Efficacy and safety of etanercept in the treatment of recalcitrant psoriasis: An open-label, retrospective, observational study in Taiwan

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Abstract

Background: Psoriasis is a chronic inflammatory disease affecting the quality of life of patients. Traditional treatments are limited by adverse side effects. Etanercept is a biological agent used as an alternative treatment for psoriasis.

Methods: This open-label, observational study conducted in Taiwan involved 22 patients with recalcitrant psoriasis who received a 24-week treatment with etanercept—50 mg twice weekly (BIW) during the first 12 weeks and 25 mg BIW in the next 12 weeks. Psoriasis Area and Severity Index (PASI) score at Weeks 0, 12, and 24 were recorded. Levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), and tumor necrosis factor-alpha (TNF-α) at baseline, Week 12, and Week 24 were obtained. Adverse events and blood tests were recorded as safety assessment.

Results: At Week 12, 54.5% and 13.6% patients achieved ≥50% improvement from baseline in PASI score (PASI 50 and PASI 75, respectively); at Week 24, 66.7% and 23.8% patients achieved PASI 50 and PASI 75, respectively. The mean improvement in PASI was 49.8% at Week 12 and 59.8% at Week 24, while 100% and 62.5% patients had reduced ESR and CRP levels, respectively. There were no deaths or serious adverse events. Four patients developed positive ANA, one of whom had poor psoriasis control. Most patients (93.8%) had higher serum TNF-α levels compared to baseline.

Conclusions: Etanercept is effective and safe in treating recalcitrant psoriasis, reduces ESR and CRP levels, and occasionally induces positive ANA titer associated with poor psoriasis control. Serum TNF-α level may increase after treatment, but this does not seem to affect PASI improvement.

Introduction

Psoriasis is a chronic inflammatory dermatological disorder that impairs the quality of life of patients both physically and psychologically. Its prevalence is estimated to be 2%,1 and the total rate of psoriasis in children younger than 18 years old, including about 3.5–16% infantile patients,2 has been reported to be 0.71%.3 In Taiwan, the mean 1-year prevalence rate is about 0.19%.4 Traditional therapies such as retinoids, methotrexate, and cyclosporine, sometimes combined with phototherapy, have been in use for a long time, but therapeutic limitations, including elevated liver function and lipid profiles in retinoids, hypertension and impaired renal function in cyclosporine, and liver toxicity in methotrexate, still exist. Moreover, some patients do not respond well to these regimens.

Biological agents, such as tumor necrosis factor (TNF) antagonists, have been developed as alternative treatments for psoriasis. Currently available TNF antagonists include infliximab, etanercept, and adalimumab.5 Etanercept, a human fusion protein, binds to the TNF receptor and inhibits the cascade of the inflammatory process. It has been approved as a treatment for moderate-to-severe plaque psoriasis in the United States and the European Union.6 In Taiwan, etanercept is used as a second-line treatment for patients with chronic, moderate-to-severe plaque or palmoplantar psoriasis. Previous clinical trials have elucidated that etanercept is effective and safe in treating patients with moderate-to-severe psoriasis.7,8 There are also published open-label, observational studies showing satisfactory Psoriasis Area and Severity Index (PASI) reduction using etanercept in patients with moderate-to-severe psoriasis in clinical practice.9,10
Efficacy assessment

Evaluation of efficacy included PASI score and laboratory data. At baseline and Weeks 12 and 24, PASI scores and results of blood tests, including ESR, CRP, ANA, TNF-α, were collected. The mean improvement and improvement in PASI scores of ≥25%, ≥50%, ≥75%, and ≥90% (defined as PASI 25, PASI 50, PASI 75, and PASI 90, respectively) were also assessed.

Safety assessment

Prior to etanercept injection, all patients had received Quantiferon-TB Gold (QFT-G) test and chest X-ray examination. Neither any positive QFT-G test nor any suspicious tuberculosis infection on chest X-ray was found prior to treatment. All patients received a follow-up of chest X-ray 6 months later. During the study period, blood tests including complete blood cell count with differential count and liver function tests were performed every month. One patient with hepatitis B virus (HBV) infection underwent serum viral load examination prior to treatment and at Week 24. Adverse events of etanercept treatment were assessed in all patients during each clinical visit.

Statistical analysis

The Mann–Whitney test was used to compare the PASI improvement between patients treated with and without concomitant topical medications and between those with and without concurrent psoriatic arthritis (PsA). All analyzed results were considered statistically significant at \( p < 0.05 \). The relationship between the increment of serum TNF-α level and the PASI improvement was evaluated using linear regression analysis.

Results

Efficacy

The mean PASI score and PASI improvement (%) at baseline and Weeks 12 and 24 are listed in Table 2. All patients completed the 12-week data collection, while 21 of 22 patients completed the 24-week treatment course. One patient withdrew from the study after Week 12 due to poor compliance. No laboratory data were obtained at Week 12 or 24 for this patient. The mean PASI improvement rate at Week 12 was 49.8%. By Week 24, the mean PASI improvement was 59.8% (Table 2). At Week 12, 19 (86.3%), 12 (54.5%), three (13.6%), and one (4.5%) patient achieved PASI 25, PASI 50, PASI 75, and PASI 90, respectively. At Week 24, 20 (95.2%), 14 (66.7%), five (23.8%), and three (14.3%) patients achieved PASI 25, PASI 50, PASI 75, and PASI 90, respectively (Figure 1). As the treatment period extended, more patients achieved PASI responses.

Six (27.3%) patients had concurrent psoriasis and PsA. The PASI improvement in patients with PsA was 50.8% at Week 12 and 70.0% at Week 24.
at Week 24 (Table 3). The difference in PASI improvement (%) between patients with and without PsA did not show statistical significance ($p = 0.94$ and $0.90$ at Week 12 and Week 24, respectively).

PASI improvements (%) at Weeks 12 and 24 in patients treated with and without concomitant topical medications are listed in Table 4. Patients treated without topical medications had better psoriasis control at both Week 12 ($p = 0.0002$) and Week 24 ($p < 0.0001$).

### Laboratory data

Four (18.1%) patients had elevated ESR level ($\geq 15$ mm/h) at baseline. At Week 12, all four (100.0%) patients had reduced ESR levels, which they maintained until Week 24 (Table 2).

Eight (36.4%) patients had elevated CRP level ($\geq 5$ mg/L) at baseline. By Week 12, all of them (100%) had reduced CRP levels. By Week 24, five of the eight (62.5%) patients maintained the reduction in CRP levels, while three (37.5%) had higher CRP levels than baseline.

Four (18.2%) patients developed positive ANA titers at Week 24. Three of them (75.0%) achieved PASI improvement of $\geq 66\%$, while one (25.0%) had poorer psoriasis control. The PASI improvement in this patient was 15.3% and 11.9% at Week 12 and Week 24, respectively.

Serum TNF-α levels were monitored in 16 (72.7%) patients (mean 26.4 pg/ml, range 6.7–175 pg/ml) at baseline and Week 12. Fifteen of the 16 (93.8%) had elevated TNF-α levels (mean 137.9 pg/ml, range 61–270 pg/ml) after treatment, while one (6.2%) had reduced TNF-α level (from 175 to 79.1 pg/ml). By Week 12, the mean PASI improvement in patients with elevated TNF-α level was 46.8%. Elevation rate (%) and PASI improvement (%) were not correlated ($R^2 = 0.096$ and $p = 0.72$).

### Discussion

This study demonstrates the efficacy and safety of etanercept in the treatment of refractory psoriasis in Taiwanese clinical practice. The dosage of etanercept was 50 mg BIW in the first 12 weeks, which tapered to 25 mg BIW in the next 12 weeks, following the treatment guidelines recommended by Menter et al. The evaluation period was 24 weeks. The results of the present study showed the response rates of PASI 50, PASI 75, and PASI 90 to be 54.5%, 13.6%, and 4.5%, respectively, at Week 12. One double-blind, placebo-controlled, randomized phase III trial with the same dosage of etanercept had response rates of PASI 50, PASI 75, and PASI 90 as 74%, 47%, and 21% at Week 12, respectively.

An open-label study in Greece that used the same dosage of etanercept to treat patients with moderate-to-severe psoriasis revealed that 46.3% patients achieved PASI 75 by Week 12. Another case series study in Taiwan showed that, at Week 12, no statistical significance was noted in PASI improvement between two groups treated with 50 and 25 mg BIW separately (40.8% vs. 49.4%, $p = 0.41$). In this study, 48%, 26%, and 3% of patients achieved PASI 50, PASI 75, and PASI 90, respectively, at Week 12, which were similar to the results of the present study (Table 3). Lower response rates in the present study compared to the data of Western countries might be attributed to the genetic difference, patient characteristics (treatment failed with ≥2 systemic agents plus phototherapy), and small sample size of the study group. Despite these, patients still achieved satisfactory reduction in PASI scores (reduction of 49.8% and 59.8% at Week 12 and Week 24, respectively). There are limited data to elucidate if patients with concurrent PsA will interfere with the treatment effect of biological agents on psoriasis. In the present study, the effect of etanercept on disease

![Figure 1](image)

**Figure 1** Response rates in patients achieving $\geq 25\%$ improvement from baseline in PASI 25, PASI 50, PASI 75, and PASI 90 scores at Weeks 12 and 24. PASI = Psoriasis Area and Severity Index.

### Table 4 Comparison of the mean PASI improvement between patients with and without PsA.

<table>
<thead>
<tr>
<th></th>
<th>PASI improvement (%)</th>
<th>PASI improvement (%)</th>
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<tbody>
<tr>
<td></td>
<td>at Week 12</td>
<td>at Week 24</td>
</tr>
<tr>
<td>(A) With PsA ($n = 6$), %</td>
<td>50.8</td>
<td>70.0</td>
</tr>
<tr>
<td>(B) Without PsA ($n = 16$), %</td>
<td>49.4</td>
<td>56.6</td>
</tr>
<tr>
<td>(C) Total ($n = 22$), %</td>
<td>49.8</td>
<td>59.8</td>
</tr>
<tr>
<td>Value of $p$ for (A) and (B)*</td>
<td>0.94</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*p* Significant at $p < 0.05.$

PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis.

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Week 24</th>
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<tbody>
<tr>
<td>PASI 25</td>
<td>PASI 50</td>
</tr>
<tr>
<td>Present study ($n = 22$), %</td>
<td>86.3</td>
</tr>
<tr>
<td>Chiu et al* ($n = 59$), %</td>
<td>—</td>
</tr>
</tbody>
</table>

PASI = Psoriasis Area and Severity Index.
control was similar for patients both with and without PsA ($p = 0.94$ at Week 12 and $p = 0.90$ at Week 24) (Table 4).

Topical medications including topical corticosteroid, vitamin D3 analogs, and anthralin had been used as adjunctive therapies in patients receiving etanercept for psoriasis treatment.18,19 In the present study, all patients did not receive systemic medication or phototherapy as a concomitant treatment. Topical medications (e.g., coal tar, topical steroid, or vitamin D3 analogs) were prescribed in 14 (63.6%) patients on their request or due to poorer disease control. In patients treated with concomitant topical medications, the PASI improvement at Week 12 and Week 24 was 48.2% and 53.3%, respectively, which showed worse disease control compared to the groups using etanercept as a monotherapy ($p = 0.0002$ at Week 12 and $p < 0.0001$ at Week 24) (Table 5). This result may be attributed to the fact that patients with poor psoriasis control needed more therapeutic options.

One analysis of three clinical trials using etanercept as a mono-therapy in treating psoriasis demonstrated its safety.7 By Week 12, the most common adverse event was upper respiratory infection (9.5%), followed by headache (8.9%) and injection site ecchymosis (6.4%) in the group with etanercept 50 mg BIW. Percentages of serious adverse events and serious infections were estimated to be 1.1% and 0.3%, respectively. In the current study, 10 (45.5%) patients had upper respiratory infection by Week 12, while no headache or injection site injury occurred. No serious adverse event or infection was noted.

In a retrospective analysis of 17 patients with concurrent psoriasis and HBV or hepatitis C, who were treated with anti-TNF-α agents, there was no abnormal liver function or increased viral load.20 The HBV carrier in the present study also showed no sign of viral reaction.

Inflammatory markers for psoriasis had previously been surveyed in one study that enrolled 41 patients treated with etanercept 50 mg BIW. ESR, high-sensitivity CRP, and other markers were measured at baseline and Week 12.12 By Week 12, all inflammatory markers were reduced ($p < 0.001$). Interestingly, better improvement of high-sensitivity CRP and ESR was correlated with more PASI 75 responses. All patients in the present study showed reduction of ESR and CRP by Week 12. Furthermore, there was no correlation between PASI 75 achievement and reduced rates of ESR and CRP.

A retrospective, observational study by Pink et al13 elucidated that 16.7% of psoriasis patients developed positive ANA titers on their first treatment with anti-TNF-α agents. When patients failed to respond with more than one anti-TNF-α agent, the possibility of ANA development might increase. In the current study, no patient received anti-TNF treatment previously. Four (18.2%) patients developed positive ANA and one of them (25.0%) had worse psoriasis control. TNF-α antagonist-induced lupus-like syndrome with the induction of autoantibodies is reportedly more commonly associated with etanercept and infliximab.21 None of the patients in this study had lupus-like syndrome during the treatment course.

Several reports have shown that serum TNF-α level may increase after using etanercept for the treatment of diseases other than psoriasis.14–17 Although there is more detectable TNF-α in blood, it is not active biologically or immunologically. However, TNF-mediated diseases may occasionally be induced.14,22–24 In the present study, 15 of 16 (93.8%) patients had increased serum TNF-α levels at Week 12. Nonetheless, the clinical response (PASI improvement) is not associated with the change in TNF-α level ($R^2 = 0.096$ and $p = 0.72$). Furthermore, diseases commonly associated with increased TNF level, such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, or heart failure, did not occur in the study patients. Longer follow-up of serum TNF-α level after Week 12 was not complete due to patient compliance for blood test and discontinuation of etanercept therapy after 24 weeks. Further large-scale, long-term studies are needed to establish a more comprehensive analysis of the relationships between serum TNF-α level and psoriasis control.

In conclusion, clinical use of etanercept is effective and safe in Asian patients to treat recalcitrant psoriasis. It can reduce serum levels of inflammatory markers, including ESR and CRP, and occasionally induces positive ANA titers with associated treatment failure. Serum TNF-α level may increase after etanercept treatment but does not seem to influence the PASI improvement.

### Table 5 Comparison of the mean PASI improvement between patients treated with and without concomitant topical medications during etanercept treatment

| (A) With concomitant topical medication ($n = 14$), % | Mean PASI improvement (%) at Week 12 | Mean PASI improvement (%) at Week 24 |
| (B) Without concomitant topical medication ($n = 8$), % | 48.2 | 53.3 |
| (C) Total ($n = 22$), % | 51.6 | 68.5 |
| Value of $p$ for (A) and (B)* | 0.0002 | <0.0001 |

* Significant at $p < 0.05$.

PASI — Psoriasis Area and Severity Index.

### References


