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ORIGINAL ARTICLE

Etanercept in the treatment of disease-modifying anti-rheumatic drug (DMARD)-refractory polyarticular course juvenile idiopathic arthritis: experience from Japanese clinical trials

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Abstract Efficacy, safety, and pharmacokinetics results from 4 studies—3 open-label (OL) and 1 randomized double-blind (DB)—have provided data for approval of etanercept for treatment of disease-modifying anti-rheumatic drug (DMARD)-refractory juvenile idiopathic arthritis (JIA) in Japan. Results from the 3 shorter-term (2 OL and 1 DB) studies are reported here. Subjects (4–17 years) enrolled in the OL studies had active JIA, i.e. ≥5 swollen joints and ≥3 joints with limitation of motion and pain or tenderness. Subjects enrolled in the primary OL study received etanercept 0.4 mg/kg subcutaneously twice weekly; in the lower-dose OL study subjects received etanercept 0.2 mg/kg. Subjects in the primary OL study who completed ≥48 weeks could continue into a 12-week DB dose-down extension study in which subjects received etanercept 0.4 or 0.2 mg/kg twice weekly. The primary endpoint in all 3 studies, i.e. 30% improvement in the American College of Rheumatology criteria for JIA (ACR Pedi 30) at 12 weeks, was achieved by ≥80% of subjects by week 2 and sustained to week 12. Common adverse events reported were injection site reactions, nasopharyngitis, and gastroenteritis. These results provide further evidence that etanercept is effective therapy for DMARD-refractory polyarticular JIA patients.

Keywords Children · Clinical trial · Etanercept · Polyarticular course · Juvenile idiopathic arthritis

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Introduction

Juvenile idiopathic arthritis (JIA) is arthritis of unknown etiology that manifests itself before the age of 16 years and persists for at least 6 weeks [1]. It is a common chronic musculoskeletal disease with a worldwide incidence of 1 in 1000 patients [2]. Children with JIA present with joint pain, stiffness, and swelling.

Therapies for JIA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), and most recently anti-tumor necrosis factor (anti-TNF) agents. The NSAIDs are effective in a third of patients with the disease only; toxicity prevents the use of DMARD therapy in the long-term management of JIA. In a large North-American multicenter placebo-controlled trial of etanercept in pediatric subjects with DMARD-refractory polyarticular JIA, etanercept was well tolerated and significantly more effective than placebo [3]. Similar improvements were observed in shorter-term open-label and observation studies in subjects with JIA [4–6]. Long-term extension studies indicate that the improvements were sustained and that etanercept continued to be well tolerated in this pediatric population [7–11].

The efficacy, safety, and pharmacokinetics of etanercept in the treatment of Japanese pediatric subjects were

evaluated in 4 studies (3 open-label studies and 1 randomized double-blind study) which provided data for approval of etanercept for treatment of JIA in Japan. This article provides the 12-week efficacy, safety, and pharmacokinetics results from the 3 shorter-term (two open-label and 1 double-blind) JIA studies[1]; results from the longer-term study (5-year open label, which included the patients from the 3 shorter studies) will be published separately.

Subjects and methods

The first study (which will be referred to as the "primary study" hereafter) evaluated the efficacy, safety, and pharmacokinetics of open-label etanercept 0.4 mg/kg delivered subcutaneously twice weekly in etanercept-naive pediatric subjects with polyarticular course JIA; subjects who responded to etanercept and tolerated the drug well at 12 weeks continued receiving etanercept for up to 104 weeks. Subjects who completed at least 48 weeks of the primary study could enter a 12-week double-blind extension study, in which a drop-down dose (etanercept 0.2 mg/kg) was compared with the original dose (etanercept 0.4 mg/kg); this second study will be referred to as the dose-down extension study hereafter. A third study (lower dose study of 12-week duration) was undertaken to evaluate the efficacy and safety of etanercept 0.2 mg/kg in etanercept-naive pediatric subjects with polyarticular course JIA.

To be eligible for entry into the open-label studies (primary and lower-dose study), subjects (4–17 years) had to have active JIA, i.e. 5 or more swollen joints and 3 or more joints with limitation of motion accompanied by pain or tenderness [12]. Subjects:

1 had to have been unable to tolerate, or have had an inadequate response to, methotrexate; and
2 had to have received nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate, irrespective of the JIA. (Eligible subjects had a 14-day methotrexate washout period before baseline assessment. Disease activity was confirmed before the washout period.)

Exclusion criteria included use of DMARDs, for example penicillamine, salazosulfapyridine, gold drugs (oral and injectable), immunosuppressants (e.g. cyclosporine), intravenous immunoglobulins, cytotoxic agents (e.g. cyclophosphamide), or injected corticosteroids, within 28 days before the baseline assessment. Subjects of childbearing age had to consent to contraception during the study. A negative pregnancy test was required for female children who had experienced menarche.

Informed consent to participate was required from subjects or their legal guardians. Subjects or their caregivers had to be capable of properly managing the storage and administration of etanercept and accurately recording required information in the patient diary.

Assessments

In all 3 studies, the primary efficacy endpoint was the American College of Rheumatology criterion for the juvenile rheumatoid arthritis definition of improvement of 30% (ACR Pedi 30) at 12 weeks [13]. Secondary efficacy endpoints were ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi core set, and disease activity score 28 (DAS28) over time.

Serum trough concentrations of etanercept were estimated at predetermined intervals during the study. Safety was assessed on the basis of reported adverse events (AEs), routine physical examinations, and laboratory tests. AEs were collected at each study visit.

Serum was obtained at screening and at predefined intervals during the studies to test for anti-etanercept antibodies.

Statistical methods

Primary efficacy analysis was performed on the full analysis set (FAS) consisting of all the subjects who had received at least one dose of the investigated drug, and ACR Pedi core set data at baseline and at one subsequent visit, at least. The last-observation-carried-forward (LOCF) imputation approach was used to replace the missing data. Secondary endpoint results were reported as observed data. Summary statistics of trough drug concentration on each assessment day were calculated.

Safety results are reported for all subjects who had received at least one dose of etanercept. Adverse events were summarized by symptom, severity, and the causal relationship with the investigated drug.

Results

A total of 24 subjects were screened in the primary study; 22 received at least 1 dose of etanercept and were included in the full analysis set. At baseline, subjects were mostly female (81.8%) with polyarticular disease (86.4%), mean age 11.4 years, and mean disease duration 4.7 years (Table 1).

[1] The 3 studies presented in this article were initiated before 27 September 2007 and completed before 26 December 2007 and were therefore not subject to the new requirements for clinical trial results registration (Clinicaltrials.gov). The primary study (including data by 104 weeks) was initiated on 23 October 2003 and completed on 26 December 2005. The dose-down extension study was initiated 20 October 2005 and completed on 29 May 2006. The lower dose study was initiated 20 October 2005 and completed 13 March 2006.

Table 1 Baseline demographics and disease characteristics

Characteristic	Primary study, $N = 22$	Dose-down extension study[a], $N = 12$		Lower dose study, $N = 13$
	0.4 mg/kg	0.2 mg/kg, $N = 6$	0.4 mg/kg, $N = 6$	0.2 mg/kg
Gender, female, *n* (%)	18 (81.8)	4 (66.7)	6 (100)	13 (100.0)
Mean age in years, *n* (%)	11.4	13.0	13.5	13.1
4–8	6 (27.3)	1 (16.7)	1 (16.7)	2 (15.4)
9–12	9 (40.9)	0 (0.0)	1 (16.7)	2 (15.4)
13–17	7 (31.8)	5 (83.3)	2 (33.3)	9 (69.2)
18+	–	0	2[b] (33.3)	–
Mean BSA (m^2)	1.14	1.16	1.31	1.31
JIA onset type, *n* (%)				
Polyarticular	19 (86.4)	4 (66.7)	5 (83.3)	11 (84.6)
Pauciarticular	2 (9.1)	1 (16.7)	1 (16.7)	2 (15.4)
Systemic	1 (4.5)	1 (16.7)	0	0
Mean duration of JIA (years)	4.7	6.87	6.68	4.78
Prior treatment, *n* (%)[c]				
DMARD	22 (100)	–	–	13 (100)
Steroid	17 (77.3)	4 (66.7)	4 (66.7)	10 (76.9)
NSAID	22 (100)	6 (100)	4 (66.7)	13 (100)
Others	22 (100)	6 (100)	5 (83.3)	13 (100)
Prior treatment for JIA, *n* (%)[c]				
Actarit	1 (4.5)	0	0	0
Salazosulfapyridine	1 (4.5)	1 (16.7)	0	0
Cyclosporine	0	0	0	1 (7.7)
Methotrexate	22 (100)	6 (100)	6 (100)	13 (100)
Sodium aurothiomalate	1 (4.5)	0	0	0
Treatment with methotrexate				
Resistant	22 (100)	5 (83%)	5 (83%)	13 (100)
Intolerant	3 (13.6)	1 (7%)	1 (7%)	0
Mean number of active joints (73 joint count)	17.7	9.7	1.5	19.3
Mean number of joints with limited range of motion (71 joint count)	14.2	9.7	0.0	13.2
DAS28, mean	5.62	5.50[d]	5.88[d]	5.96
CHAQ (score 0–3)	1.27	0.69	0.35	1.17

BSA body surface area, *CHAQ* Childhood Health Assessment Questionnaire, *DMARD* disease-modifying anti-rheumatic drug, *JIA* juvenile idiopathic arthritis, *NSAID* nonsteroidal anti-inflammatory drug

[a] Baseline data from the primary study were used to calculate percentage improvement for the primary and dose-down studies

[b] Subjects were carried forward from the primary study and were over 18 at baseline of the dose-down extension study

[c] A single subject may have received more than 1 drug

[d] Baseline data in primary study

Subjects with polyarticular JIA who had completed at least 48 weeks of the primary study could participate in the dose-down extension study, which was a 12-week randomized, double-blind, multi-center study comparing the efficacy and safety of etanercept (0.2 mg/kg (up to a maximum of 12.5 mg) vs. 0.4 mg/kg (up to a maximum of 25 mg) twice weekly). Of the 22 patients included in the primary study, 12 continued into the 12-week double-blind dose-down extension study (6 continued to receive 0.4 mg/kg and 6 received 0.2 mg/kg). Of the remaining 10, 8 enrolled in a 5-year open-label study and 2 left the primary study because of unsatisfactory response.

The 12 subjects included in the dose-down extension study were mostly female (83.3%) with polyarticular disease (75.0%), mean age 13.3 years, and mean disease duration 6.8 years. Two patients left the dose-down extension study because of requests from parents.

Table 2 Key efficacy endpoints at week 12

Endpoint	Primary study, $N = 22$ 0.4 mg/kg	Dose-down extension study, $N = 12$		Lower dose study, $N = 13$ 0.2 mg/kg
		0.2 mg/kg, $N = 6$	0.4 mg/kg, $N = 6$	
ACR Pedi 30, *n* (%)	20 (90.9)	5 (83.3)	4 (66.7)	12 (92.3)
ACR Pedi 50, *n* (%)	20 (90.9)	5 (83.3)	4 (66.7)	11 (84.6)
ACR Pedi 70, *n* (%)	17 (77.3)	5 (83.3)	3 (50.0)	11 (84.6)
DAS 28, mean	2.64	2.50	3.15	2.41
Mean (% improvement)[a]				
Physician global assessment of disease activity	0.98 (78.7)	0.28 (94.6)	0.52 (93.6)	1.65 (75.6)
Patient/parent global assessment of overall well-being	2.5 (48.0)	2.0 (71.7)	2.5 (44.9)	2.9 (32.1)
Joints with active arthritis	2.8 (83.1)	1.5 (96.6)	3.7 (91.9)	5.5 (75.5)
Joints with limited range of motion	0.8 (89.2)	0.0 (100.0)	3.5 (92.4)	1.8 (85.5)
C-reactive protein, median (mg/dL)	0.170 (83.2)	0.105 (86.5)	0.025 (97.4)	0.340 (83.2)
CHAQ (score 0–3)	0.801 (35.7)	0.375 (80.6)	0.729 (56.0)	0.625 (46.5)

ACR Pedi American College of Rheumatology criteria for definition of improvement of JIA, *CHAQ* Childhood Health Assessment Questionnaire, *DAS* disease activity score

[a] Median data provided for C-reactive protein data

The third, or lower-dose, study included 14 subjects, of which 13 received at least 1 dose of etanercept. All subjects were female, with a mean age of 13.1 years and mean disease duration of 4.8 years (Table 1).

Efficacy

In the 2 open-label studies (primary and lower dose), the primary efficacy endpoint, ACR Pedi 30 (two-sided 95% confidence interval) at week 12 was achieved by at least 80% of the subjects as early as week 2 and was sustained to week 12 (Table 2). In the primary study, 20 of 22 (90.9%) patients achieved ACR Pedi 30 and ACR Pedi 50 at week 12; ACR Pedi 70 was achieved by 17 (77.3%) of subjects. Mean DAS28 at week 12 was 2.64. Joints with active and limited range of motion improved by 83.1 and 89.2%, respectively (Table 2). Physical function as measured by CHAQ, improved by more than a third (35.7%).

In the primary study, most ($n = 18$; 82%) patients continued through 96 weeks of the study. Response to etanercept was maintained over the duration of the study. ACR Pedi 30 and ACR Pedi 50 responses were achieved by all (100%) subjects at weeks 48 and 72, and response was 94% for both at week 96. ACR Pedi 70 response was achieved by 100% of subjects at week 48, 95% at week 72, and 89% at week 96. DAS 28 values were also sustained over time: mean values were 2.52, 2.68, and 2.48, at weeks 48, 72, and 96, respectively.

In the dose-down extension study, the improvements were generally maintained. A lower proportion of subjects receiving the 0.4 mg/kg dose seemed to have sustained the ACR Pedi responses. These observed results may be a consequence of the randomization or the small numbers of patients in each group. Joints with active arthritis and joints with limited motion continued to improve during the dose-down extension study (Table 2). CHAQ also continued to improve over the 12 weeks of treatment.

The lower dose study results paralleled the improvements observed in the primary study. Proportions of subjects achieving ACR Pedi 30, 50, and 70 were 92.3, 84.6, and 84.6%, respectively (Table 2). Improvements in joints and physical function were also similar to those seen in the primary study.

Safety results

In all 3 studies, the most common adverse events were nasopharyngitis, injection site reactions, and gastroenteritis. Adverse events occurring in 3 or more subjects are listed in Table 3. The severity of the adverse events was either grade 1 or grade 2.

There were no reports of sepsis, pneumonia, opportunistic infections including fungal infections or tuberculosis, serious allergic reaction, serious blood disorder, demyelinating diseases, or lupus associated with any of these studies. Serious adverse events occurring in more than 1 patient are included in Table 4. No patients had CTC grade 4 laboratory test result abnormalities; in the primary study, one subject experienced grade 3 hemoglobin decrease that was deemed to be possibly related to etanercept. There were no deaths or study discontinuations because of adverse events during the study.

In the 3 studies, an increase in antinuclear antibodies was observed but the increase was not associated with any

Table 3 Adverse events occurring in 3 or more patients reported during the study

Event	Primary study (until week 12) $N = 22$ 0.4 mg/kg	Primary study (104 weeks) $N = 22$ 0.4 mg/kg	Dose-down extension study, $N = 12$		Lower dose study, $N = 13$
			0.2 mg/kg, $N = 6$	0.4 mg/kg, $N = 6$	0.2 mg/kg
Any adverse event, *n* (%)	22 (100)	22 (100)	6 (100)	5 (83.3)	13 (100)
Injection site reactions	12 (54.5)	17 (77.3)	0	0	8 (61.5)
Injection site hemorrhage	6 (27.3)	9 (40.9)	0	0	2 (15.4)
Headache	5 (22.7)	8 (36.4)	0	0	3 (23.1)
Rhinorrhea	3 (13.6)	8 (36.4)	0	0	1 (7.7)
Rash	2 (9.1)	7 (31.8)	0	0	0
Diarrhea	1 (4.5)	5 (22.7)	0	2 (33.3)	1 (7.7)
Abdominal pain	2 (9.1)	6 (27.3)	0	0	0
White blood cell count increased	4 (18.2)	5 (22.7)	0	1 (16.7)	0
Pyrexia	2 (9.1)	5 (22.7)	0	0	1 (7.7)
Myalgia	1 (4.5)	5 (22.7)	1 (16.7)	0	0
Arthropod sting	–	5 (22.7)	0	0	1 (7.7)
Hemoglobin decreased	2 (9.1)	5 (22.7)	0	0	0
Dry skin	1 (4.5)	5 (22.7)	0	1 (16.7)	0
Epistaxis	1 (4.5)	3 (13.6)	0	0	2 (15.4)
Hemorrhage subcutaneous	–	3 (13.6)	0	1 (16.7)	2 (15.4)
Vomiting	2 (9.1)	4 (18.2)	0	0	0
Excoriation	1 (4.5)	4 (18.2)	0	0	0
Stomatitis	1 (4.5)	4 (18.2)	1 (16.7)	0	0
Alanine aminotransferase increased	3 (13.6)	3 (13.6)	0	0	1 (7.7)
Contusion	2 (9.1)	3 (13.6)	0	0	0
Erythema	2 (9.1)	3 (13.6)	0	0	0
Hematocrit decreased	2 (9.1)	3 (13.6)	0	0	0
Pruritis	1 (4.5)	3 (13.6)	0	0	0
Urticaria	1 (4.5)	3 (13.6)	0	0	0
Dizziness	–	3 (13.6)	0	0	0
Nasal congestion	–	3 (13.6)	0	0	0
Seasonal allergy	–	3 (13.6)	0	0	0
Any infection	16 (72.7)	22 (100)	3 (50.0)	4 (66.7)	8 (61.5)
Nasopharyngitis	12 (54.5)	19 (86.4)	2 (33.3)	4 (66.7)	7 (53.8)
Gastroenteritis	4 (18.2)	12 (54.5)	0	0	0
Influenza	3 (13.6)	9 (40.9)	1 (16.7)	0	0
Upper respiratory tract infection	1 (4.5)	5 (22.7)	1 (16.7)	0	0
Impetigo	1 (4.5)	4 (18.2)	0	0	0
Pharyngitis	1 (4.5)	3 (13.6)	0	0	0

symptoms. Anti-etanercept antibodies were identified in 9 (25.7%) patients, but all cases tested negative for antineutralizing antibodies.

Pharmacokinetics

The mean serum etanercept concentration for the 0.4 mg/kg dose group increased in a dose-dependent manner; it was twice as much as the value for the 0.2 mg/kg dose group when observed from week 8 onward (Table 5). For subjects who received 0.4 mg/kg, the mean serum trough concentration of etanercept was ~3000 ng/mL by week 8; for subjects receiving the 0.2 mg/kg dose the mean serum concentration was ~1400 ng/mL by week 8. The mean apparent clearance for subjects receiving 0.4 mg/kg was between 0.047 and 0.133 L/h; it was between 0.056 and 0.141 L/h for subjects receiving 0.2 mg/kg (Table 5).

Table 4 Serious adverse events occurring in >1 patient

Event	Primary study, $N = 22$ (104 weeks) 0.4 mg/kg	Dose-down extension study, $N = 12$		Lower dose study, $N = 13$ 0.2 mg/kg
		0.2 mg/kg, $N = 6$	0.4 mg/kg, $N = 6$	
Cellulitis	1 (4.5)	0	0	0
Pneumonia mycoplasmal	1 (4.5)	0	0	0
Inguinal hernia	1 (4.5)	0	0	0
Condition aggravated	1 (4.5)	0	0	0
Uveitis	1 (4.5)	0	0	0
Joint contracture	1 (4.5)	0	0	0
Appendicitis	1 (4.5)	0	0	0

Table 5 Mean trough concentrations and mean apparent clearance over time

	Treatment (mg/kg)	Week 2	Week 4	Week 8	Week 12
Mean trough concentrations (ng/mL)					
Primary study	0.4	2941 ± 875 (21)	2217 ± 1169 (21)	2871 ± 1052 (20)	3269 ± 1265 (21)
Dose-down extension study	0.2	1770 ± 364 (6)	1779 ± 282 (6)	1405 ± 512 (5)	1439 ± 702 (5)
	0.4	3047 ± 426 (5)	3191 ± 1097 (5)	2916 ± 372 (5)	3229 ± 298 (5)
Lower dose study	0.2	1299 ± 449 (13)	1005 ± 723 (12)	1057 ± 481 (12)	1183 ± 442 (11)
Mean apparent clearance (L/h)					
Primary study	0.4	0.064 ± 0.026 (21)	0.133 ± 0.177 (21)	0.076 ± 0.062 (20)	0.059 ± 0.028 (21)
Dose-down extension study	0.2	0.056 ± 0.009 (6)	0.056 ± 0.016 (6)	0.077 ± 0.025 (5)	0.087 ± 0.048 (5)
	0.4	0.047 ± 0.011 (5)	0.050 ± 0.017 (5)	0.050 ± 0.011 (5)	0.047 ± 0.007 (5)
Lower dose study	0.2	0.083 ± 0.033 (13)	0.141 ± 0.086 (12)	0.112 ± 0.077 (12)	0.118 ± 0.119 (11)

Mean ± SD (*N*)

Discussion

Etanercept was indicated for use in the treatment of JIA in the United States and the European Union in 1999 and 2000 respectively, and has been recently approved (2009) for the treatment of DMARD-refractory polyarticular JIA in Japan. The efficacy and safety of etanercept in pediatric patients in North America and Europe are well established [3, 8–11]. The 4 studies evaluating the efficacy and safety of etanercept provided the required evidence for approval of etanercept for treatment of Japanese children with polyarticular course JIA.

In the 3 studies described here (primary, dose-down extension, and lower-dose), 35 pediatric subjects received etanercept 0.2 or 0.4 mg/kg twice weekly for at least 12 weeks. Efficacy results from the 2 open-label studies, primary (etanercept 0.4 mg/kg) and lower-dose (etanercept 0.2 mg/kg), indicated that etanercept is highly effective; the primary endpoint, ACR Pedi 30, was achieved by 91 and 92% of subjects, respectively. Similarly, in the dose-down extension study, which was a double-blind study comparing the 2 doses, there was no difference in ACR Pedi 30 between the 2 groups. At week 12, percentages of subjects achieving ACR Pedi 50 and 70 ranged between 66.7 and 91% and 50 and 85%, respectively. Major improvements seen in key efficacy endpoints in the 2 open-label studies were maintained in the dose-down extension study.

Etanercept was well tolerated in all 3 studies. There were no deaths or study discontinuations because of adverse events during the studies; no reports of sepsis, pneumonia, opportunistic infections demyelinating diseases, or lupus were associated with these studies. The increase in antinuclear antibodies observed during these studies was not associated with any symptoms; anti-etanercept antibodies detected during these studies were nonneutralizing.

In Japan, nonsteroidal anti-inflammatory drugs (NSAIDs) are not approved for use in the treatment of JIA; ibuprofen is only used for controlling the pain associated with the disease. The disease-modifying antirheumatic drug (DMARD) methotrexate was approved for treatment of JIA in Japanese pediatric subjects in 2008 [14]. However, no studies were conducted to evaluate the efficacy or safety of methotrexate in Japanese children before its approval.

Limitations of these studies include the small numbers of subjects and the short duration of the studies. However, the results from these Japanese studies agree with those from larger North American studies [3, 5] that have established that etanercept is an effective and well tolerated option for treatment of children with JIA. Study design, namely the lack of a control arm in the 3 studies, may be also regarded as a limitation of these studies. However, because etanercept may be the most effective drug approved for use in children, including a placebo arm or a drug that is not equally effective and safe would be putting these children at undue risk.

In conclusion, these 3 studies demonstrated that etanercept is highly effective and well tolerated in Japanese children with JIA. Treatment with etanercept significantly reduced the signs and symptoms of JIA with no new safety signals. These results provide further evidence that etanercept is effective therapy for Japanese patients with JIA.

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