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ORIGINAL ARTICLE

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Pharmacokinetics, efficacy, and safety of short-term (12 weeks) etanercept for methotrexate-refractory polyarticular juvenile idiopathic arthritis in Japan

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Abstract We examined and evaluated the pharmacokinetics, efficacy, and safety of etanercept in patients with methotrexate (MTX)-refractory polyarticular juvenile idiopathic arthritis (JIA) in Japan. All MTX-refractory polyarticular JIA patients 4–17 years old received 0.4 mg of etanercept per kilogram of body weight subcutaneously twice weekly for up to 3 months in the open-label, prospective, and multicenter trial. A response was defined as an improvement of 30%, 50%, 70%, or more from baseline in at least three of six indicators of disease activity, with no more than one indicator worsening by more than 30% from baseline (30%, 50%, or 70% definition of improvement, respectively), and disease activity score (DAS28) by EULAR (European League Against Rheumatism) response criteria. At the end of the 12-week study, 20 of the 22 patients (90.9%) had responses with both 30% and 50% definition of improvement after etanercept treatment. To our surprise, 15 of 22 patients (68.2%) had a response with 70% definition of improvement. Moreover, in DAS28, eight patients were evaluated as having a good response and there were no patients with a poor response to etanercept. Treatment had to be stopped in one patient who developed joint contracture during the study period, but there were no significant adverse events in the other patients. In conclusion, treatment with etanercept leads to significant improvement in patients with active polyarticular JIA in Japan. Etanercept is well tolerated by pediatric patients as well as adults.

Key words Childhood · Etanercept · Methotrexate · Serum cytokine · Tumor necrosis factor (TNF) alpha

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Introduction

Juvenile idiopathic arthritis (JIA) is adequately controlled by nonsteroidal anti-inflammatory drugs (NSAIDs) in approximately one-third of patients.[1–3] However, for the remaining two thirds there is limited choice of "second-line" agents, more aggressive therapy with antirheumatic drugs, to control the disease. Methotrexate (MTX) was shown to have a therapeutic advantage over placebo, with an acceptable safety profile, in a randomized, controlled trial in children with JIA who had polyarticular involvement with 0.2–1.0 mg per kg of body weight weekly.[4–7] However, some patients do not have an adequate response to MTX, even at doses of up to 1.0 mg/kg body weight per week.[8,9] The frequency and severity of side effects increase with higher doses of MTX, and the consequences of long-term use are not known. Exacerbation of disease during treatment with stable doses of MTX and the need to increase the MTX dose over time suggest that drug resistance to MTX may develop. Methotrexate is also not efficacious or well tolerated in some patients with JIA, and higher doses of MTX may be associated with greater toxicity.[10]

Recently, the introduction of anti-tumor necrosis factor (TNF) treatment appears to have had a major impact on the outcome of patients with polyarticular JIA. Etanercept (Enbrel; Immunex, Seattle, WA, USA), a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of human IgG_1, effectively binds TNF and lymphotoxin-alpha and inhibits their activity.[11,12] Randomized, double-blind, placebo-controlled trials showed that etanercept treatment had significant clinical benefit with minimal toxicity in adults with active rheumatoid arthritis that did not respond to other disease-modifying antirheumatic drugs (DMARDs).[13–15]

We initiated a prospective, open-label, multicenter study to assess the efficacy of and tolerance to etanercept in children in Japan with polyarticular JIA who responded poorly to MTX or who had an inadequate response to MTX. This study was prepared with a view to etanercept also becoming

a treatment for JIA in Japan subsequent to the study results mentioned here.

Patients and methods

Patients

The study population included patients aged 4–17 years old with active polyarticular JIA who are refractory to or intolerant of MTX. The following criteria should have been satisfied for inclusion: (1) age 4–17 years at the time of obtaining informed consent; (2) disease onset may have been systemic, polyarticular, or pauciarticular, but disease course must be polyarticular; (3) duration of disease is disregarded but the subject must have a history of treatment with NSAIDs and MTX; (4) patients have active disease at the time of screening, i.e., they must have ≥5 swollen joints and ≥3 joints with limitation of motion accompanied by pain and/or tenderness; (5) patients are refractory or intolerant to MTX so that a change of drug is considered valid; (6) patients have not received DMARDs (including penicillamine, salazosulfapyridine, oral or injectable gold, cyclosporin), intravenous immunoglobulin, or cytotoxic agents such as cyclophosphamide during the 28 days before the baseline assessment, and have not been administered MTX for at least 14 days prior to baseline assessment – patients currently administered these DMARDs must demonstrate active status prior to the washout period; (7) patients have not received steroid injection into the joint and soft tissue for at least 28 days prior to baseline assessment; (8) for sexually active males or females with childbearing potential, informed consent to practice adequate contraception must be obtained prior to enrollment; (9) females after first menstruation must have negative pregnancy test result at the time of screening and baseline assessment; (10) patients' parents or legal guardians are willing to give informed consent – in addition, the subjects themselves must give assent, however, informed assent is not necessarily required for patients under 7 years old; (11) patients' parents or legal guardians are capable of appropriately supervising the storage and administration of the investigational product, and of recording the time of administration, health condition, etc., accurately in the patient's diary.

Additionally, the exclusion criteria were as follows: (1) patients categorized as functional Class IV in the Classification by the American College of Rheumatology; (2) any one of the following in screening test: (a) low white blood cell count (<4000/μl), (b) low neutrophil count (<1000/μl), (c) low platelet count ($<10\times10^4$/μl), (d) hepatic aminotransferase concentrations (GOT, GPT) more than three times the normal value for age, (e) bilirubin concentration more than twice the normal value for age, (f) abnormal creatinine clearance, (g) ejection fraction by cardiac echo less than 55%, (h) past history of positive test for HIV, (i) type B hepatitis or type C hepatitis antibody positive at screening, (j) anti-double strand DNA antibody positive at screening; (3) history of treatment with anti-TNF antibody, anti-CD4 antibody, and diphtheria interleukin (IL)-2 fusion protein; (4) history of allergic reaction to protein formulations as immunoglobulin; (5) currently under steroid medication with dose exceeding prednisolone equivalent of 0.2 mg/kg per day (maximum 10 mg/day); (6) familial and social conditions rendering regular medical assessment impossible.

Methotrexate or the other disease-modifying and immunosuppressive drugs had to be withdrawn at least 14 or 28 days before the initiation of etanercept treatment, respectively. Intra-articular and soft-tissue corticosteroid injections were not permitted during or for 1 month prior to the trial. Pain medications were allowed except during the 12 h before a joint assessment. Each case was analyzed by an independent medical expert before agreement for inclusion was given. All patients and parents were enrolled in this study after parental informed consent was given. The institutional Review Board approved the study.

Study design

All patients received 0.4 mg of etanercept per kilogram (maximum, 25 mg) subcutaneously twice weekly for up to 3 months. The first injections were systematically administered at the hospital. One of the parents (and the patient, when possible) was taught how to administer the injections, so that the subsequent injections were administered at home. A standardized questionnaire was sent to each treating physician in order to collect the following data prospectively: the patient's previous medical history, physical symptoms, number of swollen joints, number of joints with limitation of motion, tenderness, or pain, the score obtained using the validated French version of the Childhood Health Assessment Questionnaire (CHAQ),[16,17] the physician's and parent's global assessment of disease activity, and the parent's assessment of pain, using a visual analog scale. Physical examinations, disease activity assessment, and laboratory tests (hematologic analysis, serum chemical analysis, and urinalysis) were performed at screening and repeated on weeks 1, 2, 4, 8, and 12 after the administration of etanercept during the study. Physical examinations and disease activity assessment had to be performed every time in every patient by the same physician, who could be the treating physician. Tolerance to etanercept was systematically recorded. Final safety assessments were made 30 days after the discontinuation of the study drug for patients who withdrew from the study or at the patient's next scheduled visit if the patient withdrew from the study because of disease flare. Serum was obtained at screening and at the end of month 3 for testing for autoantibodies [antinuclear antibodies, antibodies to double-stranded (ds) DNA, IgG and IgM anticardiolipin antibodies, antibodies to ribonucleoprotein (RNP), anti-smith (Sm) antibodies, and anti-SS-A/Ro and anti-SS-B/La antibodies], and at the end of 3 months for testing for antibodies to etanercept.

Pharmacokinetics

Sera were collected for population pharmacokinetics (PK) samples from all patients, and trough serum concentrations

were measured before and at weeks 2, 4, 8, and 12 after the initiation.

Definition of improvement

The disease was considered to have improved by 30%, 50%, or 70% if at least three of the six indicators of disease activity improved by at least 30%, 50%, or 70% with respect to baseline, and if no more than one indicator worsened by 30% or more.[18] As in the study by Lovell et al.,[19] the following indicators of disease activity were used: the number of joints with limitation of motion not due to deformity, the number of "active" joints (i.e., joints with swelling not due to deformity or joints with limitation of motion plus pain, tenderness, or both), the CHAQ score, global assessment of disease activity by the physician, global assessment of disease activity by the patient or the patient's parent, and the erythrocyte sedimentation rate (ESR). Disease flare was defined by at least 30% worsening of three or more of the six response indicators with respect to the last assessment, with at least two active joints. Patients were also evaluated for 50% and 70% improvement (50% and 70% improvement in at least three of the six response variables and a worsening of 30% or more in no more than one of the six response variables). Patients who met the criteria for disease flare had worsening of 30% or more in three of the six response variables and a minimum of two active joints. They also could have improvement of 30% or more in no more than one of the six response variables. Global assessments, if used to define flare, had to change by at least 2 units on a scale from 0 to 10. Additional assessments of disease activity included the articular severity score,[20] duration of morning stiffness, degree of pain (on a visual-analog scale), and C-reactive protein levels.

Measurement of DAS28

Disease activity score (DAS28), which includes the 28 tender and swollen joint counts, ESR, and the patient's assessment of disease activity measured with a visual analog scale (100 mm), was also calculated before and at week 12 after initiation.[21–23] DAS28 >5.1 means the patient has high disease activity and DAS28 < 3.2 means that disease activity is low. A change in DAS28 of >0.6 constitutes a change greater than the measurement error of the DAS28. A change in DAS28 of >1.2 (twice the measurement error) is a clinically significant change in the DAS28. The DAS28 is calculated as follows: DAS28 = $0.56\sqrt{}$tender 28 + $0.28\sqrt{}$swollen 28 + 0.70 ln ESR + 0.014General Health.

Safety

The events whose onset was noted after the start of investigational product administration or the complications that aggravated in comparison with the status before the investigational product administration (events that occurred during the treatment in the study; treatment emergent study events) were all handled as "adverse events." The adverse events were judged in four grades: 1, related; 2, probably related; 3, possibly related; 4, unrelated. Excluding "4, unrelated," the remaining adverse events were handled as adverse reactions.

Statistical analysis

To summarize baseline characteristics, descriptive statistics were used. Number of subjects and proportion (%) for categorical data, and mean and standard deviation (SD) for numerical data were calculated. Change of trough serum drug concentration was described with mean and SD at each time point. To show the JIA activity at each time point, the median of each item of core-set score was used, and the improvement rate at the 12th week was described using the median of % change from baseline. To evaluate the improvement, 30% (primary), 50%, and 70% were set as definition of improvement (DOI) cutoff values. The proportion (%) and two-sided 95% confidence interval based on binomial distribution was calculated for 30%, 50%, and 70% DOI. To examine the changes of cytokine or cytokine receptor, mean and SD at each time point were used. Moreover, for tolerance to etanercept, incidence of adverse events were described with number of set cases, proportion (%), two-sided 95% confidence interval based on binomial distribution, and number of episodes.

Results

Baseline characteristics

The baseline demographic and disease characteristics of the study patients are summarized in Table 1. Four male and 18 female patients were enrolled in the present study. At enrollment, the mean age was 11.4 years (range, 4–17) and the mean duration of JIA was 4.72 years. During the first 6 months of the disease, 2 patients had had extended oligoarticular arthritis, 11 rheumatoid factor (RF)-positive polyarthritis, 8 RF-negative polyarthritis, and 1 systemic arthritis (associated with spiking fever and rheumatoid rash). However, disease course type at the initiation of etanercept was polyarticular arthritis in all of the patients. All of them had previously been treated with MTX, which either was not tolerated or had failed to control the disease activity. Methotrexate had been administered at the mean dose of 12.3 mg/week.

Pharmacokinetics

Serum levels of etanercept at week 12 in this study were higher than those of overseas JIA patients; however, the change in blood level after repeated dose showed a similar pattern to United States JIA patients, as shown in Fig. 1.

Table 1. Baseline demographic and disease characteristics of the study patients

	Classification	No. of cases	
		(n = 22)	(%)
Sex	Male	4	(18.2)
	Female	18	(81.8)
Age (years old)	4–8	6	(27.3)
	9–12	9	(40.9)
	13–17	7	(31.8)
	Mean ± SD	11.4 ± 3.7	
Height (cm)	Mean ± SD	135.3 ± 18.1	
Body weight (kg)	Mean ± SD	34.9 ± 13.1	
BSA (m^2)	Mean ± SD	1.14 ± 0.29	
Disease onset type	Extended oligoarticular	2	(9.1)
	RF-positive polyarticular	11	(50.0)
	RF-negative polyarticular	8	(36.4)
	Systemic	1	(4.5)
Duration of disease (years)	<2	5	(22.7)
	2–5	8	(36.4)
	5<	9	(40.9)
	Mean ± SD	4.72 ± 3.41	
Functional classification	Class I	9	(40.9)
	Class II	11	(50.0)
	Class III	2	(9.1)
	Class IV	0	(0.0)

BSA, body surface area

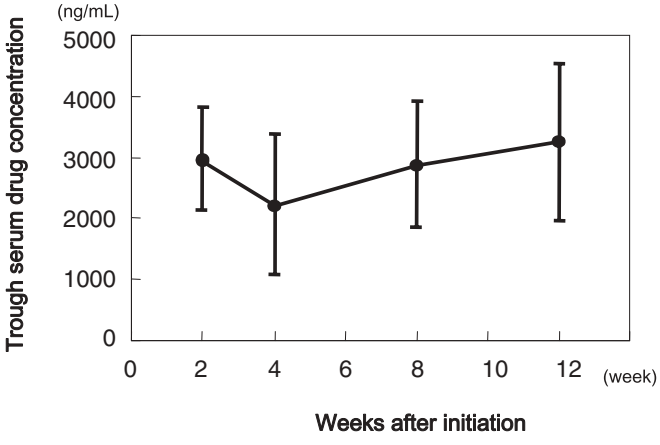

Fig. 1. Trough serum drug concentration of etanercept in juvenile idiopathic arthritis (JIA) patients in the present study. Sera were collected for population pharmacokinetics samples from all patients, and trough serum concentrations were measured before and at weeks 2, 4, 8, and 12 after the initiation. Serum level of etanercept at week 12 in this study was higher than that of overseas JIA patients; however, the change in blood level after repeated dose showed a similar pattern with United States JIA patients

Disease response at end of study

In this study, the primary end point was defined as improvement of the score for JIA activity (core-set score) of at least 30%. Secondary end points were defined as improvement of the core-set score by either 50% or 70%. The analysis was performed before and at 1, 2, 4, 8, and 12 weeks after the initiation of etanercept. The evolution of each item of the core-set score at 12 weeks was presented as descriptive data (Table 2). The definition of improvement was based on changes from baseline values, whereas disease flare was based on changes from values at each evaluation time. Scores in the disability domain of the CHAQ began to improve at the first evaluation 2 weeks after the beginning of etanercept treatment. A 30% improvement of the core-set score was achieved in 81.8% of patients (18/22) at week 2, followed by a time-dependent increase, reaching 90.9% (20/22) by week 8. Moreover, a 50% or 70% improvement of core-set score was reached in 90.9% (20/22) of the patients by week 8 or 68.2% (15/22) at week 12, respectively. Complete results for 30%, 50%, and 70% improvement for each time point are shown in Fig. 2 and Table 3. There were only two patients who had improved by <30% at week 12.

The change of DAS28 between before and at week 12 was examined to evaluate the disease activity in all patients (Fig. 3). Eight patients were evaluated as having a good response and 12 had a moderate response according to the criteria of EULAR (European League Against Rheumatism). This result showed that there were no patients with a poor response to etanercept.

Changes of serum concentrations of cytokine or cytokine receptor by etanercept

Etanercept is the fusion protein consisting of two identical TNF p80 (Type II) receptors linked by the Fc fragment of the IgG molecule, so soluble TNF receptor II concentration exactly increases by etanercept therapy. Additionally, since both free and receptor-associated TNF were measured in this immunoassay, serum TNF concentration also elevated

Table 2. Changes in JRA core set and other activity assessment items as well as the improvement rates from the baseline levels on the 12th week assessment day

	Baseline $n = 22$	2nd week assessment day $n = 22$	4th week assessment day $n = 22$	8th week assessment day $n = 22$	12th week assessment day $n = 22$	Improvement rate (%) $n = 22$
JRA core set Global assessment by physician[a] (cm)	5.6	1.8	1.4	0.9	0.6	88.8%
Global assessment by subject[b]	6	3	3	3	3	56.3%
No. of active joints[c] (*n*)	13	5	5	4	2	87.5%
No. of joints with LOM accompanied by pain and/or tenderness[d] (*n*)	10	2	1	0	0	100.0%
CHAQ[e]	2.4	1.7	1.7	1.6	1.5	10.3%
ESR (mm/h)	26	14	17	15	15	48.1%
Other activity assessment items						
Severity of pain assessed by subject[b]	6	3	4	3	3	66.7%*
Duration of morning stiffness (time)	1.0	0.1	0.2	0.3	0.2	75.0%**
CRP (mg/dl)[f]	1.70	0.11	0.61	0.18	0.17	83.2%
Rheumatoid factor[g] (IU/ml)	38	–	–	–	–	–

JRA, juvenile rheumatoid arthritis; LOM, limitation of motion; CHAQ, Childhood Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

[a] 0 cm is the best and 10 cm is the worst

[b] 0 is the best and 10 is the worst

[c] Assessment from 0 to 73

[d] Assessment from 0 to 71

[e] 1 is the best and 4 is the worst

[f] Standard value ≤0.30 mg/dl

[g] Standard value ≤20 IU/ml

* $n = 21$; ** $n = 19$

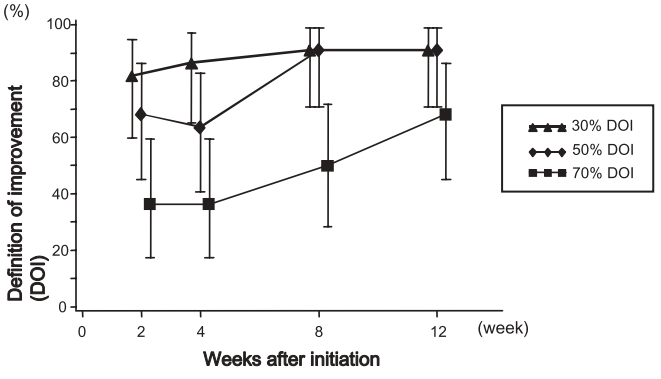

Fig. 2. Changes in definition of improvement (*DOI*). A 30% improvement of the core-set score was achieved in 81.8% of patients (18/22) at week 2, followed by a time-dependent increase, reaching 90.9% (20/22) by week 8. Moreover, a 50% or 70% improvement of core-set score was reached in 90.9% (20/22) of the patients by week 8 and in 68.2% (15/22) by week 12, respectively

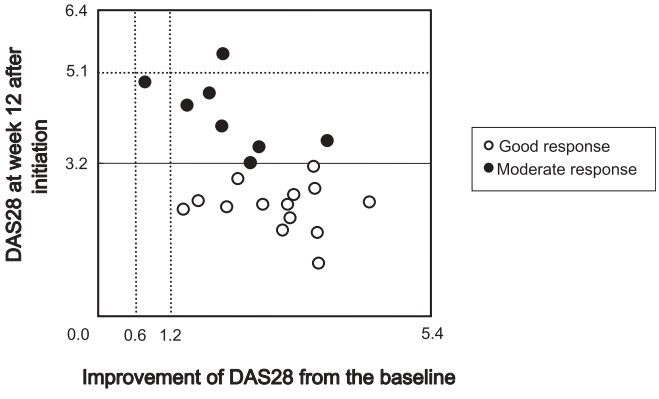

Fig. 3. Changes of European League Against Rheumatism (EULAR) response criteria based on the disease activity score (*DAS28*) in JIA patients. DAS28, which includes the 28 tender and swollen joint counts, erythrocyte sedimentation rate, and the patient's assessment of disease activity measured with a visual analog scale (100 mm), was calculated before and at week 12 after initiation. DAS28 >5.1 means the patient has high disease activity and DAS28 < 3.2 means that disease activity is low. A change in DAS28 of >0.6 constitutes a change greater than the measurement error of the DAS28. A change in DAS28 of >1.2 is a clinically significant change in the DAS28. The DAS28 is calculated as follows: DAS28 = $0.56\sqrt{\text{tender } 28} + 0.28\sqrt{\text{swollen } 28} + 0.70 \ln \text{ESR} + 0.014$ General Health. Eight patients were evaluated as having a good response, and 12 had a moderate response according to EULAR criteria using etanercept

in during the time course through treatment with etanercept (data not shown).

The secondary responses of cytokine or cytokine receptor were significantly altered by the administration of etanercept. It diminished soluble TNF receptor type I (sTNFR-1), serum IL-6, and IL-1β, as shown in Fig. 4. The results show that the concentrations of IL-6 at week 2, 4, 8, and 12, IL-1β at week 4, and sTNFR-1 at week 12 were significantly lower than those before treatment.

Table 3. Changes in 30%, 50%, and 70% definition of improvement (DOI)

Assessment day	2nd week	4th week	8th week	12th week
30% DOI (*n/N*)	81.8 (18/22)	86.4 (19/22)	90.9 (20/22)	90.9 (20/22)
Two-tailed 95% confidence interval	59.7–94.8	65.1–97.1	70.8–98.9	70.8–98.9
50% DOI (*n/N*)	68.2 (15/22)	63.6 (14/22)	90.9 (20/22)	90.9 (20/22)
Two-tailed 95% confidence interval	45.1–86.1	40.7–82.8	70.8–98.9	70.8–98.9
70% DOI (*n/N*)	36.4 (8/22)	36.4 (8/22)	50.0 (11/22)	68.2 (15/22)
Two-tailed 95% confidence interval	17.2–59.3	17.2–59.3	28.2–71.8	45.1–86.1

Table 4. Incidence of adverse events

	Overall ($n = 22$)	Infections ($n = 22$)	Reaction in the administration site ($n = 22$)	Laboratory test ($n = 22$)	Other *[3] ($n = 22$)
No. of onset cases (%)	22 (100.0)	16 (72.2)	15 (68.2)	10 (45.5)	19 (86.4)
95% confidence interval	84.6–100.0	49.8–89.3	45.1–86.1	24.4–67.8	65.1–97.1
No. of episodes *[1]	111	27	15	20	49
Grade *[2]					
1	5	5	8	4	9
2	15	11	7	5	8
3	2	0	0	1	2
4	0	0	0	0	0

*[1]: When the same symptom occurred a number of times in the same subject, the case was aggregated as one event
*[2]: The event of highest grade among those that occurred in each case
*[3]: Events from which infections, administration site reaction, and abnormal laboratory test values were excluded

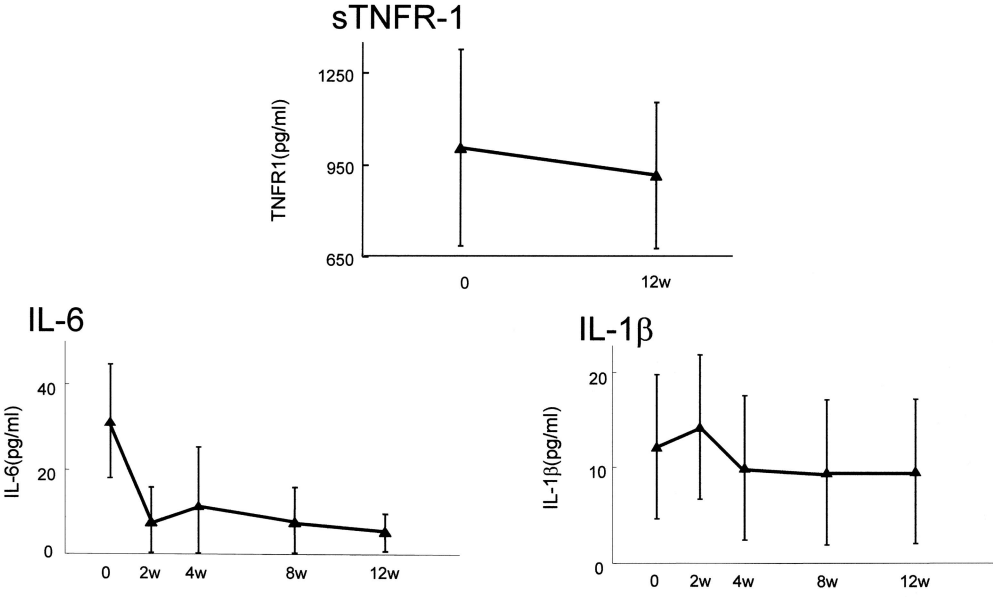

Fig. 4. Changes in serum concentrations of inflammatory cytokines or cytokine receptor by etanercept. The secondary responses of cytokine or cytokine receptor were significantly altered by the administration of etanercept. Here, we suggested that the concentrations of interleukin-6 (*IL-6*) at weeks 2, 4, 8, and 12, interleukin-1β (*IL-1β*) at week 4, and soluble tumor necrosis factor receptor type I (*sTNFR-1*) at week 12 were significantly lower than those before treatment

Tolerance to etanercept

Etanercept was safe and well tolerated. One patient withdrew because of development of joint contracture at 11 weeks and 4 days after the first dose of etanercept. The joint contracture was judged as severe by the physician because of possible "development of damage" and need for "hospitalization or extension of hospitalization." A causal relationship with the study drug was denied. Improvement was confirmed after rehabilitation at home and hospital, and staying on the treatment after week 12 was judged as appropriate. In this study, the most common adverse events were injection-site reactions (68.2% of patients), rhinitis and pharyngitis (54.5%), headache (22.7%), gastrointestinal infection (18.2%), abdominal pain (9.1%), vomiting (9.1%), and rash (9.1%). There were no laboratory abnormalities requiring urgent treatment (Table 4).

No patient had persistent elevations in autoantibodies or had signs or symptoms of another autoimmune disease. Antinuclear antibody was positive in 14 cases at screening

and 17 cases at week 12. Anti-ds-DNA antibody, anti-RNP antibody, anti-Sm antibody, and anti-SS-B/La antibody were negative in all cases. Anti-SS-A/Ro antibody was positive before and after medication in only one case. Anticardiolipin antibody was positive in three patients before medication, of whom one became negative after medication. A positive conversion (negative at screening and positive at week 12) was found in one case with anti-cardiolipin antibody and in three cases with anti-nuclear antibody. The level of all the converted cases was only slightly above the normal value. There was no other incidence of autoimmune diseases. At week 12, the autoantibody to etanercept was negative in all patients.

Discussion

We studied 22 patients with polyarticular JIA who did not tolerate or have an adequate response to MTX, and who were treated with etanercept for the short term of 12 weeks. At the end of the 12-week study, 20 of the 22 patients (90.9%) had responses with both 30% and 50% definition of improvement to etanercept treatment, and 15 patients (68.2%) had a response with 70% definition of improvement. In the change of DAS28 between before and at week 12, eight patients had a good response and 12 had a moderate response to etanercept according to EULAR criteria. We suggest that etanercept significantly diminished soluble TNF receptor type I, serum IL-6, and IL-1β. Although the treatment had to be stopped in one patient who developed joint contracture during the course, there were no significant adverse events in the other patients in the present study. In short, we showed that etanercept was effective in Japanese pediatric patients with severe polyarticular JIA.

Juvenile idiopathic arthritis is characterized by early-onset arthritis under the age of 16 years that persists in one or more joints for at least 6 weeks, and in which infectious arthritis and other well-defined illnesses have been actively excluded.[1] This criterion was proposed by an international group of pediatric rheumatologists in 1993, and most of these conditions were formerly known as juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis. Juvenile idiopathic arthritis is the most common rheumatic condition in children[2] and may be associated with severe disability and life-threatening complications, particularly in patients in whom polyarthritis develops and who do not respond satisfactorily to treatment.[3] The disease is adequately controlled by NSAIDs in approximately one third of patients. However, for the remaining two thirds there is limited choice of "second-line" agents, more aggressive therapy with antirheumatic drugs, to control the disease. Methotrexate was shown to have a therapeutic advantage over placebo, with an acceptable safety profile, in a randomized, controlled trial in children with JIA with polyarticular involvement who received 0.2–1.0 mg/kg body weight weekly.[4,5] The type of onset is the best predictor of MTX efficacy. Long-term studies showed that patients with systemic-onset JIA tend to respond poorly to MTX, whereas those with oligoarticular-onset JIA in whom polyarthritis develops secondarily are more likely than other JIA patients to respond to MTX.[4–7] However, some patients do not have an adequate response to MTX, even at doses of up to 1.0 mg/kg body weight per week.[8,9] The frequency and severity of side effects increase with higher doses of MTX, and the consequences of long-term use are not known. Exacerbation of disease during treatment with stable doses of MTX and the need to increase the MTX dose over time suggest that drug resistance to MTX may develop.[10]

Tumor necrosis factor is a proinflammatory cytokine that has a complex role in the pathogenesis of rheumatoid arthritis.[24–30] Tumor necrosis factor is elevated in both the serum and the synovial fluid of children with JIA.[31] Serum levels of soluble TNF receptor are elevated in patients with JIA, and the level is correlated with disease activity.[32] In one study, TNF was detected in 45% of samples of synovial fluid from 44 children with JIA.[33] Further evidence that TNF may amplify local inflammation and lead to joint destruction came from a study in which both TNF and lymphotoxin-alpha were detected in the majority of synovial-tissue samples from patients with JIA.[31] Tumor necrosis factor induces the release of matrix metalloproteinases and induces expression of endothelial adhesion molecules. It also leads to upregulation of the transcription factor NF-κB and induces apoptosis. Tumor necrosis factor exerts its effect via two distinct cell surface TNF receptors, p55 and p75. Etanercept, a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of human IgG1, effectively binds TNF and lymphotoxin-alpha and inhibits their activity.[11,12] Results of a multicenter pediatric trial performed in the United States demonstrated that etanercept was effective and well tolerated in 74% of children ($n = 69$) with JIA and polyarthritis, regardless of the type of disease onset.[30,34] Moreover, the safety of etanercept has been assessed in cohorts of hundreds of adults with rheumatoid arthritis, in whom the rate of severe adverse events was similar to that in patients receiving placebo[35] and lower than that in patients treated with MTX.[15,35] The first trial of etanercept in children with JIA involved 69 patients, only 2 of whom experienced severe adverse effects.[30] Moreover, the combination of etanercept and MTX was well tolerated in large series of adults[34,36] and in small series of children with chronic arthritis.[37,38]

In conclusion, we demonstrated the efficacy and safety of etanercept in patients with MTX-refractory polyarticular JIA in Japan. Interestingly, anti-TNF alpha therapy slows joint damage in adults with rheumatoid arthritis, even in the absence of clinical improvement.[35,39] Long-term studies should also be performed in patients with JIA in Japan, to monitor the effects of treatment on joint damage, growth, functional ability, and psychosocial outcome.

References

1. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991–4.
2. Petty RE, Malleson P. Epidemiology of juvenile rheumatoid arthritis. World Pediatr Child Care 1987;3:205–10.
3. Ansell BM. Prognosis in juvenile arthritis. Adv Exp Med Biol 1999;455:27–33.
4. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis: results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. N Engl J Med 1992;326:1043–9.
5. Reiff A, Shaham B, Wood BP, Bernstein BH, Stanley P, Szer IS. High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. Clin Exp Rheumatol 1995;13:113–8.
6. Graham LD, Myones BL, Rivas-Chacon RF, Pachman LM. Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediatr 1992;120:468–73.
7. Woo P, Southwood TR, Prieur AM, Dore CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849–57.
8. Wallace CA, Sherry DD. Preliminary report of higher dose methotrexate treatment in juvenile rheumatoid arthritis. J Rheumatol 1992;19:1604–7.
9. Reiff A, Shaham B, Wood BP, Bernstein BH, Stanley P, Szer IS. High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. Clin Exp Rheumatol 1995;13:113–8.
10. Wallace CA. The use of methotrexate in childhood rheumatic diseases. Arthritis Rheum 1998;41:381–91.
11. Mohler KM, Sleath PR, Fitzner JN, Cerretti DP, Alderson M, Kerwar SS, et al. Protection against a lethal dose of endotoxin by an inhibitor of tumour necrosis factor processing. Nature 1994;370:218–20.
12. Mohler KM, Torrance DS, Smith CA, Goodwin RG, Stremler KE, Fung VP, et al. Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. J Immunol 1993;151:1548–61.
13. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor(p75)-Fc fusion protein. N Engl J Med 1997;337:141–7.
14. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. Ann Intern Med 1999;130:478–86.
15. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.
16. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37:1761–9.
17. Pouchot J, Ruperto N, Lemelle I, Sommelet D, Grouteau E, David L, et al. The French version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol 2001;19 (4 Suppl 23):S60–5.
18. 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.
19. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763–9.
20. Giannini EH, Cassidy JT. Methotrexate in juvenile rheumatoid arthritis: do the benefits outweigh the risks? Drug Saf 1993;9:325–39.
21. van der Heijde DMFM, van 't Hof MA, van Riel PLCM, Theunisse LAM, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
22. Prevoo MLL, van 't Tof MA, Kuper HH, van Leeuwen MA, van de Putte LBA, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Arthritis Rheum 1995;38:44–8.
23. van Gestel AM, Prevoo MLL, van 't Tof MA,, van Rijswijk MH, van de Putte LBA, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996;39:34–40.
24. Dayer JM, Beutler B, Cerami A. Cachectin/tumor necrosis factor stimulates collagenase and prostaglandin E2 production by human synovial cells and dermal fibroblasts. J Exp Med 1985;162:2163–8.
25. Bertolini DR, Nedwin GE, Bringman TS, Smith DD, Mundy GR. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. Nature 1986;319:516–8.
26. Saklatvala J. Tumour necrosis factor a stimulates resorption and inhibits synthesis of proteoglycan in cartilage. Nature 1986; 322:547–9.
27. Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF-α antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet 1989;2:244–7.
28. Thornton SC, Por SB, Penny R, Richter M, Shelley L, Breit SN. Identification of the major fibroblast growth factors released spontaneously in inflammatory arthritis as platelet derived growth factor and tumour necrosis factor-alpha. Clin Exp Immunol 1991;86:79–86.
29. von Asmuth EJU, van der Linden CJ, Leeuwenberg JFM, Buurman WA. Involvement of the CD11b/CD18 integrin, but not of the endothelial cell adhesion molecules ELAM-1 and ICAM-1 in tumor necrosis factor-alpha-induced neutrophil toxicity. J Immunol 1991;147:3869–75.
30. Beckham JC, Caldwell DS, Peterson BL, Pippen AM, Currie MS, Keefe FJ, et al. Disease severity in rheumatoid arthritis: relationships of plasma tumor necrosis factor-α, soluble interleukin 2-receptor, soluble CD4/CD8 ratio, neopterin, and fibrin D-dimer to traditional severity and functional measures. J Clin Immunol 1992;12:353–61.
31. Grom AA, Murray KJ, Luyrink L, Emery H, Passo MH, Glass DN, et al. Pattern of expression of tumor necrosis factor α, tumor necrosis factor β, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondyloarthropathy. Arthritis Rheum 1996;39:1703–10.
32. Mangge H, Kenzian H, Gallistl S, Neuwirth G, Liebmann P, Kaulfersch W, et al. Serum cytokines in juvenile rheumatoid arthritis: correlation with conventional inflammation parameters and clinical subtypes. Arthritis Rheum 1995;38:211–20.
33. Eberhard BA, Laxer RM, Andersson U, Silverman ED. Local synthesis of both macrophage and T cell cytokines by synovial fluid cells from children with juvenile rheumatoid arthritis. Clin Exp Immunol 1994;96:260–6.
34. Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol 2001;28:1238–44.
35. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586–93.
36. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443–50.
37. Kietz DA, Pepmueller PH, Moore TL. Clinical response to etanercept in polyarticular course juvenile rheumatoid arthritis. J Rheumatol 2001;28:360–2.
38. Schmeling H, Mathony K, John V, Keysser G, Burdach S, Horneff G. A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study. Ann Rheum Dis 2001;60:410–2.
39. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594–602.