Improvement of Active Rheumatoid Arthritis After Etanercept Injection: A Single-center Experience

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Background: To study the clinical effectiveness and adverse reactions of etanercept in patients with active rheumatoid arthritis (RA), in whom combination therapies with disease-modifying antirheumatic drugs (DMARDs) had failed.

Methods: One hundred and thirty-three patients with active RA who had been treated without satisfactory effect with DMARDs were entitled, by the Taiwan Bureau of National Health Insurance, to undergo etanercept injection (25 mg subcutaneously, twice weekly) along with oral methotrexate (15 mg weekly) in Taipei Veterans General Hospital. The disease activity score in 28 swollen and 28 tender joints (DAS28), erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), rheumatoid factors (RFs), tender joint count (TJC), and swollen joint count (SJC) were recorded at the beginning, 3, 6, 9, and 12 months after treatment. Any adverse event, relevant or irrelevant to the therapy, was recorded throughout the whole course of treatment.

Results: Ninety-four patients completed the 1-year therapeutic program. There were significant improvements in all parameters (DAS28, ESR, CRP, TJC and SJC), which approached satisfactory values at the end of the first 3 months and which were sustained thereafter in most patients. Patients also tolerated the treatment protocol well, with adverse events occurring sporadically. Significant clinical response occurred as early as 3 months after the start and might last beyond 1 year in some patients. Adverse effects such as injection site reaction or infections rarely occurred.

Conclusion: Combination therapy with etanercept and DMARDs seemed to be effective at improving the aching symptoms associated with rheumatoid activity and was well tolerated in this cohort study. It was generally safe, though a small number of non-fatal infections were observed. [*J Chin Med Assoc* 2009;72(11):581–587]

Key Words: biological therapies, etanercept, rheumatoid arthritis, tumor necrosis factor-α

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease involving the synovial joints, which is mediated by various cytokines including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α).[1–4] Etanercept (Enbrel; Wyeth Pharmaceuticals, Monmouth Junction, NJ, USA) is a chimeric protein comprised of a 75-kDa soluble tumor necrosis factor (TNF) receptor (sTNFR) and the Fc portion of immunoglobulin G1 (IgG1Fc), which can competitively inhibit the interaction between TNF-α and its corresponding cell-surface receptor, thus preventing the active inflammatory process in the rheumatoid synovium.[5]

The efficacy and safety of etanercept twice weekly subcutaneous injection have been demonstrated by previous clinical investigations, which showed remarkable pain relief associated with improvement in joint destruction as well as negligible side effects.[6,7] These beneficial effects usually occur within 6 months after the start of treatment. Prevention of progression of the inflammatory process has also been demonstrated.[8] Nevertheless, occurrences of side effects such

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as injection site reaction, demyelinating disease, aggravation of congestive heart failure, or activation of tuberculosis (TB) have been infrequently reported.[5,9–11] Etanercept was first launched in Taiwan in early 2004. Since then, Taipei Veterans General Hospital (VGH) has been one of several hospitals in Taiwan that has had the opportunity to treat RA patients systematically with this agent. Herein, we present our experience with this agent in treating active and/or debilitating RA patients in this hospital, which is the first systematic post-marketing report in Taiwan.

Methods

From January 2004 to June 2007, a total of 133 patients with active RA were entitled to receive etanercept (25 mg subcutaneous injection, twice a week) in Taipei VGH by the health administrator, the Bureau of National Health Insurance (BNHI), Taiwan. The enrolment criteria included age of at least 18 years, fulfillment of the 1987 American College of Rheumatology criteria for the diagnosis of RA,[12] an active disease as defined by disease activity score in 28 swollen and 28 tender joints (DAS28) of more than 5.1 points,[13,14] and failure to respond to combination therapy with at least 2 disease-modifying antirheumatic drugs (DMARDs) for more than 6 months. These DMARDs included the requisite oral methotrexate (15 mg/week) and ≥ 1 additional compounds such as hydroxychloroquine (200 mg twice a day), sulfasalazine (2 g/day), cyclosporine A (100 mg/day) or leflunomide (20 mg/day). Patients were excluded if they had malignancy, were pregnant, or were at high risk of infection (such as those with chronic skin ulceration, a previous TB infection, septic arthritis within 12 months, infected joint prosthesis, refractory lung infection or those using an indwelling catheter in the urinary tract). After DMARD failure was verified by the BNHI, individual patients received a 3-month course of etanercept injection; they continued the injections if clinical benefit was achieved and if they had obtained a permit from the BNHI for another 3-month course.

Along with etanercept, all patients continued their previous combination regimen including the requisite methotrexate and ≥ 1 DMARDs. Oral corticosteroids (methylprednisolone or prednisolone) and nonsteroidal anti-inflammatory drugs (NSAIDs) were provided as usual, but patients could reduce the doses at will if pain improved.

We analyzed patients' erythrocyte sedimentation rate (ESR) by the Westergren method, serum rheumatoid factors (RFs) and C-reactive protein (CRP) level by nephelometric analysis, and recorded their DAS28 score every 3 months from the start of the treatment protocol. In counting DAS28, tender joint count (TJC) and swollen joint count (SJC) were also recorded. These 2 parameters were considered as additional dependent variables and were separately plotted against time course. Some of the patients exited out of the treatment protocol because of medical or non-medical reasons. If the patients agreed, serum was also collected for detection of antibodies against cyclic citrullinated peptide (anti-CCP) using a commercially available ELISA kit (Diastat; Axis Shield Diagnostics, Dundee, UK) as described previously,[15] at the beginning and end of the 6th month of etanercept therapy.

All patients were evaluated for the safety of etanercept treatment every 3 months after the start. Standard laboratory measurements were performed by the affiliated central laboratory and comprised hematology (complete blood cell and differential counts), serum biochemistry (creatinine, blood urea nitrogen, alanine transaminase, aspartate transaminase, total protein and albumin), and urinalysis. Every patient underwent plain posteroanterior chest radiographic examination before the start of the biologics. If cardiopulmonary diseases were suspected at any time during the treatment protocol, then chest X-ray examinations were performed again. Other manifestations such as injection reaction, skin rash, dyspnea, neoplasm, infection episodes or development of other autoimmune diseases, if they occurred, were also recorded.

Statistical analysis

Data are presented as mean ± standard error of the mean. Statistical significance was calculated by nonparametric Wilcoxon's signed ranks test using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows. A p value < 0.05 was taken to indicate significant difference.

Results

As shown in Table 1, in this VGH etanercept cohort, the mean age was 49.7 ± 0.3 years, with a female-to-male ratio of 5.3:1. Mean disease duration from the onset of symptoms was 0.5–15 years, and the mean number of previously prescribed DMARDs was 2.9 ±1.3 (range, 2–5). All enrolled patients took oral methotrexate (15 mg weekly) as a prerequisite before the start of etanercept, and 90% of them also took hydroxychloroquine (400 mg daily). The average DAS28 was 6.98 ± 1.02 at the start of biologics,

ESR was 55.61 ± 30.25 mm/hr, and CRP was 4.10 ± 0.39 mg/dL. The whole duration of observation was 12 months, during which there were 39 patients who had their etanercept treatment prematurely terminated by the BNHI because of administrative reasons ($n = 34$), ineffectiveness (as defined by BNHI, $n = 5$), and/or the appearance of adverse effects. There was no voluntary withdrawal due to adverse effects or aggravation of joint inflammation. The remaining 94 patients completed the entire study protocol at 12 months. There were 10 patients who intended to continue etanercept injection after 12 months because of the conspicuous treatment effect. These additional treatments were not covered by BNHI and were waived of insurance payment (data not shown).

Table 1. Demographic features and medications in 133 patients receiving etanercept therapy

Mean age (yr)	49.7 ± 2.3
Sex (female/male)	112/21
Disease duration from onset (yr)	0.5–15
Positivity of rheumatoid factors, *n* (%)	130 (97.8)
Mean number of prior DMARDs	2.9 ± 1.3
Prior methotrexate use (%)	100
Prior and concomitant corticosteroid use (%)	68
Prior and concomitant hydroxychloroquine use (%)	90
Prior and concomitant NSAID use (%)	100
% reducing or stopping NSAID after start of etanercept	16.7

DMARDs = disease-modifying antirheumatic drugs, including methotrexate (15 mg weekly), hydroxychloroquine (400 mg daily), sulfasalazine (2 g/day), cyclosporine A (2.5 mg/kg/day) and leflunomide (20 mg daily); NSAID = non-steroidal anti-inflammatory drug.

A total of 94 patients completed the 1-year course of etanercept injection. As shown in Figure 1A, the mean DAS28 score was 6.98 ± 1.02 at the beginning of treatment, 3.99 ± 1.46 at the end of 3 months of treatment, 3.30 ± 1.17 at the end of 6 months of treatment, 2.65 ± 0.90 at the end of 9 months of treatment, and 2.46 ± 0.88 at the end of 1 year of treatment. After 3 months of treatment, almost all patients had achieved significant improvement in symptoms and signs, with a significant reduction in DAS28 score accompanied by parallel falls in ESR.

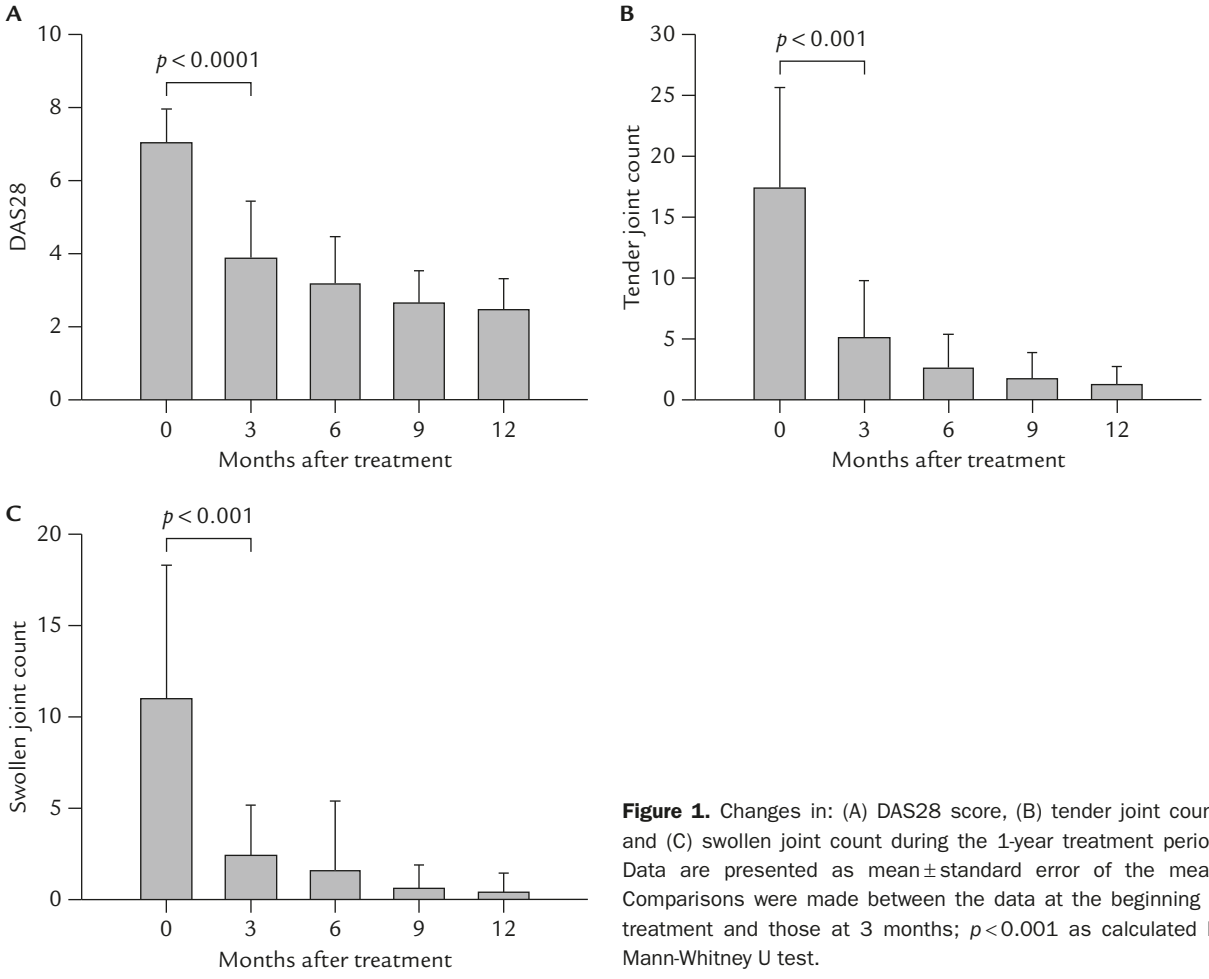

Figure 1. Changes in: (A) DAS28 score, (B) tender joint count, and (C) swollen joint count during the 1-year treatment period. Data are presented as mean ± standard error of the mean. Comparisons were made between the data at the beginning of treatment and those at 3 months; $p < 0.001$ as calculated by Mann-Whitney U test.

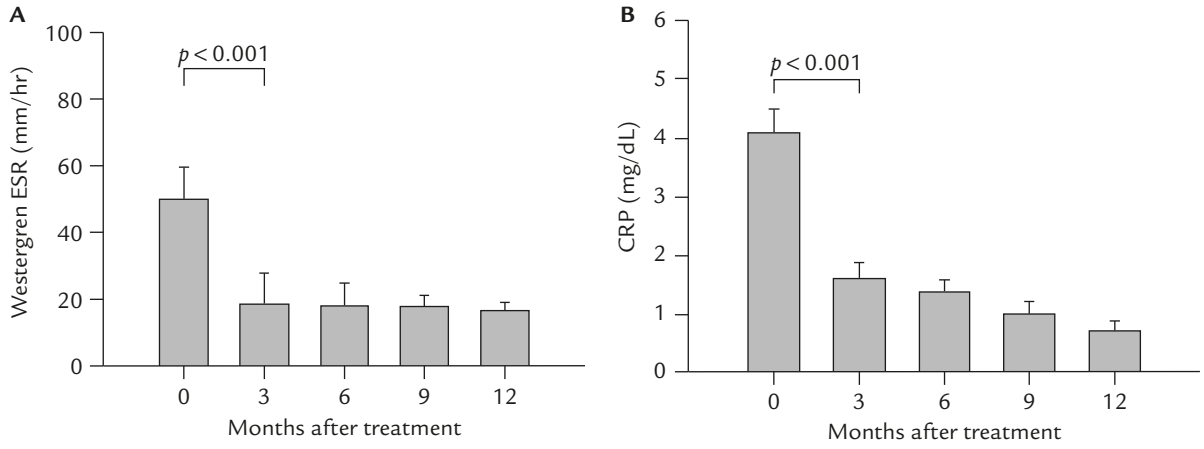

Figure 2. Changes in: (A) erythrocyte sedimentation rate (ESR), and (B) C-reactive protein (CRP) during the 1-year treatment period. ESR was measured by the Westergren method at 1 hour. CRP was measured by nephelometry. A total of 94 patients completed the 1-year course of etanercept injections. Data are represented as mean ± standard error of the mean. Comparisons were made between the data at the beginning of treatment and those at 3 months; $p < 0.001$ as calculated by Mann-Whitney U test.

As shown in Figure 2A, mean ESR was 55.61 ± 30.25 mm/hr at the beginning of treatment, 25.07 ± 23.57 mm/hr at the end of 3 months of treatment, 22.97 ± 19.87 mm/hr at the end of 6 months of treatment, 19.66 ± 13.37 mm/hr at the end of 9 months of treatment, and 17.95 ± 12.50 mm/hr at the end of 1 year of treatment. Serum CRP levels showed a similar trend. As shown in Figure 2B, mean CRP was 4.10 ± 0.39 mg/dL at the beginning of treatment, 1.61 ± 0.27 mg/dL at the end of 3 months of treatment, 1.37 ± 0.22 mg/dL at the end of 6 months of treatment, 1.02 ± 0.20 mg/dL at the end of 9 months of treatment, and 0.73 ± 0.17 mg/dL at the end of 1 year of treatment. TJC and SJC were also significantly reduced. As shown in Figure 1B, mean TJC was 17.3 ± 8.3 at the beginning of treatment, 5.1 ± 4.7 at the end of 3 months of treatment, 2.7 ± 2.7 at the end of 6 months of treatment, 1.7 ± 2.2 at the end of 9 months of treatment, and 1.2 ± 1.5 at the end of 1 year of treatment. Mean SJC was 11.0 ± 7.2 at the beginning of treatment, 2.4 ± 2.8 at the end of 3 months of treatment, 1.6 ± 3.7 at the end of 6 months of treatment, 0.6 ± 1.3 at the end of 9 months of treatment, and 0.4 ± 1.0 at the end of 1 year of treatment (Figure 1C). Some patients ($n = 21$, data not shown) even attained a remission status as defined by DAS28 score < 2.6.[16] Actually, improvement in inflammation could be seen as early as 1 week after the beginning of treatment, as evidenced by the observation that the doses of oral glucocorticoids and NSAIDs were reduced by some patients themselves when the 3rd doses of etanercept were given. As shown in Figures 1 and 2, the effect on improvement in all parameters became stabilized after 3 months of treatment, and there was no evidence of recurrence or aggravation of inflammation in the late period of the therapeutic program. Clinical response might have been sustained beyond 1 year in some patients ($n = 26$) whose treatments were not arbitrarily terminated by the BNHI. Among 39 patients who departed out of the protocol, 17 could be followed-up regularly after stopping etanercept. As shown in Figure 3, the average DAS28 scores were 6.42 ± 1.38 before the patients received etanercept therapy (baseline), 3.74 ± 1.20 at the end of etanercept therapy (0 month), and 3.14 ± 1.16, 2.92 ± 1.94, 4.19 ± 2.74 and 4.76 ± 2.27 at 3, 6, 9 and 12 months, respectively, after stopping biologics. The average DAS28 score might be sustained at a low level for a period of approximately 6 months in the presence of continuous DMARD therapy, but the disease activity began to return afterwards, suggesting a prolonged effect of etanercept.

Serum IgG, IgA, and IgM levels were not followed-up in every patient, but the available data indicated that these parameters remained stable during the treatment periods (data not shown). However, serum RFs declined remarkably in some patients (from 539.20 ± 200.15 IU/mL to 284.90 ± 122.08 IU/mL, $n = 20$) during the initial 6 months. Serum anti-CCP antibodies showed a decreasing trend in 6 patients (from 261.33 ± 145.97 U/mL to 96.67 ± 55.51 U/mL) during the first 6 months of treatment.

Of the patients who completed the treatment schedule ($n = 94$), serious treatment-related adverse effects were rarely observed throughout the whole year except in 3 patients who left the protocol because of medical reasons including development of leukemia, lymphoma and ovarian cancer. None of the patients

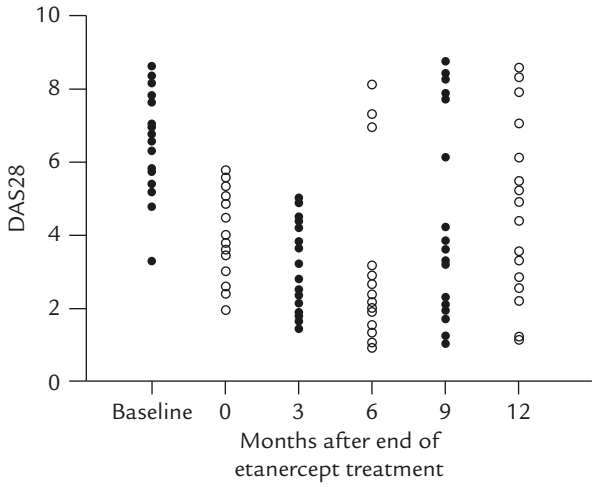

Figure 3. Follow-up of DAS28 in 17 patients who left the treatment protocol but who were still on regular medications with disease-modifying antirheumatic drugs. There was a tendency for disease activity to steadily decrease 3–6 months after stopping the biologics, but then begin to climb up again afterwards.

stopped treatment because of subjectively feeling ineffectiveness or reluctance to therapies on their own. One patient developed leukemia before the etanercept therapy. After a confirmative diagnosis was made, etanercept injection was immediately stopped at the 7th month. However, he still died of leukemia several months later. Another patient with long-standing RA was found to have ovarian cancer in the 10th month of the biologic therapy. There was no overwhelming evidence to show that etanercept injection was relevant to the development of her tumor. As shown in Table 2, injection site reaction was a frequent adverse effect, including skin rash ($n=7$) and pruritus ($n=9$). Common cold was the most common infection event ($n=9$). Other infection episodes included cellulitis ($n=2$), pneumonia ($n=1$, pathogenic microorganism not actually identified), shingles ($n=2$), and renal abscess ($n=1$, pathogenic microorganism not actually identified). The causative pathogens for cellulitis were not actually identified, but the infectious episodes in those 2 patients were well treated with intravenous ampicillin. There was no definitely confirmed TB development. One patient who was suspected to have pulmonary TB was diagnosed by mycobacterial polymerase chain reaction rather than microorganism isolation and identification. Etanercept treatment was stopped immediately after the PCR diagnosis and the patient received an empirical course of prophylactic treatment. The patient did not resume etanercept therapy subsequently. The compliance of patients was generally good except that 36 patients were forced to leave the treatment protocol by the BNHI. The reasons for suspension of treatment included migration of residence, termination of reimbursement, or randomized cessation of treatment protocol selected by the BNHI.

Table 2. Adverse events reported by the patients or recognized by the physicians during etanercept therapy

Adverse event	*n*	F:M
Skin rash other than at injection sites	7	4:3
Pruritus with or without rash at injection sites	9	6:3
Lymphoma	1	0:1
Congestive heart failure	2	2:0
Elevation of alanine/aspartate transaminase	3	1:2
Headache	1	1:0
Dyspepsia	1	1:0
Cellulitis	2	1:1
Pneumonia	1	1:0
Shingles (*Varicella zoster*)	2	1:1
Common cold	12	9:3
Newly developed hypertension	1	1:0
Leukemia*	1	0:1
Ovarian cancer	1	1:0
Renal abscess	1	1:0
Pulmonary tuberculosis (suspected)	1	1:0
Death*	1	0:1

**The same patient who was found to have leukemia during etanercept treatment, which was then stopped, died eventually of septic shock.*

Discussion

Enhanced TNF-α activity plays an important role in inflammatory arthritides, including RA.[1–4,17,18] Etanercept blocks the interaction between TNF-α and TNFR on the cell surface, thus preventing further synovial inflammation.[19,20] This 1-year open-label postmarketing study showed the efficacy of etanercept on RA patients who had failed the traditional combination therapy with DMARDs, adding more evidence to support the efficacy of etanercept in RA treatment. A significant improvement was noted in both laboratory parameters (CRP, ESR, anti-CCP antibody, RFs) and clinical parameters (DAS28, TJC, SJC).

After the emergence of biologics as the mainstay of treatment for RA as well as other autoimmune diseases, accumulating reports of increased infections in patients undergoing anti-TNF-α therapy became a great concern because of potential interruption of the normal inflammatory process by these cytokine or cytokine receptor inhibitors.[21–26] In our present etanercept cohort, 6 patients were hospitalized due to infectious episodes, not necessarily relevant to the biologic

therapy itself. These included cellulitis ($n=2$), shingles ($n=2$), pneumonia ($n=1$), and renal abscess ($n=1$). The only case receiving prophylactic antituberculous treatment did not show definite tissue proof of mycobacterial infection. All patients recovered successfully from microbial infections after adequate antibiotic treatment. Because all of the patients were concomitantly under oral methotrexate treatment, it was likely that methotrexate alone, or in addition to etanercept, rendered these patients increasingly susceptible to opportunistic infections. Indeed, among RA patients in this hospital who underwent combination therapy with methotrexate, hydroxychloroquine, and sulfasalazine but not etanercept also suffered from increased chance of getting opportunistic infections (data not shown). Because there was no patient who was treated with etanercept alone throughout the whole course, it is not known whether etanercept can really be implicated in the increased incidence of opportunistic infections, although early trials of etanercept by other authors have revealed that increased incidence of neutropenia as well as infections might occur in patients undergoing either etanercept treatment or methotrexate treatment.[27] In the patient who suffered from bacterial pneumonia, the causative pathogen was not identified. However, the pulmonary infection was completely controlled by empirical antibiotic therapy with cefuroxime. A polymerase chain reaction for *Mycobacterium tuberculosis* as well as acid-fast stain of the concentrated sputum smear had excluded the possibility of TB. In contrast to those reported by other authors who showed increased risk of TB infections in patients undergoing infliximab, etanercept, or adalimumab,[28–30] we did not find increased risk of TB in our etanercept cohort. A possible cause of this might be the strict entry criteria for etanercept therapy, excluding all the patients who were previously suspected to have active or healed typical or atypical mycobacterial infections. According to the treatment protocol set up by BNHI, we were not permitted to treat patients only with etanercept. Thus, it is difficult to infer that these sporadic infection episodes were directly relevant to the etanercept injection.

Another interesting point demonstrated in the present investigation was that 17 patients who had their etanercept treatment prematurely terminated were followed-up for an additional 6 months, during which the disease activity seemed to be kept low despite the absence of biologic therapy (Figure 3). The beneficial effect of antecedent etanercept injection seemed to be sustained for about 6 months in the presence of continuous DMARD administration. This finding has not been reported before, although previous investigations have demonstrated that etanercept together with methotrexate could exert a more beneficial effect and achieve sustained remission of rheumatoid activity than methotrexate alone.[31,32] This is interesting and inspiring because it suggests that blockade of TNF-α activity might be maintained at least for a substantial period in the presence of other DMARDs in active rheumatoid synovium. The effectiveness of etanercept was also reflected by the good compliance of our patients, with only sporadic cases having their injections stopped prematurely due to non-medical reasons. The benefits as well as drawbacks of etanercept as monotherapy for RA deserve future investigations.

In conclusion, a post-marketing investigation of etanercept in a teaching hospital in northern Taiwan has revealed that etanercept combined with methotrexate, hydroxychloroquine, sulfasalazine, cyclosporine or leflunomide is generally safe, well tolerated and effective in patients with active RA in whom traditional DMARD treatment has failed.

Acknowledgments

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