Clinical Response to Etanercept in Polyarticular Course Juvenile Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate safety and clinical response to treatment with etanercept in the polyarticular course of patients with juvenile rheumatoid arthritis (JRA).

Methods. Ten patients were studied (8 female, 2 male; 6 polyarticular JRA, 4 systemic onset; mean age 13.3 yrs; mean duration of disease 6.6 yrs). Patients received 0.4 mg/kg etanercept subcutaneously twice weekly in addition to their existing therapeutic regimen. Observed duration of treatment ranged between 4 and 12 months.

Results. Patients tolerated treatment with etanercept well. No serious adverse events were noted. Treatment response showed considerable improvement of morning stiffness (mean reduction of 96 min ≅ –93%) and joint counts including swollen joints (Δ–8.2 ≅ –40%), tender joints (Δ–9.2 ≅ –88%), and total joints (Δ–9.8 ≅ –37%). Laboratory results included decreases in ESR (Δ–46 mm/h ≅ –53%) and improvement of anemia.

Conclusion. Our results confirm etanercept is a powerful adjunct in the therapy of polyarticular JRA resistant to conventional treatment regimens. (J Rheumatol 2001;28:360–2)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS JUVENILE CHRONIC ARTHRITIS
IDIOPATHIC ARTHRITIS OF CHILDHOOD TUMOR NECROSIS FACTOR ETANERCEPT

Our understanding of the immunopathogenesis of juvenile rheumatoid arthritis (JRA), the most common rheumatic disease of childhood, has grown significantly over the last decade[1,2]. Cytokines as mediators of cell growth, differentiation, immune and inflammatory responses operate in a complex interdependent network. Derangement of a carefully regulated balance between pro- and antiinflammatory mediators in a specific milieu, e.g., the synovial fluid, may be responsible for tissue damage[3-5]. Tumor necrosis factor (TNF) is one of the major inflammatory cytokines involved in the pathogenesis of JRA. TNF is increased in synovial fluid of patients with active JRA[6]. TNF stimulates synoviocyte proliferation and triggers release of other inflammatory mediators such as interleukin 1 (IL-1), IL-6, and IL-8[7]. TNF also induces the release of matrix metalloproteinases and induces expression of endothelial adhesion molecules. It also leads to upregulation of the transcription factor NF-kB and induces apoptosis[1,2].

TNF exerts its effect via 2 distinct cell surface TNF receptors, p55 and p75. Naturally present soluble versions of these receptors (sTNFr) in body fluids are involved in regulation of TNF activity[8]. Etanercept is a recombinant dimer consisting of two p75 sTNFr molecules fused to an Fc fragment of human IgG1. Etanercept is a biologic response modifier developed for specific neutralization of TNF. Treatment with etanercept has been shown to be safe and effective in management of rheumatoid arthritis (RA) in adults[9-12]. Lovell, *et al* evaluated safety and efficacy of etanercept in children with polyarticular JRA[13-15]. We report the results of treatment with etanercept (Enbrel) in 10 patients with JRA who have been treated in our center since the end of 1998.

MATERIALS AND METHODS

Ten patients (8 female, 2 male) were included into this prospective, open, observational study (Table 1). All patients fulfilled American College of Rheumatology (ACR) criteria for JRA. The mean age of our patients was 13.3 years (range 6–20), the mean age at disease onset was 6.6 years (1–16), and the mean duration of disease 6.6 years (1–13). Six patients had polyarticular onset and 4 systemic onset JRA with a polyarticular course. Four patients were rheumatoid factor positive, and 4 had radiographic evidence of erosive disease. At the time of starting therapy no patient with systemic onset disease had fever and/or rashes. All patients had previously been treated with 2 or more disease modifying antirheumatic drugs (DMARD). Seven had received systemic steroids in the past. At the time of starting etanercept, all patients were being treated with methotrexate (≥ 10 mg/m^2, oral administration) and a nonsteroidal antiinflammatory drug (NSAID) (complete antiinflammatory dosage, e.g., naproxen 15–20 mg/kg, tolmetin sodium 20–30 mg/kg, ibuprofen 30–40 mg/kg) and 8 patients were taking hydroxychloroquine (6–8 mg/kg). Three patients were taking systemic steroids (1.5 mg qd to 5 mg po bid ≅ 0.2 mg/kg/day).

The decision to start etanercept was based on recognition of an inadequate therapeutic response to conventional treatment. This was manifested by per-

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Table 1. Patients treated with etanercept.

Patient	1	2	3	4	5	6	7	8	9	10
Age, yrs	11	6	18	20	15	16	13	8	17	9
Sex	F	F	F	F	F	F	F	M	F	M
Onset	Syst	Syst	Poly	Poly	Poly	Poly	Syst	Syst	Poly	Poly
Age at onset, yrs	2	1	5	16	5	15	4	3	9	6
Duration, yrs	9	5	13	4	10	1	9	5	8	2
ANA	–	–	–	+	+	+	–	–	+	–
RF	–	+	–	+	–	+	–	–	+	–
Erosions	–	+	+	–	–	–	+	–	–	+
Current med	M	M	M,H	M,H,P	M,H	M,H	M,H,P	M,P	M,H	M,H
Previous steroids	+	+	–	+	–	–	+	+	+	+

M: methotrexate (≅ or > 10 mg/m^2 po), H: hydroxychloroquine (6–8 mg/kg po), P: prednisone (Patient 4: 5 mg po bid, Patient 7: 2 mg po bid, Patient 8: 1.5 mg po qd). Syst: systemic onset JRA, poly: polyarticular onset JRA.

sistence of marked active synovitis as well as constitutional symptoms of a chronic inflammatory illness.

A complete baseline physical and joint examination and laboratory and radiologic evaluation were performed prior to treatment. Etanercept was added to the therapeutic regimen in a dosage of 0.4 mg/kg subcutaneously twice weekly. The medication was generally administered by the patients' parents, who had been instructed in injection technique. Etanercept was withheld in the occurrence of an acute infection. The patients were seen at least monthly for followup evaluation. Joint examination was performed by the same examiners throughout the observation period. Laboratory studies were performed regularly as needed for monitoring of drug toxicity and disease activity including complete blood cell count, erythrocyte sedimentation rate (ESR), urinalysis, creatinine, and liver function tests.

RESULTS

Clinical and laboratory data reflecting treatment results are depicted in Table 2.

Treatment duration with etanercept in the 10 patients in the observational study ranged from 4 to 12 months (average 10.4 mo). All patients tolerated etanercept well without significant side effects. Mild injection site reactions did not require treatment cessation. All patients showed impressive therapeutic responses with markedly decreased joint tenderness and swelling. Clinical improvement was recognizable within 2 weeks in most patients. On average the swollen joint score decreased by 8.2 (18.8 to 10.6), equivalent to a mean percentage decrease of 40%, the tender joint score by 9.2 (9.6 to 0.4), equivalent to mean percentage decrease of 88%, and the total joint score by 9.8 (20.6 to 10.8), equivalent to mean percentage decrease of 37%. Most patients had only minimal remaining morning stiffness (decreased from several hours to generally < 10 min) and considerably decreased fatigue. Patients showed a remarkable increase in their daily activity level and perceived a strong improvement in their sense of general well being. Our estimation of changes in constitutional symptomatology was based on the patients' and their families' narrative description and our personal impression at the time of clinic visits.

Two patients have gone into clinical remission taking medication (as defined by absence of clinical or laboratory evidence of inflammatory activity, absence of active synovitis and morning stiffness, and normalization of laboratory markers, e.g., ESR).

Treatment success has been reflected concurrently in laboratory data showing significant decreases in ESR (mean

Table 2. Clinical and laboratory data at baseline and at time of treatment.

	Mean	Range	SD
Swollen joints			
Baseline	18.8	8–35	7.1
Followup	10.6	6–16	4.1
Δ	8.2	–1–20	–8.1
Δ in %	–40		
Tender joints			
Baseline	9.6	2–25	9.4
Followup	0.4	1–2	1.5
Δ	–9.2	–1–23	–9
Δ in %	–88		
Total active joints			
Baseline	20.6	10–33	8.1
Followup	10.8	6–16	4.5
Δ	–9.8	–0–27	–8.7
Δ in %	–37		
Morning stiffness, min			
Baseline	103	10–180	50.7
Followup	5.5	0–20	7.9
Δ	–95.5	10–170	52
ESR, mm/h			
Baseline	76	45–140	41
Followup	30	5–90	28
Δ	–46	–3–92	–38
Δ in %	–53		
Hgb, gm/dl			
Baseline	9.7	7.7–11.4	1.4
Followup	11.0	8.0–12.7	2.0
Δ	+1.3	–0.4–+4.3	1.3
Δ in %	15		
Hct, %			
Baseline	29.6	25.7–33	3.5
Followup	32.6	26–37	4.1
Δ	3.0	–0.4–+8	4.1
Δ in %	+10.5		

decrease 46 mm/h, 76 to 30 mm/h, mean percentage decrease 53%) and improvement of anemia (mean Hb increased by 1.3 g/dl from 9.7 to 11.0 g/dl, mean percentage increment 15%, and increase of mean hematocrit by 3.0% from 29.6 to 32.6, mean percentage increase of 10.5%).

Some examples may illustrate the treatment's effect observed in children and adolescents with JRA. A 17-year-old who was missing school 2 to 3 days per week and unable to participate in physical education is now again able to do cartwheels. She also has not missed school for over 6 months and is making plans for college. A 16-year-old has overcome her reactive depression and has regained a positive outlook into her future. An 8-year-old is proud of not requiring the wheelchair and derives special pleasure from demonstrating his ability to jump. Another 8-year-old has regained more self-confidence, happily recognizing his improved endurance throughout the day.

In the 3 patients taking low doses of systemic corticosteroids at the beginning of treatment with etanercept, prednisone was gradually decreased over a few months and entirely discontinued in 2 patients. The third patient takes only 2 mg of prednisone. In several patients the methotrexate dosage could be lowered over time with no loss of clinical effect.

DISCUSSION

The severity of clinical manifestations of the polyarticular course of JRA in regard to both joint symptomatology and constitutional features varies significantly. JRA is a chronic systemic inflammatory condition with moderate to severe joint manifestations. It may be extremely disruptive especially to a young person's life, with negative experience of impaired functional mobility and chronic fatigue. However, many patients are well controlled with the conventional treatment regimen including NSAID, and one or 2 DMARD.

Our observational study describes 10 pediatric/adolescent patients followed in our clinic for polyarticular JRA whose disease was active as indicated by prolonged morning stiffness, joint pain and swelling, fatigue, and active synovitis on examination despite appropriate dosages of NSAID and DMARD. Lovell, *et al*[13-15] reported data on safety and efficacy of etanercept in polyarticular course JRA. Our results overall confirm their findings. The addition of etanercept resulted in impressive therapeutic effects in all patients. Striking improvement was noted in the management of synovitis. Beyond the effect on joint symptoms, we were impressed by the overall subjective benefits our patients derived from treatment with etanercept in regard to their quality of life and reduction of fatigue. The design of our observational study differed from their treatment concept, as we added etanercept to preexisting therapy with methotrexate.

In summary, etanercept has proven a very powerful adjunct in the therapy of JRA resistant to conventional treatment regimens of NSAID, corticosteroids, and DMARD.

Treatment with etanercept has been convincingly successful in regard to both the symptomatology of active synovitis (joint pain and swelling and morning stiffness) and constitutional features (fatigue, malaise, and depression). It has enabled our pediatric patients to enjoy a significantly improved quality of life resulting from fewer joint symptoms and increased mobility and energy level. Our patients and their families have been extremely enthusiastic and appreciative of etanercept. Our treatment results confirm TNF's important role in the pathogenesis of polyarticular JRA, and illustrate the new therapeutic dimension introduced by the availability of specific biologic response modifiers.

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