Safety and Efficacy of Etanercept in a Cohort of Patients with Juvenile Idiopathic Arthritis Under 4 Years of Age

CLAUDIA BRACAGLIA, PAOLA S. BUONUOMO, ALBERTO E. TOZZI, MANUELA PARDEO, REBECCA NICOLAI, ANDREA CAMPANA, ANTONELLA INSALACO, ELISABETTA CORTIS, and FABRIZIO DE BENEDETTI

ABSTRACT. ***Objective.*** To evaluate safety, tolerability, and efficacy of etanercept in a cohort of patients with juvenile idiopathic arthritis (JIA) under 4 years of age.

Methods. Data were collected at every visit during treatment with etanercept in 25 children who began treatment at a mean age of 3 years (range 18–48 months). Safety endpoints included the incidence of any adverse events. Efficacy endpoints included the American College of Rheumatology (ACR) Pediatric 30, 50, and 70 criteria for improvement.

Results. Data from 25 patients with JIA treated with etanercept for a mean period of 23 months were analyzed. All patients received concomitant medications: 24 methotrexate, 3 cyclosporin A, and 10 corticosteroids. After the first 6 months of treatment, 15 (71.4%) patients achieved an ACR Pedi30 response and at the last observation 20 (80%) achieved ACR Pedi30. ACR Pedi50 and 70 responses were, respectively, 62% and 43% at 6 months and 72% and 64% at the last followup. Five patients (20%) discontinued etanercept for lack of efficacy. Two (8%) developed adverse events, both primary varicella zoster virus (VZV) infections (both not vaccinated). One was hospitalized because of a necrotizing fasciitis secondary to VZV infection. No cases of tuberculosis, opportunistic infections, or malignancies were reported.

Conclusion. In our cohort of patients etanercept proved to be safe and efficacious in the majority of children. The response in toddlers was similar to that in older children. We observed only 1 case of severe infection that required hospitalization and stopped treatment temporarily. (J Rheumatol First Release May 15 2012; J Rheumatol 2012;39:1287–90; doi:10.3899/jrheum.111555)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS ETANERCEPT AGE UNDER 4 CHILDREN

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. It is an important cause of short- and longterm disability, possibly resulting in a poor quality of life[1,2]. Current treatment of children with JIA includes nonsteroidal antinflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs (DMARD)[3,4]. Methotrexate (MTX) is the first-line DMARD most commonly used. However, these drugs are effective only in a proportion of patients with JIA[5]: some patients with polyarticular or systemic-onset disease have incomplete or no response to MTX and require alternative medications. The course and outcome of children with JIA with unsatisfactory response to MTX and/or other DMARD have markedly improved since the introduction of tumor necrosis factor (TNF) antagonists.

Etanercept is a soluble dimeric fusion protein that binds soluble TNF, preventing its interaction with receptors on immune cells. The safety and efficacy of etanercept in children older than age 4 years with polyarticular JIA have been demonstrated in randomized clinical trials and in longterm observational registries. Sustained responses with an acceptable rate of severe adverse events (SAE) were observed in longterm treatment[6,7,8]. Etanercept, originally approved in children older than 4 years, has recently been licensed for treatment of children with polyarticular JIA older than 2 years and unresponsive to MTX, in both Europe and the USA. Only limited data are available on the efficacy and safety of etanercept in children less than 4 years of age. To date, only one experience, from the German JIA Registry, reported data on the use of etanercept in 25 patients with JIA younger than 4 years of age[9].

Our objective was therefore to investigate the safety, tolerability, and efficacy of etanercept in a cohort of children

From the Division of Rheumatology, Department of Pediatric Medicine; and Division of Epidemiology, Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy.

C. Bracaglia, MD; P.S. Buonuomo, MD, Division of Rheumatology, Department of Pediatric Medicine; A.E. Tozzi, MD, Division of Epidemiology; M. Pardeo, MD; R. Nicolai, MD; A. Campana, MD; A. Insalaco, MD; E. Cortis, MD; F. De Benedetti, MD, PhD, Division of Rheumatology, Department of Pediatric Medicine, Ospedale Pediatrico Bambino Gesù IRCCS.

Address correspondence to Dr. C. Bracaglia, Division of Rheumatology, Department of Paediatric Medicine, Ospedale Pediatrico Bambino Gesù, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy.
E-mail: claudia.bracaglia@opbg.net; claudiabrac@yahoo.it

Accepted for publication March 2, 2012.

with JIA whose age at the beginning of therapy was below 4 years.

MATERIALS AND METHODS

All patients with JIA diagnosed according to the International League of Associations for Rheumatology criteria[10] from 1998 to 2008, under 4 years of age, with unsatisfactory response to standard therapy (DMARD), were included in the study. This was a retrospective cohort study collecting data from patients treated with etanercept for a mean period of 23 months (range 6–86 mo) followed at the Division of Rheumatology of Bambino Gesù Children's Hospital. Of all patients treated with etanercept, none was lost to followup during the study period.

Etanercept was added to the current therapy of children that developed polyarthritis with unsatisfactory response to MTX administered for a mean of 9 months (range 2–41 mo) at a dose of 15 mg/m^2/week (median 14.7 mg/m^2, range 10–15.9 mg/m^2). Etanercept was also added to the therapy of 3 children with persistent oligoarticular JIA with 4 or fewer involved joints. These patients had failed to improve after 3 intraarticular injections of corticosteroid in at least 2 joints and after at least 2 months of treatment with MTX. Etanercept was added to conventional therapy early because of rapid disease progression.

Etanercept was administered subcutaneously at a dosage of 0.8–1 mg/kg once weekly, as for the older patients with JIA. The followup started when etanercept was added. Patients were seen after 1 month of therapy and every 8 weeks for the following months. Biological and clinical data and the Child Health Assessment Questionnaire (CHAQ) data were collected at each followup visit. Since use of etanercept in children under 4 years of age at the time of initiation of the study was an off-label treatment, informed consent was obtained from parents or legal guardians of each patient.

Safety analysis. Safety endpoints included the incidence of AE recorded using the Common Terminology Criteria for Adverse Events, v3.0[11]. We performed surveillance for side effects by interviews with parents at every followup visit. Other events of interest were also recorded, including opportunistic infections, tuberculosis, and malignancies.

Efficacy analysis. We assessed the effect on disease activity using the American College of Rheumatology (ACR) Pediatric 30 (Pedi30), Pedi50, and Pedi70 criteria for improvement[12]. An ACR Pedi30 response is defined as an improvement of at least 30% from baseline in at least 3 of the 6 variables in the core set (number of joints with active arthritis, number of joints with limited range 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, the erythrocyte sedimentation rate) and not more than 1 of the remaining variables worsening by > 30%. ACR Pedi50 and 70 criteria are defined as improvement from baseline of at least 50% and 70%, respectively, in at least 3 of the 6 core set variables, with not more than 1 of the remaining variables worsening by > 30%.

Statistical analysis. Demographic and background characteristics at enrollment into the study were recorded 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 drug exposure-adjusted event rate for AE, deaths, and other events of interest were summarized at every followup visit. Statistical analysis of efficacy and AE was evaluated using Kaplan-Meier estimates. Each patient's last visit was summarized according to the last observation carried forward (LOCF) method. All patients with at least 1 valid measure for a particular efficacy assessment were included in the LOCF analysis. For analysis of variables concerning the efficacy of treatment we used the Wilcoxon test for paired samples.

RESULTS

Patient characteristics. A total of 25 patients with JIA treated with etanercept and meeting eligibility criteria were observed for a mean of 23 months (range 6–86 mo). Demographics and baseline disease characteristics are shown in Table 1. Etanercept was started at an average age of 37 months (range 18–48 mo). Eight (32%) patients had systemic, 12 (48%) oligoarticular, and 4 (16%) polyarticular-onset JIA; 1 (4%) patient had psoriatic arthritis. Irrespective of the JIA subtype at onset, all patients developed a polyarticular disease course, except 3 who maintained an oligoarticular disease course.

All patients received concomitant medications. Twenty-four were given MTX 15 mg/m^2 once a week, and 3 who developed MTX intolerance were given cyclosporin A 5 mg/kg/day. Ten patients were also receiving corticosteroids, with a starting dose of 2 mg/kg/day rapidly tapered and discontinued in 1 month, when possible. In 2 patients with systemic JIA, corticosteroids were not discontinued.

Safety analysis. The overall incidence of AE was 0.3 side effects per year of treatment (95% CI 0.05–1.01). Two patients (8%) developed AE, one was a SAE. Both developed primary varicella zoster virus (VZV) infections, 1 patient after 40 months of treatment and 1 after 24 months. Neither patient had received previous chickenpox immunization. One patient was hospitalized because of a necrotizing bacterial fasciitis secondary to VZV infection: he was treated with ceftriaxone plus amikacin and linezolid for 1 month in total. Etanercept was temporarily discontinued. No intolerance or allergic reactions were observed. No cases of tuberculosis, opportunistic infections, or malignancies were

Table 1. Baseline clinical characteristic of study subjects.

Characteristic	
Female, n (%)	17 (68)
Age, months, median (range)	40 (18–48)
JIA onset type, n (%)	
Systemic	8 (32)
Oligoarticular	12 (48)
Persistent	3 (12)
Extended	9 (36)
Polyarticular	4 (16)
RF-positive	1 (4)
RF-negative	3 (12)
Psoriatic	1 (4)
ANA-positive, n (%)	16 (64)
Uveitis, n (%)	7 (28)
Duration of MTX treatment before etanercept, months, median (range)	10 (2–41)
Duration of disease at start of etanercept, months, median (range)	14.2 (4–35)
Concurrent medication, n (%)	
Methotrexate	24 (96)
Cyclosporine	3 (1.6)
Corticosteroids	10 (52.6)

JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; ANA: antinuclear antibody; MTX: methotrexate.

reported and no deaths were observed. Incidentally, 7 episodes of active anterior uveitis were observed during treatment.

Efficacy analysis. Table 2 shows mean baseline values and changes of the core set variables following etanercept treatment. All 6 core set variables showed a statistically significant improvement at the last followup. After 6 months of treatment, 15 (71.4%) patients achieved an ACR Pedi30 response and at the last observation 20 (80%) achieved an ACR Pedi30 response. Of the 5 patients who did not reach an ACR Pedi30 response, 3 had systemic-onset JIA. An ACR Pedi50 response was found in 62% (13 patients) at 6 months and 72% (25 patients) at the last followup; ACR Pedi70 response was 43% at 6 months and 64% at the last followup. The median time to achieve an ACR Pedi50 response was 16.09 months of treatment and for ACR Pedi70 response, 25.16 months.

Five patients (20%) discontinued etanercept for inefficacy and switched to another biologic drug. One patient (20%) who had developed a severe polyarticular disease course was switched to another anti-TNF agent, and 4 patients (80%) who had systemic-onset JIA were switched to interleukin 1 inhibitors.

DISCUSSION

The objective of our observational study was to evaluate safety and efficacy of etanercept as off-label treatment in children of age younger than 4 years with JIA. We report data from 25 JIA patients younger than age 4 years treated with etanercept for a mean period of 23 months. Since limited information is available about the safety and efficacy of such treatment in young children, we compared our data with those from Lovell, *et al*[7,8] and with our experience in older children[13].

Regarding the safety profile for etanercept in younger patients, we observed in our study population only 2 cases of viral infections. One needed hospitalization due to a severe infection and temporarily stopped treatment. No other cases of SAE or discontinuation due to treatment intolerance were reported. Comparing the safety data from Lovell, *et al*[8] and from our older children[13], no major differences were observed. However, the exposure to etanercept of the patients reported here was short compared to that of the older children.

Our observations raise concern about viral infection in young children, because the earlier the treatment starts the higher the risk to develop viral infection, especially VZV. Further, our observations raise the issue of chickenpox vaccination in children with chronic diseases, and particularly in those who require biologic drug treatment. Indeed, chickenpox vaccination should always be recommended at diagnosis as patients are likely to need immunosuppressive drugs during the disease course. The parents of the 2 children who developed VZV infection during anti-TNF treatment refused the vaccination before starting immunosuppressive drugs. In Italy, chickenpox vaccination is not mandatory. Evaluation of 85 patients with JIA treated with etanercept plus MTX and 71 patients treated with MTX alone revealed a low incidence of herpes zoster infection (3 cases in total), with no differences found between patients treated with MTX alone and patients treated with MTX plus etanercept. In this analysis, no patient who presented a herpes zoster infection developed severe complications (unpublished data).

Frequency of VZV infection in our JIA patients treated with etanercept was similar to data from other studies. Lovell, *et al* described 3 cases of VZV in 58 patients from a multicenter trial[6]; 1 case was reported in the German Etanercept Registry of 322 patients with JIA and 12 additional patients with non-JIA diagnosis[14]; and 1 case was reported by Tzaribachev, *et al*[9].

In our cohort of patients etanercept proved to be efficacious in the majority of children. The response in toddlers in achieving and maintaining disease remission was similar to that in older children. Five patients with a severe disease course stopped treatment for inefficacy; 4 of them (80%) presented with a systemic disease onset. Fifty percent of patients with systemic-onset JIA discontinued treatment due to inefficacy, but 4 of 8 (50%) patients with systemic-onset JIA achieved ACR Pedi50 and ACR Pedi70 at last followup. These results are similar to those in older patients with JIA treated with TNF inhibitors[15]. In the great majority of patients, etanercept was added to ongoing treatment with MTX. Etanercept was started early in only 3 patients (after 2 months of MTX treatment): they presented a similar response. Removing these patients did not lead to marked changes in the efficacy analysis (data not shown).

Comparing the improvements of younger and older children by the percentage of improvement of the ACR Pedi30, 50, and 70 criteria, we found similar responses in the 2 age groups. In children with JIA older than 4 years of age followed at our hospital, we observed an ACR Pedi70 response of 73% after 1 year of treatment (data not shown). Our data

Table 2. American College of Rheumatology core set variables at baseline and at last followup.

Measure	Baseline* (range)	Last Followup* (range)	p
Physician VAS, mm	80 (40–100)	25 (0–100)	< 0.01
Parents VAS, mm	90 (50–100)	20 (0–100)	< 0.01
No. active joints	5 (3–48)	0 (0–27)	< 0.01
No. joints with limited motion	5 (1–48)	1 (0–24)	< 0.01
CHAQ	0.7 (0.27–1)	0.04 (0–1)	< 0.01
ESR, mm/h	56 (8–145)	19 (3–130)	< 0.05

* Median of disease activity measures of the total patient group. VAS: disease assessment on 100-mm visual analog scale; CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate.

are similar to those for young children reported by Tzaribachev, *et al* in the German registry[9].

Our results suggest that etanercept therapy is a suitable and efficacious treatment option for patients with JIA under the age of 4 years, with no significant differences from those in children older than 4 years. In this regard, longterm safety data from large multicenter international registries are required.

REFERENCES

1. Petty R, Malleson P. Epidemiology of juvenile rheumatoid arthritis. World Pediatr Child Care 1987;3:205-10.
2. Cassidy JT, Petty RE, Laxer RM, editors. Textbook of pediatric rheumatology. 5th ed. Philadelphia: Elsevier; 2005.
3. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. JAMA 2005;294:1671-84.
4. Wallace CA. Current management of juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol 2006;20:279-300.
5. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, Oliveira S, Falcini F, et al, for the Pediatric Rheumatology INternational Trials Organization (PRINTO). A randomized trial of parenteral methotrexate comparing an intermediate with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 2004;50;2191-201.
6. 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: Interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum 2003;48:218-26.
7. 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.
8. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al; for the Pediatric Rheumatology Collaborative Study Group. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58:1496-504.
9. Tzaribachev N, Kuemmerle-Deschner J, Eichner M, Horneff G. Safety and efficacy of etanercept in children with juvenile idiopathic arthritis below the age of 4 years. Rheumatol Int 2008;28:1031-4.
10. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
11. US National Cancer Institute. National Institutes of Health. Cancer therapy evaluation program. Common terminology criteria for adverse events. Version 3.0. August 9, 2006. [Internet. Accessed March 23, 2012.] Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
12. 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.
13. Insalaco A, Bracaglia C, Cortis E, Campana A, Ugazio AG. Side effects of etanercept in a cohort of 76 children with rheumatic diseases. EULAR June 2006. Ann Rheum Dis 2006;65 Suppl II:246.
14. Horneff G, Schmeling H, Biedermann T. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis 2004;63:1638-44.
15. Russo RA, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. J Rheumatol 2009;36:1078-82.