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Taiwan experience with etanercept in juvenile rheumatoid arthritis

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A surge in demand in the field of therapy for chronic destructive arthritis has stimulated the development of new, more effective and less toxic antirheumatic drugs, such as cyclosporine and leflunomide. Although these agents produce significant improvement in disease control, their effects in prevention of joint destruction remain unsatisfactory. Under such circumstances, the emergence of so-called biologic agents offers hope for conventional drug-refractory destructive arthritis as well as for many other autoimmune disorders. Aside from significantly increased therapeutic efficacy, these biologic agents such as tumor necrosis factor (TNF) blockers, interleukin (IL)-1 receptor antagonist and the synthetic immunomodulatory agent CTLA4-Ig (soluble synthetic CTLA4 fusion protein) have much improved side effects profiles compared with conventional antirheumatic drugs like corticosteroids, cyclophosphamide and cyclosporine. These biologic agents are becoming more and more important as a means of stopping the destructive process of autoimmune joint disorders.

Why TNF-alpha?

Since the detection of the presence of a "factor" that potentially causes tumor necrosis (so called TNF) in 1975 [1] and the cloning of this factor in 1985 [2,3], there has been a "silent period" for the study of this molecule in scientific research. Part of the reason for this is concern about the probable "redundancy" in cytokine family molecules that may share not only biologic functions but also sequences and structures among individual members [4]. Indeed, the similarities in many different aspects between TNF-alpha (TNF-α) and lymphotoxin (also known as TNF-beta [TNF-β]) or between TNF-α and IL-1 are evident. However, subsequent studies in both cellular and molecular analysis have disclosed many potential differences in these cytokines [5,6]. A further interesting observation that has attracted researchers' attention to this molecule is the finding that there seem to be cytokine cascades present in nearly all of the inflammatory responses. Accordingly, investigations looking for "the first" or "the most upstream" cytokine responsible for sequential cytokine-mediated inflammatory events become critical. The experiments conducted with rheumatoid synovial membrane cells demonstrate that blocking TNF-α but not IL-1 greatly reduces the production of a variety of cytokines, including IL-1, IL-6, IL-8 and granulocyte-monocyte colony-stimulating factor, critical cytokines in inflammatory responses [7]. Many other studies also indicate that in order to effectively "stop" cytokine-mediated tissue damage, TNF-α may be the primary cytokine target.

Like many other cytokines, TNF-α levels are appreciably increased in serum and synovial fluid of rheumatoid arthritis (RA) and in many other autoimmune and inflammatory diseases. Meanwhile, TNF-α also contributes significantly to the pathogenesis of inflammatory disorders. The mechanisms for pathogenic roles of TNF-α include at least: 1) the induction of matrix metalloprotease release from chondrocytes and immune effector cells; 2) the induction of the expression of endothelial adhesion molecules that may facilitate the migration of inflammatory cells to cause tissue damage; and 3) the evocation of vicious cytokine cascades in immune-mediated diseases.

Therapeutic Benefit of Blocking TNF-α

The significance of TNF-α in immune-mediated diseases was examined in animals and in human beings. Studies in several collagen-induced arthritis models reveal promising therapeutic effects by blocking TNF-mediated

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events via either monoclonal anti-TNF antibody or anti-TNF fusion protein [8-10]. The therapeutic success of TNF blockade in animal studies is also confirmed in patients with RA [11-13]. Currently, anti-TNF therapy has been extensively prescribed for RA experiencing refractory response to conventional disease-modifying antirheumatic drug (DMARD) treatment [14]. There are three agents currently available as specific TNF blockers, including etanercept, infliximab, and adalimumab. The only TNF antagonist available in Taiwan, etanercept, is a soluble fusion protein comprising the extracellular domain of TNF receptor (p75) and Fc portion of human immunoglobulin G1, and is the drug of choice for DMARD-refractory RA. This fusion protein binds both TNF-α and TNF-β, and prevents their interaction with respective receptors on cell surface. Aside from RA, all 3 agents are effective in other inflammatory diseases, including psoriasis, psoriatic arthritis and ankylosing spondylitis. Moreover, the therapeutic efficacy of TNF blockade has been demonstrated in patients with juvenile RA (JRA) [15-18], although some data are less supportive [19]. Although blocking TNF effect is the primary therapeutic consideration for different anti-TNF agents, their clinical efficacies in various TNF-associated diseases such as Crohn's disease, sarcoidosis and Wegener's granulomatosis appear to differ [20].

Experience of Etanercept in JRA in Taiwan

In this issue of the *Journal of Microbiology, Immunology and Infection*, there are 2 independent studies conducted by 2 different medical centers examining the therapeutic effect of etanercept in JRA. Interestingly, both therapeutic efficacy and tolerability appeared to be somewhat different in these 2 studies enrolling 3 patients each. Despite both reports demonstrating a consistent therapeutic benefit of etanercept in polyarticular JRA, their results on systemic JRA were somewhat different [21,22]. The results of Liang et al [21] revealed significant improvement in both clinical and laboratory parameters of JRA in response to etanercept treatment, whereas the observed improvement by Hung and Huang [22] was relatively less impressive (probably because of the longer observation period) yet with noticeably few adverse events happening in 2 patients. According to Hung and Huang, in a patient with systemic JRA, the symptoms of arthritis responded fairly within 2 weeks after etanercept treatment; however, the symptoms re-appeared 6 weeks later, while etanercept was still being administered. Unexpectedly, this patient developed seizure 4 days after discontinuance of 3-month etanercept treatment. Because seizure attack has not been linked with patients receiving etanercept therapy, the cause of this episode remains unclear. Although certain cortical dysfunction was observed in electroencephalogram, given the negative findings in both cerebrospinal fluid analysis and computed tomography scan examination, this rare adverse event happening in an etanercept-treated patient needs to be further clarified. Meanwhile, 2 out of 3 patients developed symptoms of acute upper respiratory tract infection after 4 or 5 weeks' etanercept therapy. These episodes resolved uneventfully. Because infection has been observed in patients receiving etanercept treatment, these episodes may therefore be adverse events of this drug.

Therapeutic Effects and Adverse Events of Etanercept

In a 2-year experience of etanercept treatment of 43 patients with severe, long-standing, methotrexate-resistant polyarticular JRA in the United States, the response rate appeared to be very favorable, with 81% of patients showing 30% improvement, 79% of patients showing 50% improvement, and 67% of patients showing 70% improvement [17]. The reported therapeutic effect of etanercept in 10 patients with polyarticular JRA in Finland is also very promising with American College of Rheumatology Paediatric 75 (75% improvement) around 67% after 12 months of treatment [23]. In addition, a study conducted in New Zealand confirms the efficacy of etanercept in patients with polyarticular JRA [24]. A separate study performed in the United States establishes the therapeutic efficacy of etanercept in 22 patients with polyarticular JRA over a 2-year period [25]. The report from Italy is also supportive for etanercept in polyarticular JRA [26].

In contrast to the therapeutic effect in polyarticular JRA, etanercept does not seem to be that promising in systemic JRA. According to the experience from Germany and Austria, it is noticeable that the therapeutic efficacy of etanercept is limited in patients with systemic JRA [27]. In a retrospective analysis on 82 systemic JRA patients who received etanercept therapy in the United States, the response was rated as fair or poor in more than half of the study population [28]. A French study including 61 patients revealed 30% improvement in 73% of patients after 3 months of therapy; however, this proportion decreased to 39% after 12 months of

treatment. Nevertheless, this group of researchers observed a better response rate in oligoarticular or polyarticular JRA compared to that in systemic JRA [29]. Amazingly, 12 out of 61 patients stopped the medication because of variable patterns of adverse drug events [29].

Aside from severe infection, other rare adverse events have been reported in patients receiving etanercept therapy. These adverse events include optic neuritis, lupus nephritis, neurologic or psychiatric disorders, retrobulbar optic neuropathy, macrophage activation syndrome, cutaneous vasculitis, atopic dermatitis, hemorrhagic diarrhea, uveiitis flare, diabetes mellitus, and pancytopenia [29-34]. According to Federal Drug Admininstration Adverse Event Reports, at least 18 (not limited to JRA) patients are found to have experienced exacerbation of previously quiescent multiple sclerosis or had new-onset demyelinating neurologic disease after etanercept treatment [35].

Conclusion

Although most of the studies appear to be supportive for the use of etanercept in JRA, some studies are less encouraging. In light of these reported experiences with some inconsistency, the possible existence of ethical differences may need to be clarified. Because etanercept is less effective in systemic JRA compared with polyarticular or pauciarticular JRA, after a period of treatment, if the response is limited or unsatisfactory, then the medication may be discontinued to avoid unnecessary side effects. Nevertheless, etanercept remains the drug of choice in JRA refractory to conventional DMARDs in the absence of more powerful antirheumatic drugs or biologic agents. Because there were only 6 patients in total in the 2 studies reported in this issue, it is too early to reach definite conclusions. Evidently, we need more experiences and more cases to be examined. Finally, physicians must be alert for potential adverse events that may develop after long-term etanercept treatment.

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