

Safety and Efficacy of High Dose Etanercept in Treatment of Juvenile Rheumatoid Arthritis

SYUJI TAKEI, DONNA GROH, BRAM BERNSTEIN, BRACHA SHAHAM, KERRY GALLAGHER, and ANDREAS REIFF

ABSTRACT. Objective. To evaluate safety and efficacy of high dose etanercept (> 0.8 mg/kg, maximum 25 mg subcutaneously twice weekly) (Enbrel®) in children with juvenile rheumatoid arthritis (JRA) and inadequate prior response to standard dose etanercept.

Methods. Retrospective chart review of 8 children (6 girls, 2 boys, mean age 8.4 yrs, range 5–16 yrs). Five children had systemic onset, polyarticular course JRA; 2 had polyarticular onset; and one had pauciarticular onset, polyarticular course JRA. All children had failed at least 3 mo (mean 9 mo) treatment with standard dose etanercept (0.4 mg/kg SC twice a week). All 8 children had increase in the etanercept dose to at least 0.8 mg/kg (mean 1.1 mg/kg, maximum 25 mg SC twice weekly) for a mean of 7 mo (range 3–10 mo). Efficacy of high dose etanercept was evaluated by changes in joint count, laboratory data, and ability to decrease concomitant medication.

Results. Improvements in the joint count and laboratory findings (erythrocyte sedimentation rate, hemoglobin and platelet count) were observed in 2 of 8 (25%) children. In these 2, concomitant prednisone was reduced or discontinued. In contrast, no changes in disease activity or laboratory findings were observed in the other 6 children. Overall, high dose etanercept was well tolerated. No laboratory abnormalities were detected and no child withdrew because of adverse events.

Conclusion. High dose etanercept is safe and well tolerated in children, but efficacy seems limited. In children with unsatisfactory response to standard dose etanercept, an increased dose or treatment prolongation may not offer any additional benefit. (J Rheumatol 2001;28:1677–80)

Key Indexing Terms:

ETANERCEPT

CHILDHOOD

TREATMENT

JUVENILE RHEUMATOID ARTHRITIS

TUMOR NECROSIS FACTOR- α

Tumor necrosis factor alpha (TNF- α), a proinflammatory cytokine, has been implicated in the pathogenesis of synovitis and joint destruction in rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA)^{1–7}. Elevated levels of TNF- α correlating with disease activity have been measured in serum and synovial fluid of children with JRA. Since the introduction of biologic response modifiers blocking TNF, it has been well established that inhibition of TNF- α has a significant effect on controlling inflammatory arthritis.

Etanercept, a recombinant human TNF- α receptor Fc fusion protein (Enbrel®, Immunex Co., Seattle, WA, USA), consists of 2 identical chains of the extracellular portion of

the recombinant human TNF receptor p75 monomer fused to an Fc domain of human IgG1. It competitively inhibits binding of TNF- α to its cell surface receptors, inactivating the biological action of TNF- α on the inflammatory process.

Clinical trials in adults and children with arthritis who had failed prior disease modifying antirheumatic drugs, such as methotrexate (MTX), showed that etanercept is safe, well tolerated, and able to significantly reduce disease activity in a dose dependent manner^{8–11}. In a recent study in 69 children with polyarticular course arthritis who did not tolerate or had an inadequate response to prior MTX, etanercept at a dose of 0.4 mg/kg (maximum 25 mg) was found to be safe and highly efficacious¹². However, 19 of the initially enrolled 69 children (28%) discontinued etanercept due to lack of efficacy. Thirteen children discontinued within the first 3 months of the trial, and 6 additional children discontinued the drug due to disease flare during the subsequent 4 months of trial¹².

Although an etanercept dose of 0.4 mg/kg per injection has been recommended as the pediatric equivalent of the adult 25 mg dose, it remains unclear if this dose provides sufficient TNF receptor blockade to control arthritis.

We examined the safety and efficacy of high dose etanercept (> 0.8 mg/kg per injection, biweekly) in 8 JRA

From the Division of Rheumatology, Department of Pediatrics, Keck School of Medicine, University of Southern California, Children's Hospital Los Angeles, Los Angeles, California, USA.

S. Takei, MD, Associate Professor of Pediatrics, Kagoshima University, Kagoshima, Japan; D. Groh, MS, Division of Physical and Occupational Therapy; B. Bernstein, MD, Professor of Pediatrics, Head, Division of Rheumatology; B. Shaham, MD, Assistant Professor of Pediatrics; K. Gallagher, MD, Assistant Professor of Pediatrics; A. Reiff MD, Assistant Professor of Pediatrics, Division of Rheumatology, Children's Hospital Los Angeles, Keck School of Medicine.

Address reprint requests to Dr. S. Takei, 8-35-1 Sakuragaoka, Kagoshima City, 890-0075 Japan. E-mail: syuji@m2.kufm.kagoshima-u.ac.jp

Submitted October 5, 2000; revision accepted January 23, 2001.

patients with inadequate response to prior standard dose etanercept (0.4 mg/kg per injection, biweekly).

MATERIALS AND METHODS

A retrospective chart review was conducted on 8 children with active, persistent arthritis and inadequate response to standard dose etanercept (0.4 mg/kg subcutaneously twice a week) for at least 3 mo (Table 1). In these patients etanercept had been increased to a maximum of 25 mg per injection and concomitant medications were continued.

Mean age at study entry was 8.4 years (range 5.1–16.3) and mean disease duration was 5.3 years (range 1.5–14.8). All children had active polyarticular JRA: 5 with systemic onset, 2 with polyarticular onset, and one with pauciarticular onset. At the time of review 3 of 8 children had Steinbrocker functional class of 2 and 5 of 8 children class 3¹³.

Prior to standard dose etanercept all 8 children had received varying doses of steroids up to 1.8 mg/kg/day of prednisone for a mean of 39 mo (7–63 mo) and MTX at 0.5–1.0 mg/kg/wk (mean 0.8 mg/kg/wk) for a mean of 22 mo (6–52 mo). In addition, cyclosporine A at a dose of 3.5–4.0 mg/kg/day (mean 4.3 mg/kg/day) had been used in 7 of 8 children for a mean of 17 mo (1–43 mo). Two patients were treated with intravenous cyclophosphamide (IV CyP). All had been treated with 0.4 mg/kg of etanercept (6–12.5 mg/injection) biweekly for a mean of 9 mo (3–25 mo). After the etanercept dose was increased to 25 mg twice a week, the 8 children received an equivalent of 0.8–1.8 mg/kg (mean 1.1 mg/kg) twice a week for at least 3 mo (range 3–10 mo).

Outcome variables recorded were active joint count (swelling and/or limitation of motion with pain on motion), laboratory tests [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, platelet count], and ability to reduce concomitant medications. Active joint was defined as the joints with swelling and/or limitation of motion with pain on motion, which was different from the American College of Rheumatology criteria.

Adverse events had been monitored by clinical assessment and monthly measurement of complete white blood cell count, transaminases, urea nitrogen, creatinine, electrolytes, serum total protein, and urinalysis. Antinuclear antibody titers and immunoglobulins had been examined at baseline and every 3 to 4 mo during the treatment period.

RESULTS

Efficacy of high dose etanercept. Clinical improvement was observed in 2 of 8 children taking high dose etanercept (Patients 1 and 2, Tables 2 and 3). Both had systemic onset disease. Patient 1, who had received regular dose etanercept as part of the JRA etanercept trial, had shown remarkable improvement during the first 3 mo of the study, but had flare during the placebo phase and had to be discontinued despite reintroduction of active drug for 3 mo. He was restarted on standard dose etanercept in combination with cyclophosphamide pulse therapy, with limited effect. After 3 mo etanercept was increased to 25 mg biweekly (1.1 mg/kg). At this time he had 30 joints with active inflammation. Within 5 mo his arthritis symptoms completely resolved and ESR and CRP normalized, from 95 to 15 mm/h ESR and from 8.6 mg/dl to negative CRP (Table 2). As a result prednisone was decreased from 15 to 5 mg/day and IV CyP pulses were discontinued (Table 3).

Patient 2, who had also been a participant in the initial JRA trial, had shown only partial improvement with standard dose etanercept. She eventually had flare and had to be discontinued from the study. At that time she had 27 joints with active inflammation and ESR 60 mm/h. Consequently, she was treated with IV CyP pulse and later oral CyP and IV steroid pulses. However, the disease remained uncontrolled until etanercept 25 mg biweekly (1.4 mg/kg) was reintroduced. Within 7 mo of high dose etanercept her arthritis had almost completely resolved and laboratory variables had normalized (Table 2). She was able to discontinue the prednisone, which she had been taking for more than 4 years

Table 1. Patient demographics.

Patient	Sex	Diagnosis*	Age at Study Entry, yrs	Disease Duration, yrs	Functional Class**	Treatment Prior to Etanercept				Duration of Etanercept		
						Prednisone, mo	MTX, mo	CsA, mo	Other	Standard Dose†, mo	High Dose, mo	mg/kg
1	M	Systemic polyarticular	7.7	4.3	3	20	13	8	IV CyP	4, 3	5	1.1
2	F	Systemic polyarticular	6.5	4.5	3	47	19	3	IV CyP, oral CyP	16	7	1.4
3	F	Systemic polyarticular	11.0	5	3	31	33	14	AZ, SASP	6	10	0.8
4	F	Systemic polyarticular	5.1	2.3	2	22	10	—		5	3	1.0
5	F	Systemic polyarticular	8.0	5.3	2	63	9	43	SASP	3	3	0.8
6	M	Polyarticular	6.1	1.5	2	7	6	1		6	10	1.1
7	F	Polyarticular	6.7	5.0	3	58	32	14	SASP	25	5	1.8
8	F	Pauciarticular polyarticular	16.3	14.8	3	60	52	39	AZ, gold, SASP	3	10	0.8

*Onset/disease course; **Steinbrocker classification, †0.4 mg/kg/injection.

MTX: methotrexate, CsA: cyclosporin A, AZ: azathioprine, SASP: sulfasalazine, CyP: cyclophosphamide, gold: gold sodium thiomalate.

Table 2. Changes in joint symptoms and laboratory data with regular and high dose etanercept.

Patient	Etanercept Dose	Joint Symptoms		Laboratory Tests							
		Active Joint Count		ESR, mm/h		CRP, mg/dl		Hemoglobin, g/dl		Platelets, 1000/ μ l	
		Start	End	Start	End	Start	End	Start	End	Start	End
1	Standard 1*	18	0	71	6	8.7	0	10.2	12.1	1065	385
	Standard 2*	34	30	68	95	6.5	8.6	9.3	9.1	817	797
	High	30	0	95	15	8.6	0	9.1	12.0	797	500
2	Standard	53	12	95	125	23.4	5.6	9.9	9.9	460	581
	High	27	2	60	10	ND	0	9.9	13.4	666	363
3	Standard	17	5	54	98	ND	16.0	11.1	10.0	398	535
	High	5	5	98	83	16.0	ND	10.0	9.9	535	479
4	Standard	3	5	40	30	ND	7.6	11.2	10.7	525	634
	High	5	23	30	60	7.6	20.4	10.7	9.6	634	888
5	Standard	4	28	39	48	ND	ND	10.7	12.6	433	268
	High	28	30	48	74	ND	ND	12.6	10.4	268	558
6	Standard	34	23	120	70	ND	ND	11.1	10.6	327	326
	High	23	21	70	77	ND	0	10.6	10.7	326	267
7	Standard	61	38	70	61	26.9	ND	8.9	9.2	681	490
	High	38	31	61	45	ND	ND	9.2	10.6	490	400
8	Standard	13	16	8	24	ND	1.5	15.0	13.1	320	403
	High	16	17	24	25	1.5	ND	13.1	13.8	403	307

*See text.

Active joint: joints with swelling and/or pain on motion. ND: not done.

Table 3. Changes in concomitant medications with regular and high dose etanercept.

Patient	Etanercept Dose	Weight, kg	Concomitant Medications					
			Prednisone, mg/day		MTX, mg/wk		Immunosuppressants, mg/day	
			Start	End	Start	End	Start	End
1	Standard 1*	22	0	0	0	0	None	None
	Standard 2*	24	15	15	25	25	IV CyP q3w	IV CyP q3w
	High	22	15	5	25	25	IV CyP q3w	IV CyP DC
2	Regular	16	8	10 + IVP	0	7.5	None	IV CyP q3w
	High	18	15	0	0	0	Oral CyP 37.5	Oral CyP 37.5
3	Standard	30	0	0	20	15	CsA 100	CsA 25
	High	30	0	0	15	15	CsA 25	CsA 0
4	Standard	26	15	7	0	0	None	None
	High	26	7	2	0	0	None	None
5	Standard	19	2	2	0	0	None	None
	High	20	2	10 + OP	0	0	None	None
6	Standard	23	7.5	0	5	5	None	None
	High	22	0	0	5	0	None	None
7	Standard	14	3	5	0	15	None	None
	High	14	5	10	15	15	None	CsA 100
8	Standard	30	10	10	17.5	0	None	None
	High	30	10	10	0	0	None	None

MTX: methotrexate, CsA: cyclosporin A, CyP: cyclophosphamide, IV: intravenous, q3w: every 3 weeks, DC: discontinued, IVP: intravenous pulse, OP: oral pulse (3 mg/day \times 5 days every 3 weeks). * See text.

(Table 3). She currently continues a decreased dose of oral CyP and etanercept.

The remaining 6 children failed to improve in clinical symptoms and laboratory variables despite high dose etanercept. Two (Patients 4 and 5) experienced flare while receiving high dose etanercept. Patient 4 had flare after 3 mo

of high dose etanercept during a further attempt to taper prednisone dose (when prednisone was decreased to 2 mg/day). Patient 5 gradually worsened in both joint symptoms and laboratory variables, so that etanercept was discontinued after 3 mo. The other 4 children showed no changes in clinical symptoms or laboratory findings.

Safety of high dose etanercept. High dose etanercept was safe and well tolerated by all 8 children. No patient withdrew from etanercept because of adverse events. One child reported a transient erythema at the injection site after the first injection. Three patients had transient mild upper respiratory tract infections: one with pharyngitis, 2 with rhinitis. No other adverse events were noted.

No laboratory abnormalities suggesting adverse events were observed during the study. There was no new development of antinuclear antibody in any of the children.

DISCUSSION

Etanercept has been established as a safe and highly efficacious agent in the treatment of refractory arthritis and related autoimmune disorders⁹⁻¹². However, it appears that about 30% of the patients fail to respond. In studies in adult patients with RA the failure rate to achieve the ACR 20 criteria varied from 25% to 38%, including a 34% failure rate of the etanercept/MTX combination⁹⁻¹¹. In the JRA trial with 0.4 mg/kg etanercept twice weekly, 19 of 69 children (28%) discontinued etanercept due to lack of efficacy¹².

It has been speculated that higher doses of etanercept might increase efficacy, and studies in adult RA patients are under way to examine this question. We evaluated the safety and efficacy of high dose etanercept in children with JRA whose prior response to standard dose etanercept was inadequate. Although the size of our sample was small, it appeared that additional efficacy from more than double the recommended dose for children was limited.

The majority of children in our study population had systemic onset JRA, which may explain the lack of response to etanercept. Besides TNF- α , other cytokines such as interleukin 6 (IL-6) contribute importantly to the pathogenesis of systemic JRA, and IL-6 may be more essential in this disease than in the other JRA subtypes¹⁴.

That some patients are unresponsive to anti-TNF treatment may be explained by a polymorphism in the TNF gene in certain subsets of JRA. Recent reports suggest that children with systemic onset JRA may have a linkage of certain alleles of the TNF- α gene to certain HLA types, such as DRB1*0405¹⁵. Children with this genetic background seem to have a particularly high level of TNF production, and quantitative TNF receptor blockade with the regular etanercept dose may be insufficient in these patients. Our observation in *Patient 1*, who had an inconsistent response to a regular dose of etanercept at 2 different time points, however, implies that the response to etanercept is not defined by genetic background or disease onset alone. Further studies investigating this issue will be necessary.

Of note, the 2 children with systemic onset JRA who responded to the higher dose etanercept had also received potent concomitant immunosuppressive therapy, cyclophosphamide. It is therefore possible that the apparent effectiveness of high dose etanercept in these 2 children was, in fact, solely due to the longer duration of CyP therapy.

A high dose of etanercept was safe and well tolerated in 8 children with JRA, but efficacy was limited. It appears that children with no response to standard dose etanercept within 3 months are unlikely to respond to higher doses or prolonged treatment. Children with an unsatisfactory response to standard dose etanercept may be more effectively treated with other agents, such as combination therapy with other disease modifying antirheumatic drugs, rather than higher doses of etanercept.

REFERENCES

1. Chu CQ, Field M, Maini RN. Localization of tumor necrosis factor α in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. *Arthritis Rheum* 1991;34:1125-32.
2. Saxne T, Palladino MA Jr, Heinegard D, Talal N, Wollheim FA. Detection of tumor necrosis factor α but not tumor necrosis factor β in rheumatoid arthritis synovial fluid and serum. *Arthritis Rheum* 1988;31:1041-5.
3. Singu M, Nagai Y, Isayama T, Naono T, Nobunaga M, Nagai Y. The effects of cytokines on metalloproteinase inhibitors (TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelial cells. *Clin Exp Immunol* 1993;94:145-9.
4. MacNaul KL, Chartrain N, Lark M, Tocci MJ, Hutchinson NI. Differential effects of IL-1 and TNF α on the expression of stromelysin, collagenase and the natural inhibitor, TIMP, in rheumatoid synovial fibroblasts. *Matrix* 1992; 1 Suppl:198-9.
5. Ahmadzadeh N, Shingu M, Nobunaga M. The effect of recombinant tumor necrosis factor- α on superoxide and metalloproteinase production by synovial cells and chondrocytes. *Clin Exp Rheumatol* 1990;8:387-91.
6. Moser RB, Schleiffenbaum B, Groscurth P, Fehr J. Interleukin 1 and tumor necrosis factor stimulate human vascular endothelial cells to promote transendothelial neutrophil passage. *J Clin Invest* 1989;83:444-55.
7. Mange H, Kenzian H, Gallistl S, et al. Serum cytokines in juvenile rheumatoid arthritis: correlation with conventional inflammation parameters and clinical subtypes. *Arthritis Rheum* 1995;38:211-20.
8. Moreland LW, Margolies G, Heck LW Jr, et al. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. *J Rheumatol* 1996;23:1849-55.
9. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *New Engl J Med* 1997;337:141-7.
10. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
11. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *New Engl J Med* 1999;340:253-9.
12. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *New Engl J Med* 2000;342:763-9.
13. Steinbrocker O, Traeger CH, Battersman RC. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1994;271:659-62.
14. Keul R, Heinrich PC, Muller-newen G, Muller K, Woo P. A possible role for soluble IL-6 receptor in the pathogenesis of systemic onset juvenile chronic arthritis. *Cytokine* 1998;10:729-34.
15. Date Y, Seki N, Kamizono S, et al. Identification of a genetic risk factor for systemic juvenile rheumatoid arthritis in the 5'-flanking region of the TNF- α gene and HLA genes. *Arthritis Rheum* 2000;42:2577-82.