The high cost of anti-TNFα drugs for rheumatoid arthritis: Can a low-price product be developed in the future?

Previously published epidemiology surveys have demonstrated that the prevalence of rheumatoid arthritis (RA) is about 0.4% of the population of Taiwan. In order to better understand disease activity, we found that 26% of patients were severe RA have a disease activity score (DAS) > 5.1, 53% of patients with moderate RA have a DAS score of 3.2–5.1, and 21% with mild RA have a DAS score <3.2.

Rheumatoid arthritis is an autoimmune disease. Without adequate treatment, a large proportion of patients develop joint damage and deformities. Since 1980, methotrexate and other nonbiological disease-modifying antirheumatic drugs (DMARDs) (e.g., sulfasalazine, plaquenil, etc.) have been used to treat RA, with 70–80% of patients experiencing either symptomatic relief or a decrease in their radiologic progression. However, 20–30% of severe RA patients do not demonstrate a good clinical response and require other advanced therapies. By the year 2000, biologic DMARDs, especially anti-tumor necrosis factor α (anti-TNFα) antagonists, had entered into the market, where they were appeared as the miracle drugs needed to treat those RA patients who had either a low or poor response to conventional DMARDs.

Accumulating evidence shows that TNFα plays a pivotal role in inflammatory arthritis. Many cells in the inflammatory synovium, when activated, can release different cytokines. Among them, TNFα is a potent proinflammatory cytokine that exerts pleiotropic effects on various cell types. The biologic functions of TNFα include: (1) activating macrophages; (2) increasing MHC expression; (3) increasing intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) expression; (4) decreasing the invasion of bacteria or tuberculosis (TB)-causing bacteria; (5) enhancing osteoclast maturation and activation; and (6) stimulating synovial fibroblast matrix metalloproteinase (MMP) production. The abnormal release of TNFα and MMP in RA can cause bone and joint erosion and destruction.

Over the past 10 years, TNFα inhibitors, including etanercept, have been shown to be very effective for treating severe RA, ankylosing spondylitis (AS), and psoriatic arthritis (PSA). Currently, five anti-TNFα blockers have been approved and are used to manage inflammatory arthritis. Infliximab (remicade) is the earliest-approved anti-TNFα therapy for RA. It is administered intravenously at a dosage of 3–5 mg/body weight/q6w–q8w. Another TNFα blocker, etanercept (enbrel), possesses chemical structure entirely different from that of infliximab. Etanercept can remove TNFα because its high-affinity p75 TNFα receptor can bind to soluble TNFα. However, infliximab can remove both soluble and membrane-bound TNFα because the monoclonal antibody of infliximab binds to TNFα. Different from infliximab, etanercept is administered by a subcutaneous route and because of its short half-life it should be injected every 3–4 days. Later, in order to reduce the frequency of injection, adalimumab (humira) should be administered every 14 days, and the recently developed golimumab (simponi) can be used to extend the period between injections to 1 month. Another unique TNFα inhibitor, certolizumab (cimzia), is also administered as a once-monthly injection, but its monoclonal antibody only preserves the Fab portion of immunoglobulin and removes theFc portion. Among these four monoclonal antibodies (infliximab, adalimumab, certolizumab, and golimumab), only infliximab is prepared in its chimeric form (mouse and human), while the other three are humanized.

Due to the different chemical structures and preparations, the efficacy and side effects of these drugs are also different. Through many randomized clinical trials that have been conducted in the US and Europe over the last 5–10 years, the cumulative evidence demonstrates that all anti-TNFα blockers have equal or similar efficacies for treating RA and AS. It is obvious that anti-TNFα therapies present many advantages for treating the clinical, pathological, and radiological aspects of these diseases. In comparison with the traditional DMARDs (e.g., methotrexate) for the treatment of RA, TNFα blockers are superior in terms of providing pain relief, joint function and quality of life improvements, reducing erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and decreased inflammation on magnetic resonance imaging (MRI). Moreover, the rapid onset (usually 2 weeks after injection) and persistence of drug survival are two major advantages. In spite of the high cost, anti-TNFα drugs can easily help physicians and patients to reach the treatment-to-target (T2 T) goals, including freedom from clinical symptoms, the prevention of joint damage and deformities, and long-term clinical and radiological remission.
An early tight-control-in-RA (TICORA) trial confirmed that intensive treatment, including anti-TNFα therapies, result in a significant reduction in DAS when compared with other routine or regular treatments.\(^3\) In 2004 and 2005, Klarslkog and van der Heijide reported etanercept plus methotrexate could result in clinical remission (DAS <1.6) in 36% of RA patients, but only 16% and 13% of patients reached this goal with etanercept alone or MTX alone, respectively.\(^4,12\) In terms of radiologic progression, a similar trend has also been shown, namely that the combination group fared much better than the groups that were treated with a single drug.\(^3,8\) The Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) extension study reconfirmed that after 4 years, 47% of RA patients could achieve DAS remission (<1.6) if treated with a combination of drugs. A more recent study on early RA (disease duration <2 years), the Combination of Methotrexate and Etanercept in Early Rheumatoid Arthritis (COMET) trial, demonstrated that etanercept in combination with MTX is the optimal therapy for treating early RA. Targeting both clinical and radiologic remission is key to achieving an optimal outcome.\(^8\)

In Taiwan, so far, only two anti-TNFα drugs are available: etanercept and adalimumab. For adalimumab, the famous global study was the combination therapy with Adalimumab Plus Methotrexate Versus Methotrexate alone or Adalimumab alone in Patients with Early, Aggressive Rheumatoid Arthritis (PREMIER) trial. Again, the combination group (adalimumab plus MTX) showed superior clinical results compared with single-drug groups.\(^5\) There was no significant difference, in terms of efficacy for treating RA, between etanercept and adalimumab.

In order to determine the clinical effects of TNFα blockers in a Chinese population, we have used etanercept to treat either RA and AS over the past several years.\(^13,14\) For RA, after 6 months of etanercept treatment, all clinical parameters, including the number of swollen joints, disease activity score (DAS) 28, and ESR, CRP, and anti-CCP levels, show rapid improvements. On the other hand, the efficacy of short-term (12 weeks) etanercept treatment for AS is much better in Chinese patients than Caucasian patients. As far as the long-term efficacy and safety of etanercept in Chinese populations, it remains unknown and needs further study.

The major adverse effects of anti-TNFα therapy, particularly in Chinese populations, are the reactivation of hepatitis B or C and TB infections. In Taiwan, the prevalence of hepatitis B surface antigen (HBSAg) carriers is approximately 15%, and a few cases of fulminant hepatitis have been reported in carriers who were treated with TNF blockers.\(^11\) In order to reduce this incidence, screening patients for HBSAg and hepatitis B virus DNA (HBVDNA) is becoming a routine procedure, and patients should be treated if they are positive before being administered an anti-TNFα drug. TB is still an endemic disease in most countries in Asia, including Taiwan. Based on data from the European registry, TNFα blockers, especially monoclonal antibodies such as infliximab and adalimumab, result in a higher incidence of TB compared with etanercept.\(^10\) However, TB infection rates can be reduced if patients receive prophylactic treatment with isoniazid (INH) if they show a positive purified protein derivative (PPD) skin test or Quantiferon blood test.

Although in Taiwan government reimbursement for both etanercept and adalimumab has been approved for the management of severe RA, AS, and PSA, the high cost (US$1200/month per each patient) of anti-TNFα drugs is really a huge burden to the government and patients. In China, a generic version of etanercept (Yisaipu) has been used to treat RA for many years. The price is much cheaper than that of etanercept (US$64.50/injection for Yisapu versus US$375/ injection for etanercept). However, the biological effects and safety of this product should be carefully evaluated before applying it clinically.

In conclusion, TNFα blockers are highly effective for treating the clinical symptoms, as well as pathologic inflammation, in early and long-standing RA patients. Earlier treatment results in a better prognosis. In order to use TNFα blockers more conveniently, relatively looser clinical guidelines and lower drug prices, which can be obtained by developing similar domestic products such as Tunex (see the current issue of JCMA\(^15\)), should be encouraged.

Chung-Tei Chou
Division of Allergy-Immunology-Rheumatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: cttchou@vghtpe.gov.tw

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