept (efficacy study) were eligible to receive etanercept in the long-term open-label extension (OLE) trial. NSAIDs = nonsteroidal antiinflammatory drugs.

† Rheumatoid factor (RF) was assessed in 56 of the patients enrolled and 25 of those who entered the eighth year of the trial.

steroids at some time over the course of the RCT or the OLE.

Patient retention during etanercept treatment.

The numbers of patients who enrolled in and discontinued the RCT and OLE are presented in Figure 1. The Kaplan-Meier curve represents the continuation curve for the original 69 patients who enrolled in the RCT. A total of 26 of the 69 patients (38%) entered their eighth year of etanercept treatment, and the continuation curve has remained approximately linear from the start of the OLE at month 7 to the last time point examined, month 96. Of the 58 patients who enrolled in the OLE, 20 (34%) remain in the OLE. Of the 38 patients who discontinued the OLE (66%), 21 discontinued during the first 4 years.

Of the 58 patients who enrolled in the OLE, 7 (12%) discontinued the OLE because of a suboptimal

clinical response, 5 (9%) discontinued because of parent or guardian refusal to continue participation, 4 (7%) discontinued because of adverse events, and 3 patients each (5% each) discontinued because of patient refusal to continue, because of protocol issues, or because they were lost to followup. The mean baseline characteristics of the 58 patients who enrolled in the OLE and the 26 patients who entered their eighth year of treatment were similar. One exception was that a lower percentage of patients with systemic-onset JRA entered their eighth year of treatment than initially entered the OLE (Table 1).

Findings of the safety analysis. Safety data for all 69 patients who enrolled in the original RCT have been reported (13). Table 2 provides the total exposure-adjusted rates of SAEs and MIs in both the RCT and the OLE, as well as rates for each year of etanercept exposure. In total, 16 of the 69 patients who entered the

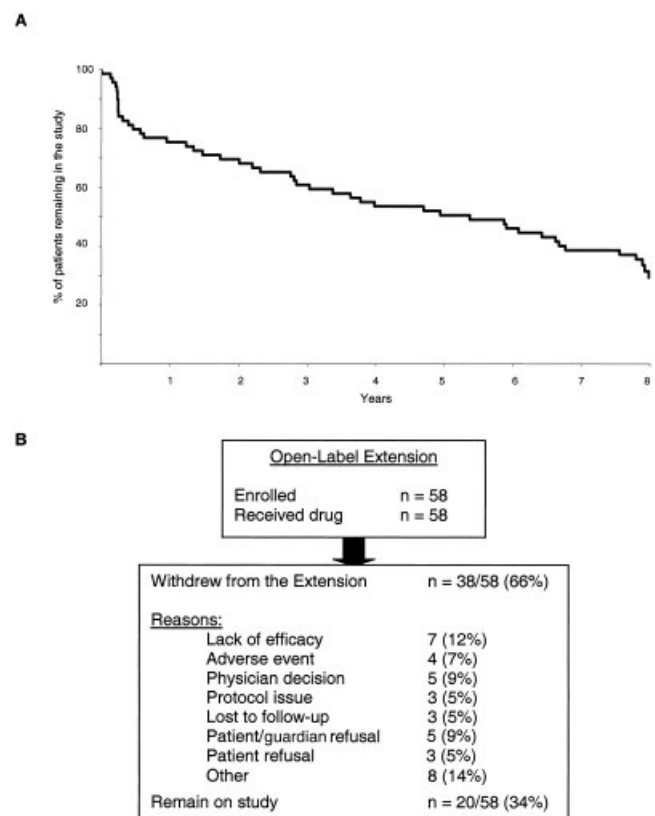


Figure 1. Continuation of study patients during the randomized controlled trial and the open-label extension trial. **A**, Kaplan-Meier curve showing the proportion of patients remaining in the study over 8 years, including the randomized controlled trial (69 patients enrolled) and the open-label extension trial (58 patients enrolled). **B**, Reasons patients discontinued the study during the open-label extension trial.

Table 2. Exposure-adjusted rates of serious adverse events and medically important infections during each year of etanercept treatment

Year of etanercept treatment*	No. of patients†	No. of patient-years	Serious adverse events‡		Medically important infections§	
			No. of events	No. of events/patient-year	No. of events	No. of events/patient-year
1	69	57	5	0.09	2	0.04
2	52	50	8	0.16	3	0.06
3	48	45	9	0.20	2	0.04
4	42	40	5	0.13	1	0.03
5	37	36	2	0.06	0	0.00
6	34	33	0	0.00	0	0.00
7	31	29	4	0.14	0	0.00
8	26	24	3	0.12	1	0.04
9	14	4	0	0.00	0	0.00
Total	69	318	39	0.12	9	0.03

* From the beginning of the original randomized controlled trial (excluding gaps between the randomized controlled trial and the open-label extension trial).

† Represents the number of patients entering each year of treatment.

‡ Serious adverse events occurring during the study or within 30 days of the last dose of etanercept.

§ Defined as infections resulting in the need for intravenous antibiotic therapy or hospitalization.

RCT (23%) reported 39 SAEs, for an overall exposure-adjusted rate of 0.12 events per patient-year. No increase in the rate of SAEs was seen with longer-term exposure to etanercept. SAEs from the first 4 years of the OLE have previously been reported (17). A total of 9 SAEs were reported in 4 patients after >4 years of etanercept exposure, encompassing 126 patient-years. These SAEs included 6 cases of disease flare and 1 case each of pyelonephritis, arthralgia, and allergic reaction. No cases of lupus, demyelinating disorders, malignancies, or lymphomas were reported.

A total of 8 patients reported 9 MIIs over the course of the OLE, for an exposure-adjusted rate of 0.03 events per patient-year. Eight of the MIIs have previously been described (16,17). The single case of pyelonephritis mentioned above was the only MII reported by patients since the report at 4 years of study. No increase in the rate of MIIs was seen with longer-term exposure to etanercept. None of the reported MIIs over the course of the RCT and the OLE was determined to be opportunistic in nature, and no cases of tuberculosis were reported. No deaths were reported.

Findings of the efficacy analysis. Efficacy was assessed in all 58 patients who entered the OLE trial, and these values were compared with the baseline values from the original RCT. Pediatric measures of disease or measures of disease that are scored in a similar manner for adults and children are reported for all patients. Adult-specific measures of disease for patients ≥18 years of age are not included in these analyses (n = 5 each at years 7 and 8). The proportions of patients achieving ACR Pedi 30, 50, 70, 90, and 100 responses

were calculated over time for all patients who had data available at each time point (Figure 2). Patients demonstrated a durable response over 8 years of etanercept treatment. These durable response rates were also demonstrated at 8 years using the LOCF method of analysis, since ACR Pedi 30, 50, 70, 90, and 100 response rates were 83% (40 of 48 patients), 77% (36 of 47 patients), 61% (28 of 46 patients), 41% (19 of 46 patients), and 18% (8 of 45 patients), respectively. Mean and median measures of disease activity were also maintained over time in patients who were still enrolled in the OLE trial

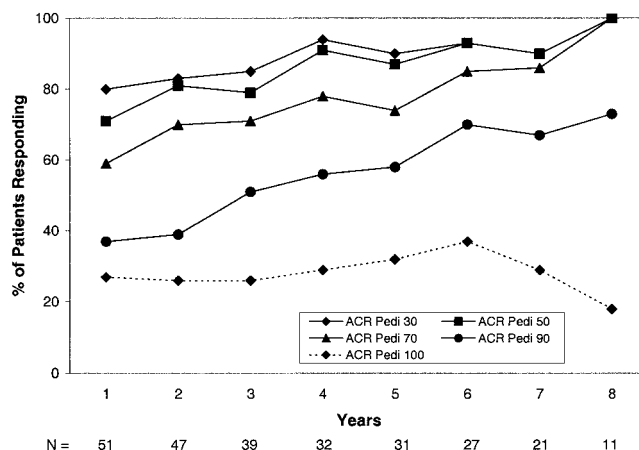


Figure 2. Percentages of all patients with available data at each time point who met the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), Pedi 50, Pedi 70, Pedi 90, and Pedi 100 criteria for improvement. Values were not available for all patients at years 2, 3, and 4.

Table 3. Disease activity, C-HAQ scores, and CRP levels at baseline of the efficacy study in patients who entered the OLE trial, in those who completed years 4, 7, and 8 of the OLE trial, and at the last visit*

	Baseline (n = 58)	Long-term extension			Last visit (LOCF) (n = 58)
		Completed year 4 (n = 32)	Completed year 7 (n = 26)	Completed year 8 (n = 16)	
Total no. of joints with active arthritis [†]					
Mean ± SEM	30.1 ± 1.9	6.7 ± 1.9	2.4 ± 0.7	2.2 ± 0.9	9.8 ± 2.2
Median	28.5	2.0	1.0	1.0	2.0
Total no. of joints with LOM and P/T [†]					
Mean ± SEM	13.8 ± 1.7	2.4 ± 0.9	0.8 ± 0.4	0.0 ± 0.0	1.4 ± 0.4
Median	9.0	0.0	0.0	0.0	0.0
Total no. of joints with LOM [†]					
Mean ± SEM	27.5 ± 2.0	14.3 ± 3.1	11.3 ± 2.9	11.8 ± 4.4	19.9 ± 2.6
Median	23.5	7.5	4.0	6.0	16.0
Physician's global assessment					
Mean ± SEM	6.4 ± 0.3	1.9 ± 0.4	1.8 ± 0.2	1.6 ± 0.3	2.9 ± 0.3
Median	6.5	1.0	1.5	1.0	2.0
Patient's/parent's global assessment [‡]					
Mean ± SEM	4.8 ± 0.3	2.1 ± 0.4	2.0 ± 0.3	2.0 ± 0.6	2.4 ± 0.3
Median	5.0	2.0	2.0	1.0	2.0
Pain score [§]					
Mean ± SEM	3.7 ± 0.3	1.7 ± 0.4	1.3 ± 0.3	1.8 ± 0.5	2.0 ± 0.3
Median	3.6	0.9	0.6	0.6	1.2
C-HAQ score [†]					
Mean ± SEM	1.5 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	0.9 ± 0.1
Median	1.4	0.3	0.3	0.3	0.6
CRP, mg/dl [¶]					
Mean ± SEM	6.7 ± 1.1	0.6 ± 0.2	1.1 ± 0.6	1.1 ± 0.5	2.3 ± 0.6
Median	3.4	0.1	0.1	0.2	0.3

* Seventy-four joints were assessed for tenderness and/or pain on motion (P/T), 71 joints were assessed for limitation of motion (LOM), and 66 joints were assessed for swelling. Physician's global assessment, patient's/parent's global assessment, and pain were scored on a 0–10 scale (0 = best and 10 = worst). The range of scores for the Childhood Health Assessment Questionnaire (C-HAQ) is 0–3 (0 = best and 3 = worst). OLE = open-label extension; LOCF = last observation carried forward.

[†] Values based on 21 patients for year 7, 11 patients for year 8, and 48 patients for the last visit.

[‡] Values based on 31 patients for year 4 and 57 patients for the last visit.

[§] Values based on 57 patients for the last visit.

[¶] A new high-sensitivity method of analyzing the C-reactive protein (CRP) level became available in December 2004. The data for year 7 represent the average of the values with the old and new methods; the data for year 8 represent the value with the new method only. With the old method, the normal range is 0–0.79 mg/dl, and with the new method, the normal range is 0–0.287 mg/dl. Values for the last visit are based on 53 patients.

(Table 3), as were the percentages of patients with scores of zero on disease activity measure or with CRP values within the normal range (Table 4).

DISCUSSION

In this study, we examined the long-term safety and efficacy of up to 8 years of continuous treatment with etanercept in patients with polyarticular-course JRA in whom previous therapy with traditional DMARDs had failed. Until very recently, no other biologic agent has been approved for use in JRA patients, and data from other long-term studies are not available.

We report data from a total of 318 patient-years

of drug exposure. This report includes data from 26 patients who have entered their eighth year of continuous treatment with etanercept, 14 of whom have completed their eighth year and entered their ninth year of continuous etanercept treatment. A total of 20 patients (34%) remain in the study. These data are noteworthy, since studies have shown that between 25% and 70% of children with JRA will still have active disease 10 years after onset (9,14) and that most JRA patients fail to achieve a state of disease inactivity of 12 months or longer while off their medication regimen (15).

The long-term safety profile of etanercept was maintained during up to 8 years of continuous drug use. Exposure-adjusted rates of SAEs did not increase over

Table 4. Percentages of patients with scores of zero on disease activity measures or with a CRP value within the normal range at baseline of the efficacy study in those who entered the OLE trial, in those who completed years 4, 7, and 8 of the OLE trial, and at the last visit*

	Baseline (n = 58)	Long-term extension			Last visit (LOCF) (n = 58)
		Completed year 4 (n = 32)	Completed year 7 (n = 26)	Completed year 8 (n = 16)	
No joints with active arthritis†	0	38	38	36	31
No joints with LOM and P/T†	5	63	67	100	65
No joints with LOM‡	2	22	29	27	15
Physician's global assessment score of 0	0	28	8	6	9
Patient's/parent's global assessment score of 0‡	3	16	12	19	14
Pain score of 0§	7	22	15	25	14
C-HAQ score of 0‡	3	34	38	45	31
CRP in the normal range¶	16	78	69	50	51

* Seventy-four joints were assessed for tenderness and/or pain on motion (P/T), 71 joints were assessed for limitation of motion (LOM), and 66 joints were assessed for swelling. Physician's global assessment, patient's/parent's global assessment, and pain were scored on a 0–10 scale (0 = best and 10 = worst). The range of scores for the Childhood Health Assessment Questionnaire (C-HAQ) is 0–3 (0 = best and 3 = worst). OLE = open-label extension; LOCF = last observation carried forward.

† Values based on 21 patients for year 7, 11 patients for year 8, and 48 patients for the last visit.

‡ Values based on 31 patients for year 4 and 57 patients for the last visit.

§ Value based on 57 patients for the last visit.

¶ A new high-sensitivity method of analyzing the C-reactive protein (CRP) level became available in December 2004. The data for year 7 represent the average of values with the old and new methods; the data for year 8 represent the value with the new method only. With the old method, the normal range is 0–0.79 mg/dl, and with the new method, the normal range is 0–0.287 mg/dl. The value for the last visit is based on 53 patients.

time, and the most common new SAEs reported beyond 4 years of drug exposure were a flare or worsening of disease (6 of 9 SAEs [67%]). Overall, only 7% of the study population discontinued the study because of an adverse event. This durable long-term safety profile is similar to the safety profiles reported for the long-term use of etanercept in adults across a variety of rheumatic disorders, including rheumatoid arthritis (19), psoriatic arthritis (20), and ankylosing spondylitis (21). In addition, there were no reported cases of malignancies, lymphomas, demyelinating disorders, or lupus. These results are also similar to those from a study of a large German registry, representing 592 patient-years of etanercept exposure in patients with JRA (22).

The exposure-adjusted rates of infections that led to hospitalization or treatment with intravenous antibiotics remained low over the period of study. Specific concerns have been raised regarding the use of TNF-inhibiting drugs and opportunistic infections and tuberculosis (23). In this study, no cases of tuberculosis or other opportunistic infections were reported.

Improvements in measurements of disease activity were maintained throughout the duration of the trial. These results are similar to those of studies showing sustained efficacy with the long-term use of anti-TNF agents (infliximab, etanercept, adalimumab) in adults with RA (19,24,25). Of note, however, were the declines

at years 7 and 8 in the proportion of patients achieving an ACR Pedi 100 response and the proportion of patients achieving a score of zero on the physician's global assessment. These declines, however, can likely be explained by the small number of patients represented at these later time points and by fluctuations in disease activity over time, since improvements in other measures with similarly stringent response criteria, such as the ACR Pedi 90 and achieving disease activity scores of zero, were maintained for up to 8 years.

A limitation of this long-term study is that efficacy data are reported at each time point only for the patients who chose to continue to receive etanercept treatment. A concern arises that the study population then becomes enriched with patients who are responders, since nonresponders withdraw from the study and seek different treatment. However, over the course of this study, only 7 patients (12%) withdrew because of a lack of efficacy, and when the response rates at the last visit were examined using the LOCF method, improvements over baseline values were observed for all measures.

The results of the present study show that in this population of patients with JRA, long-term continuous treatment with etanercept was well tolerated for up to 8 years, without an increase in the rates of SAEs over time. In addition, these data demonstrate that continu-

ous treatment with etanercept resulted in sustained improvements in clinically important signs and symptoms of JRA for up to 8 years.

ACKNOWLEDGMENTS

The authors would like to acknowledge the significant contribution made to this study by the following members of the Pediatric Rheumatology Collaborative Study Group: R. W. Nickeson, Jr., MD, O. Y. Jones, MD, PhD, R. Schneider, MD, J. Nocton, MD, L. D. Stein, MD, A. Gedalia, MD, J. B. Whitmore, PhD, B. White, MD, B. Bernstein, MD, G. D. Cawkwell, MD, PhD, B. Feldman, MD, MSc, FRCPC, B. Gottlieb, MD, MS, B. Graham, MD, R. Laxer, MD, FRCP, J. C. Olson, MD, M. Passo, MD, A. Reed, MD, B. Shaham, MD, M. Sher, MD, D. Sherry, MD, and E. D. Silverman, MD. The authors thank the following study site coordinators for assistance with the study: Nicola J. Bradford, RN, MS, Barbara Feldman, MS, PT, OTR, Karen Felty, RN, Anne Johnson, BS, Norma Liburd, RN, Cathy Mobley, RN, Eileen Pagano, RN, MS, and Jannalee Taylor, RN. We thank Marc D. Kubasak, PhD (Amgen Inc., Thousand Oaks, CA), for assistance with the writing and preparation of the manuscript. We also thank the patients and their parents who made this study possible.

AUTHOR CONTRIBUTIONS

Dr. Lovell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Lovell, Reiff, Ilowite, Giannini.

Acquisition of data. Lovell, Reiff, Ilowite, Wallace, Chon, Lin.

Analysis and interpretation of data. Lovell, Reiff, Ilowite, Chon, Lin, Baumgartner, Giannini.

Manuscript preparation. Lovell, Reiff, Ilowite, Wallace, Lin, Baumgartner, Giannini.

Statistical analysis. Lovell, Chon, Lin.

ROLE OF THE STUDY SPONSORS

Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and Wyeth Pharmaceuticals facilitated the study design and the writing of the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication.

REFERENCES

- Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis: why does it vary so much? *J Rheumatol* 2002;29:1520–30.
- Gare A. Juvenile arthritis—who gets it, where and when? A review of current data on incidence and prevalence. *Clin Exp Rheumatol* 1999;17:367–74.
- Foster HE, Marshall N, Myers A, Dunkley P, Griffiths ID. Outcome in adults with juvenile idiopathic arthritis: a quality of life study. *Arthritis Rheum* 2003;48:767–75.
- Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology (Oxford)* 2002;41:1428–35.
- Ilowite, NT. Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002;109:109–15.
- Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA* 2005;294:1671–84.
- Stokes DG, Kremer JM. Potential of tumor necrosis factor neutralization strategies in rheumatologic disorders other than rheumatoid arthritis. *Semin Arthritis Rheum* 2003;33:1–18.
- Carrasco R, Smith JA, Lovell D. Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. *Paediatr Drugs* 2004;6:137–46.
- Lovell DJ. Update on treatment of arthritis in children: new treatments, new goals. *Bull NYU Hosp Jt Dis* 2006;64:72–6.
- Munro JE, Murray KJ. Advances in paediatric rheumatology: beyond NSAIDs and joint replacement. *J Paediatr Child Health* 2004;40:161–9.
- Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum Dis* 2003;62:245–7.
- Gerloni V, Pontikaki I, Gattinara M, Desiati F, Lupi E, Lurati A, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor α monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. *Arthritis Rheum* 2005;52:548–53.
- Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al, for the Pediatric Rheumatology Collaborative Study Group. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000;342:763–9.
- Levinson JE, Wallace CA. Dismantling the pyramid. *J Rheumatol* 1992;33:6–10.
- Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. *Arthritis Rheum* 2005;52:3554–62.
- Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, et al, for the Pediatric Rheumatology Collaborative Study Group. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: results from an on-going multicenter, open-label, extended treatment trial. *Arthritis Rheum* 2003;48:218–26.
- Lovell DJ, Reiff A, Jones OY, Schneider R, Nocton J, Stein LD, et al, for the Pediatric Rheumatology Collaborative Study Group. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2006;54:1987–94.
- Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202–9.
- Moreland LW, Weinblatt ME, Keystone EC, Kremer JM, Martin RW, Schiff MH, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006;33:854–61.
- Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264–72.
- Davis JC, van der Heijde DM, Braun J, Dougados M, Cush J, Clegg D, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005;64:1557–62.
- Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis* 2004;63:1638–44.
- Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol* 2006;2:602–10.
- Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al, for the Anti-Tumor Necrosis Factor Trial in

Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004;50:1051-65.

25. Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. *Ann Rheum Dis* 2006;65:753-9.