

Etanercept therapy in children with juvenile rheumatoid arthritis

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Etanercept is an effective inhibitor of tumor necrosis factor that has shown a beneficial effect in patients with juvenile rheumatoid arthritis (JRA) that did not respond to other disease-modifying drugs. Here we report 3 patients with JRA who were refractory to traditional therapy; 1 with systemic JRA and 2 with polyarticular JRA. They received etanercept 0.4 mg/kg (maximum 25 mg) subcutaneously, twice a week for 3 months. The symptoms of arthritis improved significantly except that the patient with systemic JRA had disease flare-up during etanercept therapy. Two patients had upper respiratory tract infection during etanercept therapy and 1 suffered from seizure attack. The 2 patients with polyarticular JRA had disease flare-up within 2 months after etanercept was discontinued. This is the first report of etanercept treatment in JRA patients in Taiwan.

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

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in children [1,2]. The proinflammatory cytokine tumor necrosis factor (TNF) has been shown to play a central regulatory role in the pathophysiology of JRA and it is elevated in both the serum and synovial fluid [3,4]. The traditional therapy for JRA is non-steroidal anti-inflammatory drugs, corticosteroid, and disease-modifying antirheumatic drugs [5,6].

However, some children do not respond satisfactorily to this treatment. Etanercept, a dimeric fusion protein consisting of the extracellular portion of the human p75 TNF receptor linked to the Fc portion of human immunoglobulin G1, effectively binds TNF and lymphotoxin- α and inhibits their activity [7,8]. It has a beneficial effect in patients with JRA that have not responded to other disease-modifying drugs [9-11]. We report 3 patients with JRA who were refractory to traditional therapy and received 0.4 mg of etanercept per kilogram (maximum, 25 mg) subcutaneously, twice weekly for 3 months. Complete blood cell counts and C-reactive protein (CRP) were checked at 2-week intervals during the period of etanercept therapy.

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Case Report

Case 1

A 12-year-old girl was diagnosed as having polyarticular JRA at age 6 years. She received prednisolone, naproxen and methotrexate (MTX) and had been complaining of bilateral wrist and elbow arthralgia, swelling and morning stiffness for the previous 1 year. Therefore, etanercept was administered twice a week. Laboratory data before the use of etanercept were as follows: white blood cell (WBC) count of 8300/mm³, hemoglobin of 12.9 g/dL, platelet count of 344,000/mm³, and CRP of 17.3 mg/dL. The symptoms of arthritis improved 2 weeks after use of etanercept and the level of CRP declined (Fig. 1). There were no side effects or infection episodes noted. The patient discontinued etanercept 3 months later. However, the patient once again complained of bilateral elbow swelling and arthralgia and raised CRP level was noted 1 month after etanercept was discontinued.

Case 2

This 11-year-old boy had a diagnosis of systemic JRA at age 2 years. The symptoms of arthritis persisted in spite of oral prednisolone, naproxen, cyclosporine and MTX. Cyclophosphamide plus methylprednisolone pulse therapy was administered monthly for 6 courses since January 2003. However, the symptoms flared

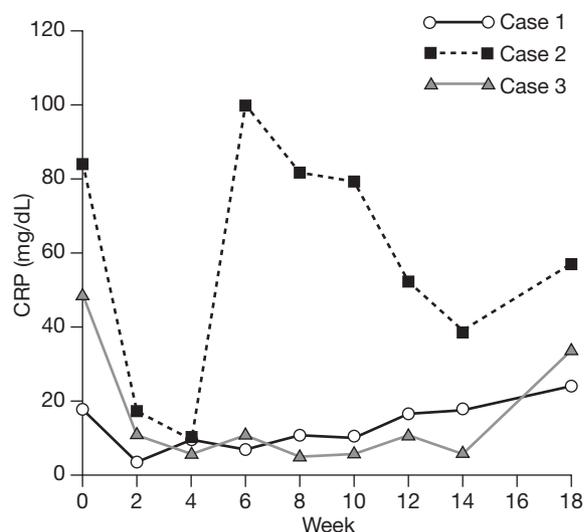


Fig. 1. C-reactive protein (CRP) levels during etanercept therapy in the 3 patients; etanercept was discontinued from week 14.

intermittently and persistently raised CRP was noted. Therefore, he was enrolled for etanercept therapy. He had been complaining of left wrist, hip, right knee arthralgia before use of etanercept and the laboratory findings were as follows: WBC count of 11,100/mm³, hemoglobin of 9.5 ng/dL, platelet count of 718,000/mm³, and CRP of 83.6 mg/dL. The symptoms of arthritis improved in the second week after etanercept was administered and the level of CRP declined (Fig. 1). He complained of fever, cough and rhinorrhea 5 weeks after etanercept therapy, and these symptoms resolved a few days later. However, intermittent fever and arthralgia flared again after use of etanercept for 8 weeks and raised CRP level was noted. The dosage of prednisolone was increased for symptom control, but the response was limited. Etanercept was discontinued after 3 months. However, sudden onset of generalized seizure episode was noted 4 days after etanercept was discontinued. He denied seizure disorder history and brain computed tomography and cerebrospinal fluid (CSF) examination provided negative findings. Electroencephalogram showed diffuse cortical dysfunction over bilateral hemisphere and no epileptiform discharge. No evidence of central nervous system infection was found and no neurologic sequelae was noted thereafter.

Case 3

An 8-year-old girl was diagnosed as having polyarticular JRA at age 5 years. She received oral prednisolone, naproxen and MTX, but the response was poor. Bilateral knees and left elbow arthritis were noted before use of

etanercept and laboratory data were as follows: WBC count of 9500/mm³, hemoglobin of 10.2 g/dL, platelet count of 560,000/mm³, CRP of 48.3 mg/dL. The joint swelling and pain improved in the second week of etanercept therapy and the level of CRP declined (Fig. 1). She suffered from fever, cough and running nose 4 weeks after starting etanercept. Upper respiratory tract infection was impressed and symptoms were resolved 5 days later. Etanercept was discontinued after use for 3 months. She complained of bilateral wrist arthralgia and swelling 2 months after etanercept was discontinued and the CRP level was raised again. The dosage of prednisolone was increased to control the symptoms of arthritis.

Discussion

According to previous reports, etanercept leads to significant improvement in patients with JRA who are refractory to traditional therapy [9-12]. However, Quartier et al reported that the response rate was significantly lower in patients with systemic-onset JRA than in those with oligoarticular- or polyarticular-onset JRA [13]. Etanercept demonstrated benefit soon after initiation of treatment in patients with refractory systemic JRA, but flares and progressive loss of effectiveness were observed with continued treatment in most patients [12]. In our experience, the response was limited in the patient with systemic JRA because the disease flared during etanercept therapy. In the other 2 patients, with polyarticular JRA, the response to etanercept was satisfactory. However, both of them had disease flare within 2 months after etanercept had been discontinued. In a multicenter study, 81% of patients with polyarticular JRA had disease flare after the initial 3-month etanercept treatment had been discontinued and the median time of flare was 28 days [9]. The high relapse rate after etanercept is discontinued suggests that the agent should be considered for long-term use. However, the cost of the agent has led to concerns about the economic burden and insurance coverage issues. Another concern is the long-term efficacy and safety of etanercept in children. Two previous studies found that etanercept continued to be clinically effective and well tolerated in patients with polyarticular JRA over a 2-year period [10,11]. There were no increases in the rates of adverse events over time [11].

The most concerning adverse event of etanercept therapy was infection. The most commonly reported infections were upper respiratory tract infection, skin

infection, flu syndrome and otitis [11]. No major infection was noted among our patients and only 2 of them had upper respiratory tract infection during the study period. The role of TNF-alpha in the immune response is very complex and it is not clear whether TNF-alpha inhibitors influence immune function. Previous reports suggested that the majority patients were able to tolerate etanercept for longer than 6 months and had no obvious trends in susceptibility to serious infection [14]. Another study performed several measures of immune function in patients receiving etanercept treatment, including T cell proliferative response, delayed-type hypersensitivity, neutrophil function, and serum immunoglobulin levels. They failed to demonstrate gross immunologic impairment in these patients [15].

One of our patients suffered generalized seizure attack after 3 months of etanercept therapy. Central nervous infection was not favored due to negative CSF findings and the cause of the seizure was uncertain. No previous report mentioned the adverse effect of seizure disorder, and 1 study reported neurologic disorder including retrobulbar optic neuropathy, headache and marked dysesthesia in patients receiving etanercept [14]. Psychiatric disorder including depression and personality disorder was reported in 2 studies [9,14]. Whether the seizure episode was related to etanercept therapy is uncertain and further study is necessary.

The preliminary results of etanercept use in the patients discussed showed a beneficial effect soon after initiation of treatment but disease flare was noted with continued treatment or after treatment was discontinued. No major adverse effects or infection was noted after etanercept therapy.

References

- Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Juvenile rheumatoid arthritis in Rochester, Minnesota 1960-1993. Is the epidemiology changing? *Arthritis Rheum* 1996; 39:1385-90.
- Wu CJ, Huang JL, Yang MH, Yan DC, Ou LS, Ho HH. Clinical characteristics of juvenile rheumatoid arthritis in Taiwan. *J Microbiol Immunol Infect* 2001;34:211-4.
- Grom AA, Murray KJ, Luyrink L, Emery H, Passo MH, Glass DN, et al. Patterns of expression of tumor necrosis factor alpha, tumor necrosis factor beta, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. *Arthritis Rheum* 1996;39:1703-10.
- Ou LS, See LC, Wu CJ, Kao CC, Lin YL, Huang JL. Association between serum inflammatory cytokines and disease activity in juvenile idiopathic arthritis. *Clin Rheumatol* 2002;21:52-6.
- Huang JL. Methotrexate in the treatment of children with chronic arthritis--long-term observations of efficacy and safety. *Br J Clin Prac* 1996;50:311-4.
- Huang JL, Chen LC. Sulphasalazine in treatment of children with chronic arthritis. *Clin Rheumatol* 1998;17:359-63.
- 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 tumor necrosis factor processing. *Nature* 1994; 370:218-20.
- 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.
- 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.
- Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two years period. *Ann Rheum Dis* 2002;61: 171-3.
- Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, et al; Pediatric Rheumatology Collaborative Study Group. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003;48:218-26.
- Russo RA, Katsicas MM, Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002;20: 723-6.
- Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis Rheum* 2003;48:1093-101.
- Phillips K, Husni ME, Karlson EW, Coblyn JS. Experience with etanercept in an academic medical center: are infection rates increased? *Arthritis Rheum* 2002;47:17-21.
- Moreland LW, Bucy RP, Weinblatt ME, Mohler KM, Spencer-Green GT, Chatham WW. Immune function in patients with rheumatoid arthritis treated with etanercept. *Clin Immunol* 2002;103:13-21.