

Treatment with etanercept for patients with juvenile rheumatoid arthritis in Taiwan — a preliminary report

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Tumor necrosis factor (TNF) is a major inflammatory cytokine involved in the pathogenesis of juvenile rheumatoid arthritis (JRA). Etanercept, approved in the United States and in Europe for use in patients with rheumatoid arthritis (RA) and JRA, is an effective inhibitor of TNF that has been shown to provide rapid and sustained improvement in both diseases. Here we report the preliminary results of etanercept use in 3 cases of JRA with poor response to traditional therapy including non-steroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs. Two of the patients had polyarticular JRA and 1 had systemic JRA. Etanercept was administered at a dosage of 0.4 mg/kg (maximum 25 mg) subcutaneously twice a week. Clinical as well as inflammatory parameter improvement was noted after use of etanercept in all cases. The preliminary results of etanercept use in these 3 cases showed significant clinical benefit without obvious adverse effects.

Key words: Etanercept, juvenile rheumatoid arthritis, tumor necrosis factor-alpha

Juvenile rheumatoid arthritis (JRA) is a common chronic disease in childhood, and represents a major cause of functional disability in children [1]. JRA, by definition, develops in children before 16 years of age and involves arthritis changes in 1 or more joints [2]. Its incidence has been reported to range between 6 and 20 cases per 100,000 per year. Overall, girls are affected more often than boys [3]. Traditional therapy is not always effective and has known toxic side effects. 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 JRA [4-6]. 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 the inhibition of TNF- α has a significant effect in controlling inflammatory arthritis [7,8].

Here the preliminary results of etanercept use in 3 patients who were diagnosed as having JRA with poor response to traditional therapy in our hospital are reported.

Case Report

Case 1

An 8-year-old boy was diagnosed as having systemic JRA after with initial presentation of prolonged fever, skin rashes, and splenomegaly at age 2 years. Since then, his arthritic symptoms persisted in spite of medical treatment. Therefore, he started etanercept at a dose of 0.5 mg/kg/dose twice a week subcutaneously. Before the use of etanercept, he was treated with prednisolone 0.3 mg/kg/day, meloxicam 0.2 mg/kg/day, and cyclosporine A 4.7 mg/kg/day. But he still suffered from swelling of bilateral knees and ankles and the joint pain interfered with his normal daily activity. The patient reported improvement with regard to his arthritic symptoms with decreased joint tenderness and swelling within 2 weeks. Thus, he discontinued etanercept 2 months later. No more local swelling or local tenderness was found at that time and he could carry out normal daily activities. He then received the following medications: prednisolone 0.6 mg/kg/day, meloxicam 0.4 mg/kg/day, and azathioprine 1.6 mg/kg/day. The laboratory findings also showed much improvement. TNF- α dropped from 132 pg/mL to 107 pg/mL, and interleukin (IL)-6 dropped from 2.4 pg/mL to 1.7 pg/mL in the 2 months after etanercept use. Inflammatory parameters C-reactive protein (CRP), erythrocyte sedimentation rate

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Table 1. Laboratory data from 3 cases of juvenile rheumatoid arthritis treated with etanercept

Sample ^a	Case 1			Case 2			Case 3		
	1	2	3	1	2	3	1	2	3
CRP (mg/dL)	8.2	<0.1	0.82	12	0.17	0.32	12.2	4.1	4.34
ESR(1) [mm/h]	31	15	15	>100	29	29	88	63	44
ESR(2) [mm/h]	62	36	103	>120	59	59	118	104	44
C3 (mg/dL)	125	93.5	102	190	93.5	107	175	135	121
C4 (mg/dL)	28	21.9	28.4	44.5	21.9	23.2	29	20.5	22.1
WBC (/mm ³)	10,390	7760	10,019	8030	5350	8690	11,730	11,770	9070
Hb (g/dL)	13.1	13.3	13.9	9	10.4	10.7	11.5	10.1	10.7
Platelet (× 1000/mm ³)	282 K	2585 K	296 K	536 K	311 K	311 K	493 K	610 K	577 K
TNF- α (pg/mL)	132	107		67.8	54.8		86.7	51.4	
IL-6 (pg/mL)	2.4	1.7		15.7	3.3		19.7	2	

Abbreviations: CRP = C-reactive protein; ESR(1) = first hour erythrocyte sedimentation rate; ESR(2) = second hour erythrocyte sedimentation rate; C3 = complement factor 3; C4 = complement factor 4; WBC = white blood cell count; Hb = hemoglobin; TNF- α = tumor necrosis factor-alpha; IL-6 = interleukin-6

^aSample number represents blood sample obtained at indicated times as follows: 1 = before therapy in all 3 cases; 2 = 2 months after initiation of therapy in case 1 and case 2, and 1 month after initiation of therapy in case 3; 3 = 6 months after initiation of therapy in case 1 and case 2, and 4 months after initiation of therapy in case 3.

(ESR), and levels of complement factors C3 and C4 decreased. Changes in laboratory findings are summarized in Table 1. Adverse events were monitored by clinical assessment and measurement of complete white blood cell count, transaminases, urea nitrogen, creatinine, electrolytes, and urinalysis. Antinuclear antibody titers were examined at baseline and every 4 months during the treatment period. No laboratory abnormalities suggesting adverse events were observed during treatment with etanercept. There was no infective episode during the treatment course.

Case 2

A 10-year-old girl was diagnosed with polyarticular JRA with intermittent involvement of the bilateral hips, knees, and ankles at age 5. She had received 6 courses of cyclophosphamide pulse therapy and methylprednisolone pulse therapy from 1991 to 1992 for the control of symptoms. Before the use of etanercept, she was treated with prednisolone 0.3 mg/kg/day, naproxen 18 mg/kg/day, cyclosporine A 4.8 mg/kg/day, azathioprine 1.2 mg/kg/day, and methotrexate 0.36 mg/kg/day. However, swelling and local tenderness of bilateral knees and ankles were noted in spite of medication control. She began to receive etanercept with a dose of 0.4 mg/kg/day twice a week subcutaneously on August 21, 2003. The patient reported improvement with regard to arthritic symptoms including tenderness and swelling within 1 month after the beginning of etanercept treatment. Subjectively, she felt nearly complete resolution of all arthritic symptoms within

2 months. She continued on medication of azathioprine 2.4 mg/kg/day and celecoxib 9.5 mg/kg/day, in addition to etanercept. The laboratory findings also showed much improvement after use of etanercept. TNF- α dropped from 67.8 pg/mL to 54.8 pg/mL, and IL-6 dropped from 15.7 pg/mL to 3.3 pg/mL in the 2 months after etanercept cessation. Inflammatory parameters such as CRP, ESR, and complement factors C3 and C4 decreased. Other laboratory findings are summarized in Table 1. No laboratory abnormalities suggesting adverse events were observed during treatment with etanercept. There was no infective episode during the treatment course.

Case 3

A 7-year-old boy was diagnosed as having systemic JRA with presentations of prolonged fever, skin rashes, and arthritis of the bilateral knees, ankles, and proximal and distal intercarphalangeal joints for the previous 2 years. Since the appearance of systemic symptoms, the arthritic symptoms persisted in spite of regular medication. Therefore, therapeutic trial with etanercept at a dose of 0.4 mg/kg/day subcutaneously twice a week was started on October 22, 2003. Prior to the use of etanercept, swelling and local tenderness over 20 joints including bilateral wrists, knees, and proximal and distal intercarphalangeal joints were noted and interfered with daily activity. He was treated with medications of prednisolone 1 mg/kg/day, naproxen 18 mg/kg/day, azathioprine 1.2 mg/kg/day, and sulfasalazine 47.6 mg/kg/day at that time. After use of etanercept, he felt much improvement in his arthritis

symptoms such as tenderness and swelling and numbers of involved joints within 1 month and could carry normal daily activity. The patient continued to receive prednisolone 0.5 mg/kg/day, and sulfasalazine 47.6 mg/kg/day, in addition to etanercept. Laboratory findings also showed much improvement after use of etanercept. TNF- α dropped from 86.7 pg/mL to 51.4 pg/mL, and IL-6 dropped from 19.7 pg/mL to 2 pg/mL in the month after etanercept cessation. Inflammatory parameters such as CRP, ESR, and complement factors C3 and C4 decreased. Other laboratory findings are summarized in Table 1. No laboratory abnormalities suggesting adverse events were observed during treatment with etanercept. There was no infective episode during the treatment course.

Discussion

JRA is a group of inflammatory autoimmune conditions specific to children. Three subgroups including oligoarthritis (pauciarticular disease), polyarthritis and systemic-onset disease are recognized according to the number of joints involved during the first 6 months of the disease and the presence of systemic features such as rashes, serositis and fever. The course of JRA is characterized by changes in the degree of inflammation [9]. There is no universally accepted definition of disease flare in JRA, although such disease flares have prompted clinicians to intensify the development of therapies [10].

Etanercept is a biologic response modifier that binds the cytokines TNF and lymphotoxin- α , thus blocking their interaction with cell-surface TNF receptors. Etanercept is a genetically engineered fusion protein consisting of 2 p75 soluble TNF receptor molecules fused to the Fc fragment of human immunoglobulin G1, expressed in mammalian cells. As a dimeric soluble receptor, it binds to 2 sites on the TNF molecule; this action provides greater inhibition of TNF than monomeric soluble receptors [11].

The direct mechanism of action of etanercept is inhibition of TNF binding to cell-surface TNF receptors, preventing TNF-mediated cellular response and rendering TNF biologically inactive [12].

Etanercept 25 mg subcutaneously twice weekly is effective and generally well tolerated in the treatment of adults with RA [13]. Etanercept received Federal Drug Administration approval in May 1999 for reducing signs and symptoms of moderate to severe active polyarticular JRA in patients who have had an inadequate response to 1 or more disease-modifying antirheumatic

drugs. The recommended dose of etanercept for children aged 4 to 17 years with polyarticular JRA is 0.4 mg/kg (up to a maximum of 25 mg per dose) administered twice weekly, 72 to 96 h apart, as a subcutaneous injection [14].

Since there have been few case reports of etanercept use in JRA in Taiwan, we hereby present our preliminary experiences. These 3 cases were classified into polyarticular and systemic JRA. All of the cases were difficult to control with traditional medications but responded to etanercept with significant improvement in both subjective symptoms and laboratory findings. In both case 2 and case 3, the arthritic symptoms could be well controlled with decreased dose of traditional medications and etanercept. There was no new development of antinuclear antibody in any of the children. Development of antinuclear antibodies has been described in patients treated with infliximab [15, 16], but the clinical significance of antibody formation remains to be determined and the relationship with autoimmunity has not been investigated. The results of treatment with etanercept in these patients show significant clinical benefit and generally good tolerability.

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