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ORIGINAL ARTICLE

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The clinical application of etanercept in Chinese patients with rheumatic diseases

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Abstract Over a 2-year period, to evaluate the efficacy and safety of biologic agents, etanercept (25 mg twice per week, s.c.) was used to treat 57 rheumatoid arthritis (RA) patients, 9 ankylosing spondylitis (AS) patients, 6 psoriatic arthritis (PSA) patients, and 4 juvenile rheumatoid arthritis (JRA) patients. In addition to inflammatory arthritis, I have used this tumor necrosis factor (TNF) blocker in other rheumatic diseases including idiopathic thrombocytopenic purpura (ITP), Behçet's disease with intractable oral ulcer, fibromyalgia syndrome, and systemic lupus erythematosis with intractable pleural effusion and acute lumbar disc herniation. For RA, after 6 months of etanercept treatment, all the parameters including number of swollen joints, number of tender joints, disease activity score, erythrocyte sedimentation rate, C-reactive protein, and global health status were rapidly improved ($P < 0.001$ or $P < 0.0001$). The anticyclic citrullinated peptide (anti-CCP) antibody and rheumatoid factor also significantly declined. For spondyloarthropathy, it also gave a similar effect as to RA. Both Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index also improved. One of the two cases with Behçet's disease with intractable oral ulcer had a long-term remission after etanercept. The other Behçet's disease patient with oral ulcer and another with ITP obtained a good response temporarily. The short-term use of etanercept (<3 months) did not bring a significant effect for cases of fibromyalgia syndrome, pleural effusion, and lumbar disc herniation. In conclusion, a dramatic and rapid clinical response in different kinds of arthritis patients can be achieved by etanercept. Moreover, the TNF-α inhibitor also can treat other severe rheumatic-related symptoms. In general, except for a few cases with infection and two cases with malignancy, etanercept was safe in our arthritis patients. We need to study a larger number of patients in order to better understand the efficacy and safety of etanercept.

Key words Ankylosing spondylitis (AS) · Etanercept · Psoriatic arthritis (PSA) · Rheumatic disease · Rheumatoid arthritis (RA) · Tumor necrosis factor (TNF)-α blocker

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Introduction

Arthritis is a common disease in the general population. Osteoarthritis is a highly prevalent rheumatic disease, particularly in aged people. Other forms of inflammatory arthritis that are frequently encountered include gout, rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PSA). Rheumatoid arthritis is an articular disease characterized by a chronic and persistent inflammation and juxta-articular bone destruction.[1,2] The disease is frequent, with a prevalence of 0.4%–0.5% in the Chinese population.[3] Research over the past 10 years has shown that in spite of treatment, over 50% of subjects experience substantial functional loss within 5 years, resulting in occupational disability and/or unemployment.

For inflammatory arthritis, the initial medication is nonsteroid anti-inflammatory drugs (NSAIDs). Furthermore for RA, AS, or PSA, many disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), sulfasalazine, plaquenil, cyclosporine, and leflunomid have been used to treat moderate or severe arthritis.[4–9] On average, 70%–80% of RA patients or 60% of PSA may be beneficial after MTX or leflunomid treatment. Sulfasalazine is only indicated in AS with progressive or intractable peripheral arthritis. In general, 15%–20% of cases of inflammatory arthritis have had no response to DMARDs therapy in combination with NSAIDs; therefore, new therapy to treat severe arthritis is strongly suggested.

Since tumor necrosis factor (TNF)-α is a keystone in the activation of inflammatory cascade within the rheumatoid synovium,[10–12] a specific biologic therapy has been used for RA.[12–16] Recently this anti-TNF-α biologic agent was

referred to be applied in patients with AS and PSA, based upon some evidence-based studies.[17–25] Currently, there are three anti-TNF-alpha agents; infliximab and adalimumab are monoclonal antibodies and etanercept is a TNF-receptor recombinant fusion protein. In Taiwan, only etanercept has entered the market, and only RA patients have the opportunity to be given etanercept without paying money, if they fulfill the criteria of the "guideline to use etanercept in RA," subject to government approval.

Over the past 2 years, in order to judge the efficacy and safety of etanercept in Chinese patients with different types of arthritis or immune diseases, we have collected and analyzed all cases of patients who have experienced at least 3 months of etanercept treatment.

Patients and methods

Patients

From 2003 to 2005, all patients who had received etanercept treatment for inflammatory arthritis or other immune-related diseases that were refractory to traditional management were enrolled in this study. The minimal duration for etanercept treatment was at least 3 months. The diagnosis of RA in patients met the American College of Rheumatology 1987 criteria,[26] AS the Modified New York criteria,[27] PSA the classification criteria by Moll and Wright,[28] JRA the International League of Associations for Rheumatology (ILAR) criteria,[29] and undifferentiated spondyloarthropathy (USPA) required the classification criteria provided by the European Spondylitis Group (ESSG) published in 1991.[30] The diagnosis of other rheumatic or immune disease was also based upon the criteria of clinical as well as imaging findings. Approximately 80% of RA patients obtained the etanercept from the Government Health Insurance Bureau but only if the disease were active, i.e., (1) Disease Activity Score (DAS) ≥5.1, (2) failure of combination therapy of DMARDs (MTX >15 mg/week + plaquenil 400 mg/day or salazopyrin >2 g/day), and (3) treatment duration for DMARDs must be more than 6 months. The remaining 20% of RA patients purchased etanercept and their disease activity was also active (DAS ≥5.1). The reasons for buying this expensive medicine were (1) the application for etanercept from the government was not approved and (2) patients could not tolerate pain for a long time.

More than 90% of patients who began etanercept treatment used methotrexate in combination. The remaining patients were treated with etanercept alone because they could not tolerate the side effects of methotrexate. When etanercept significantly improved symptoms, the dosage of methotrexate was reduced (from 6–8 tablets/week to 3 tablets/week).

Besides RA, patients with other rheumatic disease or immune disease had to pay about US$1500/month for the etanercept to treat their disease. Each disease (RA, AS, PSA, USPA, etc.) had its own special questionnaire to record the demographic, clinical, laboratory, and X-ray findings.

A few cases with intractable rheumatic disease including systemic lupus erythematosus (SLE) with persistent pleural effusion, fibromyalgia syndrome, Behçet's disease with frequent and diffuse oral ulcer, severe acute lumbar disc herniation, and intractable thrombocytopenia also received etanercept treatment. The reason to try the TNF-α blocker was mainly treatment failure, and a good efficacy was reported in some sporadic cases.

Those patients who entered our clinical trial had to sign an informed consent form. The study was approved by the ethics review board of Veterans General Hospital, Taipei.

Disease evaluation

Patients with RA were evaluated by number of swollen and tender joints, physician and patient global assessment, and DAS score, which was counted before and after etanercept treatment based upon the clinical findings and laboratory tests including ESR. Disease was considered active when the DAS score was ≥5.1. After etanercept treatment, a good response was achieved when the DAS score was ≤3.2 or at least dropped more than 1.2 from the initial score.

We used the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI) to measure the disease activity of AS and PSA, as Calin and colleagues described.[31,32] There are six questions (fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness, and duration of morning stiffness) in BASDAI and ten questions in BASFI. The Global Index (BASGI; from 0 to 100) was used to indicate health status. A higher score represented worse health condition. Currently, BASDAI is a very common measurement for disease activity in AS, and BASDAI ≥4 is considered active in AS. In this study, etanercept was indicated in patients with AS when (1) BASDAI ≥4, and (2) the patient had not responded to at least 2 NSAIDs within 3 months or at least 3 months' treatment with salazopyrin (2 g/day) for AS or PSA with peripheral arthritis. We recorded the number of tender and swollen joints if the patient had peripheral arthritis and painful sites of enthesopathy, etc. Like AS, the disease activity in psoriatic spondyloarthropathy (PSA) was assessed by using BASDAI and BASFI, and skin involvement was evaluated by the Psoriasis Area and Severity Index (PASI) score.[33,34]

Laboratory tests

Before and after etanercept, erythrocyte sedimentation rate (ESR) was measured by the Westergren method, and serum levels of rheumatoid factor (RF) and C-reactive protein (CRP) were measured by nephelometry (Behring Nephelometer Analyzer-II). We used the commercially available second-generation ELISA kit to measure the anti-CCP antibody (Diastat; Axis Shield Diagnostics, Dundee, UK).

Statistical analysis

After etanercept treatment, a paired *t*-test was used to compare the baseline data (month 0) with the data in months 3, 6, and 9. The data between months 0 and 12 in 22 RA patients and between months 0 and 3 in 9 AS patients before and after etanercept treatment were analyzed using the Wilcoxon signed-rank test. A *P* value less than 0.05 was considered significant.

Results

In the 2 years of study, etanercept was used in a variety of rheumatic diseases, including 57 RA, 9 AS, 6 PSA, 4 USPA, 4 JRA, 2 Behçet's disease, 2 fibromyalgia syndrome, 1 SLE with intractable pleural effusion, 1 idiopathic thrombocytopenic purpura (ITP), and 1 lumbar disc herniation. All patients received at least 3 months of treatment.

Among 57 RA patients, 50 were women and 7 men. Age was 50.5 ± 14.8 years. Rheumatoid factor was positive in 95% of patients. Other clinical and laboratory data are shown in Table 1. After 3 months of treatment, a significant reduction of tender and swollen joints was observed. The high DAS 28 score (6.9) was also improved significantly and it dropped to 3.6 ($P < 0.001$). Patients subjectively felt comfortable and health status improved from 77.0 to 31.2 ($P < 0.0001$). After 6 months of treatment, patients remained in a very stable condition, and the number of tender and swollen joints was much reduced when compared to the data of 3 months (Table 2). The laboratory parameters ESR and CRP also decreased dramatically from the elevated level (ESR 60.8, CRP 3.08) down to the normal level by 3 months (22.3 and 1.0, respectively) ($P < 0.0001$) or by 6 months' treatment (21.5 and 1.1, respectively) ($P < 0.0001$). Out of 57 RA patients, 22 had more than 1 year of management with etanercept. Again, a significant improvement either in clinical features or in laboratory data was demonstrated (Table 3). Three patients received etanercept for $1^1/_2$ years. The DAS score, number of swollen joints, and ESR are shown in Figs. 1–3.

During this RA study, alongside ESR and CRP we also measured the anti-CCP antibody and RF titer. Like ESR and CRP, etanercept was able to significantly suppress the anti-CCP antibody level from 60 to 49 ($P = 0.007$) and RF from 87 to 64 ($P = 0.0006$).

We also analyzed 9 AS patients who received etanercept treatment after they had no response to previous DMARDs and NSAIDs. The demographic data are shown in Table 4. All patients had peripheral arthritis and many of them had enthesopathy. The disease activity was measured by BASDAI and function by BASFI. After 3 months of treat-

Table 1. Demographic and other baseline characteristics in 57 patients with rheumatoid arthritis before etanercept treatment

Demographic data	No. (percentage)
Sex, *n* (%)	
Male	7 (12%)
Female	50 (88%)
Rheumatoid factor, *n* (%)	
Positive	54 (95%)
Negative	3 (5%)
Age, years (mean ± SD)	50.5 ± 14.8
DAS 28	6.9 ± 1.2
No. of tender joints	15.9 ± 8.7
No. of swollen joints	10.6 ± 6.3
ESR (mm)	60.8 ± 32.2
CRP (mg/dl)	3.1 ± 2.9
Global health (0–100)	77.0 ± 19.7

DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

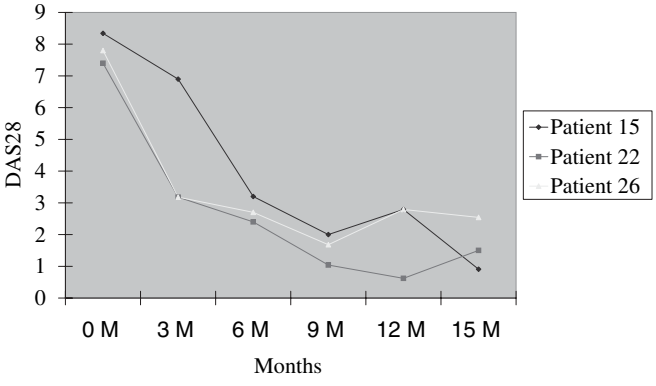

Fig. 1. Change in disease activity score (*DAS*) during 15-month follow-up in three cases after etanercept treatment for rheumatoid arthritis

Table 3. Change in clinical and laboratory parameters from baseline to month 12 after etanercept treatment in 22 rheumatoid arthritis patients

	Baseline	Month 12	*P* value
DAS score	6.6 ± 2.1	2.7 ± 0.9	<0.0001
No. of tender joints	16.0 ± 9.5	2.0 ± 2.9	<0.0001
No. of swollen joints	11.1 ± 7.3	0.5 ± 0.8	0.0039
Global health	73.4 ± 29.1	11.4 ± 6.6	0.0002
ESR	55.9 ± 36.2	15.1 ± 14.8	0.0004
CRP	2.8 ± 2.7	0.4 ± 0.4	0.0005

Table 2. Change in clinical and laboratory parameters from baseline to month 3, month 6, and month 9 after etanercept treatment for rheumatoid arthritis

	Baseline	Month 3	Month 6	Month 9
DAS score	6.9 ± 1.2	3.6 ± 1.6	3.1 ± 1.1	2.6 ± 1.0
No. of tender joints	15.9 ± 8.7	5.2 ± 5.6	2.5 ± 2.5	2.1 ± 2.4
No. of swollen joints	10.6 ± 6.3	2.7 ± 3.1	1.1 ± 1.8	0.4 ± 0.9
Global health	77.0 ± 19.7	31.2 ± 21.9	22.7 ± 16.5	14.0 ± 9.9
ESR	60.8 ± 32.2	22.3 ± 24.8	21.5 ± 19.9	17.2 ± 12.5
CRP	3.1 ± 2.9	1.0 ± 2.0	0.9 ± 1.9	0.7 ± 1.7

Table 4. Demographic data of 9 patients with ankylosing spondylitis who received treatment with etanercept

No.	Sex	Age (years)	Age at onset	Disease duration (years)	LBP	Peripheral arthritis	Enthesitis	Uveitis	DMARDs
1	F	26	24	2	+	+	–	–	(SZ)
2	F	44	36	8	+	+	+	–	(SZ)
3	M	26	18	8	+	+	+	–	(MTX + SZ)
4	M	24	10	14	+	+	+	–	(MTX + SZ)
5	M	24	18	6	+	+	–	–	(SZ)
6	F	42	23	21	+	+	+	–	(MTX + SZ)
7	M	27	21	6	–	+	+	+	(MTX)
8	F	36	16	20	+	+	+	+	(MTX + SZ)
9	M	50	20	30	+	+	–	+	(SZ)

M:F ratio = 5:4. Age (mean ± SD) = 33.9 ± 4.2
MTX, methotrexate; SZ, salazopyrin; DMARDs, disease-modifying antirheumatic drugs; LBP, low back pain

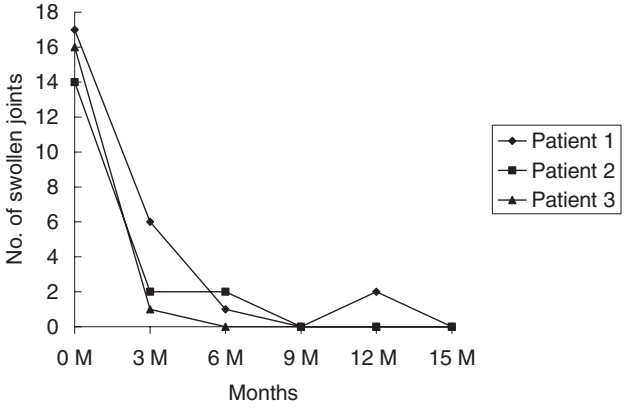

Fig. 2. Change in number of swollen joints during 15-month follow-up in three cases after etanercept treatment for rheumatoid arthritis

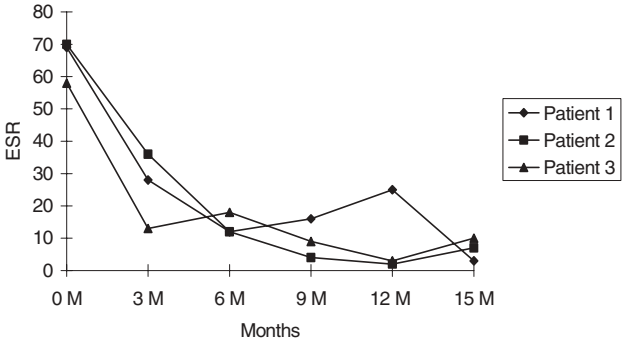

Fig. 3. Change of erythrocyte sedimentation rate (*ESR*) during 15-month follow-up in three cases after etanercept treatment for rheumatoid arthritis

ment, the BASDAI was becoming much lower, from 5.74 ± 2.95 to 3.90 ± 2.59 ($P = 0.036$) (Table 5). BASDAI includes six items. The majority of items showed improvement after etanercept treatment but only item 5 disclosed a significant change (6.17 ± 3.84 vs 4.28 ± 2.87, $P = 0.025$). For BASFI in AS patients, there was no significant change before and after 3 months of etanercept treatment. However, it presented a dramatic effect for the BASGI in AS patients with etanercept treatment (7.12 ± 3.15 vs 5.86 ± 2.70, $P = 0.005$). In patients with psoriatic arthritis, the biologic compound also achieved a very good response either in skin lesions or arthritis (data not shown).

For those 4 cases with JRA and 4 with USPA, etanercept could effectively suppress the swollen and tender joints, although one JRA patient (Still's disease) suffered from fever intermittently at the beginning but recently was stable. Two cases with Behçet's disease with intractable oral ulcer were resistant to any kind of treatment. After short-term etanercept injection, one of two cases had a long-term remission and the other still had the same complaint. One young female with ITP that did not respond to steroid and after etanercept treatment, had a temporary elevation of platelet count (from 30000 to 90000) but which was only maintained for 1 month. Etanercept was also applied in another two cases – one SLE with intractable pleural effusion; the other, acute lumbar disc herniation – but the results were disappointing. The same situation was also found in two patients with fibromyalgia syndrome.

In general, etanercept was safe in the majority of patients. One elderly man recently died of sepsis with adult respiratory distress syndrome that was probably related to etanercept. Malignancy was found in two cases just a few months after etanercept. One of these patients contracted acute leukemia and the other lymphoma. Pulmonary tuberculosis (TB) has not been demonstrated but one case was suspected to have atypical myocobacteria. Five cases had upper respiratory tract infection and one had pneumonia. A 60-year-old woman who had been on etanercept treatment for RA was admitted to the hospital due to the severe dyspnea, and her heart failure quickly responded to diuretic treatment.

The most common side effects in etanercept were injection site reaction and skin rash (Table 6). The cellulitis was not serious in one case and subsided after antibiotic treatment. Headache and mild liver function impairment occurred in a few cases.

Discussion

Currently, three anti-TNF-α biologic agents have been used to treat severe arthritis. Among them, infliximab and

Table 5. Change in BASDAI, BASFI, and BASGI scores before and after 3 months of etanercept treatment in 9 patients with ankylosing spondylitis

	Before etanercept	After etanercept	*P* value
BASDAI	5.74 ± 2.95	3.90 ± 2.59	0.036*
BASDAI 1	5.83 ± 2.24	4.43 ± 2.98	0.232
BASDAI 2	6.69 ± 3.07	4.42 ± 2.66	0.053
BASDAI 3	6.09 ± 3.68	3.53 ± 2.87	0.071
BASDAI 4	4.93 ± 3.72	2.41 ± 2.82	0.177
BASDAI 5	6.17 ± 3.84	4.28 ± 2.87	0.025*
BASDAI 6	4.74 ± 4.14	4.31 ± 3.90	0.584
BASFI	6.01 ± 2.46	4.43 ± 2.97	0.070
BASFI 1	5.29 ± 3.27	3.79 ± 3.03	0.144
BASFI 2	6.58 ± 2.86	4.67 ± 3.34	0.260
BASFI 3	5.39 ± 3.02	4.11 ± 3.57	0.161
BASFI 4	6.64 ± 2.93	4.48 ± 3.44	0.096
BASFI 5	5.80 ± 3.35	5.01 ± 3.49	0.603
BASFI 6	7.02 ± 2.03	4.38 ± 3.28	0.057
BASFI 7	5.38 ± 3.40	4.28 ± 3.37	0.201
BASFI 8	5.44 ± 3.77	4.10 ± 3.71	0.578
BASFI 9	6.22 ± 3.05	4.73 ± 3.25	0.220
BASFI 10	6.33 ± 3.13	4.72 ± 3.38	0.061
BASGI	7.12 ± 3.15	5.86 ± 2.70	0.005*
BASGI 1	7.28 ± 3.14	5.13 ± 3.00	0.033*
BASGI 2	6.97 ± 3.42	6.58 ± 2.64	0.005*

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASGI, Bath Ankylosing Spondylitis Global Index
* Statistically significant

Table 6. Adverse events probably related to etanercept in 57 patients with rheumatoid arthritis

Event	No.
Injection site reaction	5
Headache	2
Skin rash	5
Respiratory treatment infection	5
Atypical mycobacteria	1
Heart failure	1
Malignancy	2
Sepsis	1
Cellulitis	1
SGOT, SGPT elevated	1

SGOT, serum glutamate oxaloacetate transaminase; SGPT, serum glutamate pyruvate transaminase

adalimumab are monoclonal antibodies against TNF-α and they can lyse cells. Etanercept is a recombinant fusion protein that binds soluble TNF-α through the receptor. It cannot lyse cells but can bind lymphotoxin-α. To date, only etanercept has entered our market and only RA cases have had the opportunity to use it when the patient has the indications that fulfill the government-proposed criteria. The treatment guideline for etanercept in RA in Taiwan is as follows. Failure of at least 2 DMARDs after active therapy. In combination with the 2 DMARDs there should be methotrexate in combination with at least one DMARD, plaquenil, salazopyrin, leflunomide, etc. The duration of treatment must be over 6 months and for at least 2 months the MTX and other DMARD combinations should reach the standard target dose (MTX 15 mg/week, plaquenil 400 mg/day, salazopyrin 2 g/day). The treatment guideline to use TNF-α blocker in AS or PSA has not been approved by our government. The proposed indication to use etanercept in AS or PSA at present is (1) more than 2 NSAIDs within 3 months having no significant effect, and (2) failure of salazopyrin at least 2 g/day after 3 months' treatment.

Among the TNF-α agents, infliximab was the first to be used for RA. The ATTRACT 2-year study showed that the combination of infliximab and methotrexate was superior to the methotrexate alone.[12] Adalimumab, the fully humanized antibody, during the PREMIER clinical trial, was able to effectively reduce total sharp score in the group of adalimumab plus MTX and adalimumab alone when compared to the MTX group.[35] Etanercept has been tested for its efficacy in patients with RA.[12–16,36–40] Both Bathon et al. and Genovese et al. completed a clinical trial in early RA and found a significant decrease in erosion and total sharp scores in patients who received etanercept and methotrexate when compared to methotrexate alone.[15,37] Kremer et al. found 20% improvement in ACR 20, 47% in ACR 50, and 23% in ACR 70 after RA patients were treated with etanercept.[36] When patients felt comfortable, 56% discontinued steroid, 62% decreased MTX dosage, and 29% stopped MTX. A large clinical trial (TEMPO study) involving 686 RA patients showed that etanercept and MTX significantly diminished joint damage (decreased sharp score), which was better than etanercept or MTX alone.[39,40] In this study, we had the same clinical results in RA patients with etanercept management. Not only ESR and CRP, but both RF and anti-CCP antibody declined after TNF-α inhibitor.[41] The correlation between clinical symptoms and laboratory data was evident.

Followed by the approval on RA, the U.S. Food and Drug Administration (FDA) approved etanercept for use in patients with severe AS. Ankylosing spondylitis is one of the seronegative spondyloarthropathies. The prevalence of AS in Caucasians varies from 0.1% to 1.0%[42,43] and in

Chinese from 0.3% to 0.4%.[3,44] The positivity of HLA-B27 in Chinese AS patients can reach up to 97% and B2704 was the predominate subtype in both AS patients and healthy subjects.[43,45] Earlier studies by Brandt et al. showed that either infliximab or etanercept was successful in treating active AS.[17,19,21,46] Gormen et al. reported that 80% of AS patients had a good response after 4 months of etanercept treatment.[47] Long-term efficacy and safety of infliximab was observed in the treatment of AS by Braun et al.[19,48,49] A recent study by Brandt et al. showed 57.5% of AS patients had >50% improvement of BASDAI, 20% of AS AS 20, and 62.5% of AS AS 40.[50] In this study, only limited numbers of AS patients received etanercept treatment, mainly due to the fact that patients needed to pay by themselves. Therefore, the majority of patients took 3 months' remedy. In fact, 1 month after etanercept was initiated, both BASDAI and BASFI had decreased significantly. However, BASFI after 3 months' treatment did not change very much. The small sample sizes and short treatment duration may influence the efficacy. We may expand our case numbers in order to evaluate the outcome of etanercept in our AS patients.

Psoriatic arthritis has five clinical subtypes: (1) arthritis involving distal interphalangeal joints; (2) symmetric seronegative polyarthritis simulating rheumatoid arthritis; (3) monoarthritis or asymmetric oligoarthritis; (4) sacroiliitis and spondylitis; and (5) arthritis mutilans.[28] Among these, the most serious type is polyarthritis, in which some cases may progress in a short time toward joint destruction and deformity. A few cases with the spondyloarthropathy pattern may also rapidly change to ankylosis of the spine and kyphoscoliosis, or hip joint destruction. NSAIDs may not retard the disease progression. Tumor necrosis factor-α inhibitors have been successfully used in recent years to treat intractable skin lesions or arthritis.[22]

Etanercept has been shown to be effective in the treatment of PSA. After 12 weeks of treatment, Mease et al. found a significantly greater percentage of patients in their etanercept group achieved ACR 20 (59%) compared with placebo-treated patients (15%).[22] On evaluating the radiologic progression after etanercept, Mease et al. disclosed a significant difference between the etanercept group and the placebo group (P = 0.0001) during 1- and 2-year follow-up.[23,51] The IMPACT study (Infliximab Multinational Psoriatic Arthritis Controlled Trial) by Antoni et al. showed that after 50 weeks of treatment, infliximab achieved an ACR 20 response of 65%, ACR 50 of 46%, and ACR 70 of 29%. It also significantly improved the radiographic progression and PSA index scores.[52]

In this hospital, about 100 cases of psoriatic arthritis have been seen in my clinic in the past 6 years. Only six patients have recently agreed to use etanercept. Two of six cases had severe knee and finger arthritis, which had no response to NSAID and DMARD therapy. Etanercept treatment led to patients being free of arthritis and diminished skin lesions in 2–3 months, a stable condition being maintained even after stopping etanercept for several months. More patients need to be enrolled in order to better know the drug's efficacy for severe peripheral arthritis in PSA and even axial symptoms.

Etanercept has been tried in many rheumatic and autoimmune diseases including Wegener's granulomatosis, Behçet's disease, Crohn's disease, Sjögren's syndrome, adult-onset Still's disease, sarcoidosis, and uveitis.[53–62] Approximately 25%–30% of AS patients may develop uveitis. Only a small number of patients had severe and recurrent attacks of anterior uveitis, for which steroid or salazopyrin failed. For severe refractory uveitis either from AS or panuveitis from Behçet's disease, TNF-α blockers have been used successfully.[62] For Crohn's disease, etanercept is not approved by the FDA. In contrast, infliximab has been proven to be efficacious in the treatment of Crohn's disease.[53,54] One study revealed that etanercept was effective for the treatment of oral ulcers or nodular skin lesions. The oral ulcer in one of our two cases with Behçet's disease improved clinically after etanercept treatment. The efficacy of etanercept to a variety of immune or inflammation-mediated disorders is still under investigation.

One patient with SLE with intractable pleural effusion also received etanercept treatment because all treatments for his persistent effusion had failed. The treatment duration was only 3 months. The disease activity was stable and anti-DNA was not increased. Compared to the infliximab, the relative lower incidence of positive ANA occurred during the etanercept treatment for RA (11% vs 55% in infliximab). Only a few cases develop drug-induced lupus or lupus-like syndrome.[63] However, more care will be required when SLE patients are to receive TNF-α blocker treatment.

In this study, infection was not a major problem in the majority of patients who received the biologic agent. As others have reported, local cellulitis or upper respiratory tract infection – was not uncommon.[13–16,40,64] Only one elderly man recently died of pulmonary infection and sepsis 6 months after etanercept treatment for RA. He was a thin man with body weight of only 40 kg. This mortality case may suggest that the physician should carefully monitor the respiratory tract infection and moreover might have to reduce the etanercept dosage from 25 mg twice per week to either 12.5 mg twice per week or 25 mg once per week.

Pulmonary TB is still an endemic infectious disease in Taiwan. However, more than 100 cases have so far received etanercept and no one has as yet been identified as having pulmonary TB. Only one atypical mycobacteria was suspected. The results are contradictory to the findings from Spain and Belgium that TB incidence was rather higher (1893/100 000 in the year 2000 from Spain) after infliximab treatment.[65–67] To date, nothing certain is known about the relationship between TB and etanercept. We have to follow up our cases over a longer period and increase our patient numbers in order to discover whether TB is a real problem in patients who are administered any biologic agent.

Two cases developed malignancy after etanercept treatment. Both contracted hematologic tumor, one leukemia and the other lymphoma, and the duration from the onset of TNF-α blocker injection to the discovery of tumor was less than 1 year. Previous community-based studies in RA patients showed an increased overall tumor risk compared with the general population.[68,69] To date, there is no clear information on the relationship between anti-TNF inhibi-

tors and the risk of malignancy, and this needs further investigation.[70–72]

Only one case in this study developed heart failure. She had been on etanercept for treatment of RA over 6 months but suddenly noticed exertional dyspnea and oliguria. Congestive heart failure was improved after stopping the etanercept and adding diuretics. In point of fact, any relationship between heart failure and anti-TNF therapy cannot be concluded, although 47 patients who developed new or worsening heart failure during TNF antagonist therapy were identified by the FDA's MedWatch program.[73]

In conclusion, the short-term efficacy is confirmed by the only biologic agent – etanercept – in Taiwanese patients with intractable arthritis. However, the long-term efficacy and safety need further evaluation.

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