Better short-term clinical response to etanercept in Chinese than Caucasian patients with active ankylosing spondylitis

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Abstract Tumor necrosis factor-alpha (TNF-α) inhibitors including etanercept have been demonstrated to be very effective in severe ankylosing spondylitis (AS) in Caucasian patients. However, clinical efficacy of etanercept to treat active AS in Chinese patients has not been reported. In this study, a prospective, open-label trial of etanercept (25 mg BIW), involving 46 AS patients from 16 medical centers of Taiwan, was conducted. Questionnaire was utilized to record demographic data and clinical parameters, including Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Bath AS Global Index (BASGI), Assessment in Ankylosing Spondylitis (ASAS) 20, 50, and 70, and others, before and at different time intervals after etanercept treatment. Laboratory tests

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including blood chemistry, hematology, urine analysis, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were done at baseline and at weeks 4, 8, and 12. In this 12-week study, etanercept demonstrated rapid and significant improvement in the ASAS20 response criteria (91.3%), at as early as 2 weeks of therapy (71.3%). Partial remission of AS was achieved in 49.3% of patients after 12 weeks of treatment. Disease activity (BASDAI) and function (BASFI) were also significantly improved after 12 weeks etanercept treatment (\( p < 0.0001 \) and \( p < 0.0001 \), respectively). In addition, significant increase of chest expansion (2.77 ± 1.69 cm versus 3.56 ± 1.82 cm, \( p = 0.0004 \)) and lumbar flexion (2.11 ± 2.76 cm versus 2.58 ± 3.42 cm, \( p = 0.0075 \)) and significant reduction of occiput-to-wall distance (6.59 ± 7.14 cm versus 5.32 ± 6.65 cm, \( p = 0.0006 \)) were also demonstrated. Both ESR and CRP declined significantly after patients were treated with etanercept. There were no severe adverse effects during the treatment period. Etanercept is generally safe, well tolerated, and effective in Chinese patients with severe AS. Clinical efficacy, including partial remission and BASDAI, is even better in Chinese than in Caucasian patients. Further study is required to assess long-term efficacy and safety in Chinese patients with AS.

**Keywords**  Ankylosing spondylitis · Chinese · Efficacy · Etanercept · Partial remission

**Introduction**

Ankylosing spondylitis (AS), one of the seronegative spondyloarthritides (SpA), occurs predominately in young men and produces pain and stiffness as a result of inflammation of the sacroiliac, intervertebral, and costo-vertebral joints [1, 2]. In Chinese, the frequency of human leukocyte antigen B27 (HLA-B27) in the general population was reported from 4% to 8%, and the prevalence of HLA-B27 in Taiwanese patients with AS was about 95% [3]. Although a genetic factor is suspected, the mechanism of AS is unknown, and there are few effective therapies [3–6].

Early reports by different investigators demonstrated that tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)) was elevated in sera of patients with AS, and TNF-\( \alpha \) messenger RNA (mRNA) was overexpressed in synovial biopsy tissue of inflamed joints in patients with AS [7–9]. By using microarray, Gu et al. [10] observed that the TNF-\( \alpha \) gene was activated in both peripheral blood mononuclear cells (PBMC) and synovial fluid cells, and they hypothesized that TNF-\( \alpha \) plays a significant role in AS. Further evidence for the importance of TNF-\( \alpha \) in AS is the efficacy of anti-TNF medication in treatment of severe AS [11–20].

Etanercept is a bioengineered fusion protein incorporating 2 molecules: soluble tumor necrosis factor receptor (TNFR) p75 and the Fc component of IgG 1. This recombinant product binds specifically and avidly to TNF-\( \alpha \) and lymphotxin, inhibiting their interaction with cell receptors. More recently, etanercept has shown efficacy in treatment of adults with AS [12, 14, 17, 20, 21]. However, until now, clinical study of etanercept to treat active and persistent AS in Chinese patients has not been published in the English-language literature. Such study can help us to understand the efficacy and safety of etanercept to treat active AS in Chinese patients.

**Patients and methods**

**Patients and clinical assessment**

This was a multicenter, open-label study of etanercept in treatment of patients with AS. A total of 46 patients with severe AS who failed nonsteroidal anti-inflammatory drugs (NSAIDs) and/or salazopyrin from 16 medical centers of Taiwan were enrolled within 1 year (2006–2007). Diagnosis of AS was based on modified New York criteria [22].

The primary end point of this study was ASAS20 at 12 weeks [23]. The second end point was to evaluate: (1) efficacy of etanercept in patients with AS by using the ASAS response criteria at 50% and 70% levels at week 12, (2) frequency and time to partial remission achieved by etanercept, and (3) patient global assessment, physician global assessment, nocturnal and total back pain, Bath AS Functional Index (BASFI) [24], and Bath AS Disease Activity Index (BASDAI) [25]. When BASDAI score was >4, disease activity was classified as high [26]. The Chinese version of questionnaires for BASDAI, BASFI, and Bath AS Global Index (BASGI) have already been validated by Wei [27].

Etanercept was suggested for use in active AS (BASDAI >4) and in patients who failed to respond to at least 3 months treatment with more than 2 NSAIDs. Etanercept was provided by Wyeth Company and given by subcutaneous injection 2 times/week. Duration of etanercept treatment for each patient was 12 weeks.

**Spinal mobility test**

Before and after etanercept injection, modified Schober’s test, chest expansion, and occiput-to-wall distance were measured [16].
Other evaluation

In case of peripheral joint involvement, swollen and tenderness were recorded.

Safety measurement

Any serious or nonserious adverse events that occurred during or after treatment were recorded. Laboratory tests including blood biochemistry [blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT)/aspartate aminotransferase (AST)], hematology (white blood cell count, hemoglobin, platelets, etc.), and urine analysis were done at baseline, week 4, and week 12.

Laboratory tests of acute-phase reactants

CRP and ESR were measured at different time points during the 12 weeks treatment.

Statistical analysis

Statistical analyses were carried out using the SPSS statistical package. All data are summarized as mean (standard deviation, SD) for continuous variables and as ratios for categorical variables. The primary efficacy endpoint was the number of responders as determined by ASAS response criteria for improvement at 20% level at week 12. All patients who withdraw before 12 weeks were considered as nonresponders for this endpoint as well as ASAS50 and ASAS70.

Time to achieve partial remission was analyzed by using Kaplan–Meier estimates at all visits. Changes (and percentage changes) from baseline at each visit in the individual components of the ASAS Working Group criteria [visual analog score (VAS) patient global assessment, VAS physician global assessment, VAS total and nocturnal pain, BASFI, BASDAI, spinal mobility measures, complete joint assessment, evaluation of hip involvement, and laboratory assessments of inflammation] were analyzed by using paired t test. Intragroup comparison used single-sample t test or Wilcoxon signed-rank test.

Results

Demographic and baseline characteristics

Summary statistics of demographic characteristics for all patients are presented in Table 1. Mean patient age was 35.8 years, ranging from 19 to 60 years, while 84.8% were male and 15.2% were female (M:F = 5.5:1). About 50% of patients suffered from AS before 23 years old, and mean duration of ankylosing spondylitis was about 9.5 years (112.7 months) for the patients enrolled into this trial. At baseline, mean ± SD (range) height and weight were 166.8 ± 8.39 cm (150–190 cm) and 70.8 ± 13.36 kg (40–103 kg), respectively.

Table 1 Summary of demography and baseline characteristics in 46 patients with ankylosing spondylitis

<table>
<thead>
<tr>
<th>AS (N = 46)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.8 ± 10.75</td>
</tr>
<tr>
<td>Sex (n (%))</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (84.8)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>26.4 ± 10.88</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>112.7 ± 77.51</td>
</tr>
</tbody>
</table>

Table 2 Summary of ASAS and partial remission at different time points after etanercept treatment in 46 patients with ankylosing spondylitis

<table>
<thead>
<tr>
<th>Response</th>
<th>Week 2 (%)</th>
<th>Week 4 (%)</th>
<th>Week 8 (%)</th>
<th>Week 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS20</td>
<td>71.7</td>
<td>87.0</td>
<td>87.0</td>
<td>91.3</td>
</tr>
<tr>
<td>ASAS50</td>
<td>34.8</td>
<td>58.7</td>
<td>63.0</td>
<td>71.7</td>
</tr>
<tr>
<td>ASAS70</td>
<td>13.0</td>
<td>28.3</td>
<td>37.0</td>
<td>45.7</td>
</tr>
<tr>
<td>Partial remission</td>
<td>13.0</td>
<td>30.4</td>
<td>41.7</td>
<td>49.3</td>
</tr>
</tbody>
</table>

Efficacy evaluation

ASAS response criteria

ASAS 20% response was achieved by 33 (71.7%) of the 46 patients at week 2, and by 40 (87.0%) after 4 weeks of study medication (Table 2). The primary efficacy analysis at week 12 showed that 91.3% of patients achieved 20% improvement in the ASAS criteria. ASAS20 response was apparent at as early as 2 weeks after beginning etanercept treatment and increased continuously over the 12 weeks of the study.

Using the ASAS50 and ASAS70 response criteria, 71.7% and 45.7% of patients, respectively, were responders at week 12.

Partial remission

Analysis of time to partial remission by the Kaplan–Meier method is shown in Fig. 1 and the percentage of partial remission in Table 2. Mean days until onset of partial remission was 62 days (about 9 weeks) after receiving the first dose of study drug. After 12 weeks of study drug, 22 patients achieved partial remission, meaning that the
12-week partial remission rate was 49.27% by Kaplan–Meier method. In addition, mean ± SD time to partial remission was 38.3 ± 24.06 days for patients who achieved partial remission during the study period.

**BASDAI**

Measured mean ± SD of BASDAI scores at baseline was 68.18 ± 16.54, while at week 2 it was 38.11 ± 22.56 (p < 0.0001). Sustained improvements were apparent in total BASDAI score (Fig. 2). At the end of treatment (week 12), the mean score decreased to 21.60 ± 20.44 (p < 0.0001) (Table 3). All single items of BASDAI analyzed separately also improved significantly. Intragroup comparison using single-sample t test revealed significant changes at all time points in BASDAI and its independent components.

**Outcome measures: BASFI and other ASAS components**

The results of the BASFI measure are shown in Table 4. Overall, all parameters showed significant improvement after 3 months treatment. Changes over time for individual components, such as patient global assessment or physician global assessment, are shown in Fig. 3.

**Spinal mobility measure**

Improvements in spinal mobility were reflected by an increase in chest expansion measurements and modified Schober test and by decrease in the occiput-to-wall measurement.

Chest expansion at baseline was 2.77 ± 1.69 cm, while at week 2 it was 3.13 ± 1.62 cm (p = 0.0734). Modified Schober index at baseline was 2.11 ± 2.76 cm, while at week 2 it was 2.50 ± 2.79 cm (p = 0.0163). Occiput-to-wall distance at baseline was 6.59 ± 7.14 cm, while at week 2 it was 6.11 ± 6.66 cm (p = 0.0242). Sustained improvements were apparent in all spinal mobility measurements. At the end of treatment (week 12), the mean chest expansion score had increased to 3.56 ± 1.82 cm (p = 0.0004), the mean modified Schober index had increased to 2.58 ± 3.42 cm (p = 0.0079), and the mean occiput-to-wall distance had decreased to 5.32 ± 6.65 cm (p = 0.0006) (Table 5). Intragroup comparison using Wilcoxon signed-rank test revealed significant changes at all time points for all three spinal mobility measurements.

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**Table 3** Summary of BASDAI changes at baseline and at end of etanercept treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of study (week 12)</th>
<th>Change from baseline p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASDAI average score</strong></td>
<td>68.18 ± 16.54</td>
<td>21.60 ± 20.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Fatigue/tiredness</strong></td>
<td>73.02 ± 22.00</td>
<td>24.33 ± 23.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>AS pain</strong></td>
<td>80.37 ± 15.48</td>
<td>22.33 ± 23.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Other pain</strong></td>
<td>65.57 ± 26.75</td>
<td>21.91 ± 22.60</td>
<td>0.0028</td>
</tr>
<tr>
<td><strong>Pressure discomfort</strong></td>
<td>54.63 ± 25.96</td>
<td>17.39 ± 19.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Morning stiffness</strong></td>
<td>67.34 ± 22.53</td>
<td>22.07 ± 21.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Level of morning stiffness</strong></td>
<td>72.78 ± 20.84</td>
<td>22.46 ± 22.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Length of morning stiffness</strong></td>
<td>61.89 ± 27.88</td>
<td>21.67 ± 22.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Acute-phase reactants

Improvements in acute-phase reactants were reflected by a decrease in CRP and ESR levels. CRP level at baseline was 2.37 ± 1.76 mg/dL, while at week 2 it was 0.42 ± 0.65 mg/dL (p < 0.0001). ESR level at baseline was 35.28 ± 23.08 mm/h, while at week 2 it was 13.52 ± 12.28 mm/h (p < 0.0001). Sustained improvements were apparent in CRP and ESR. At the end of treatment (week 12), mean CRP level had decreased to 0.51 ± 0.65 mg/dL (p < 0.0001) and mean ESR level had decreased to 7.76 ± 7.95 mm/h (p < 0.0001) (Table 6).

Drug-related adverse events

Drug-related adverse events were those adverse events assessed by investigators to be related to study medication. Table 7 summarizes incidence of all reported drug-related adverse events during the 12 weeks treatment period. Overall incidence of drug-related adverse events was 20%. The most frequently reported adverse event was liver function impairment (6 patients, 13.0%). All of these

**Table 4** Summary of BASFI changes before and at 12 weeks after etanercept treatment

<table>
<thead>
<tr>
<th></th>
<th>N = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>BASFI average score</td>
<td>57.80 ± 24.87</td>
</tr>
<tr>
<td>Sock aid</td>
<td>48.02 ± 30.32</td>
</tr>
<tr>
<td>Pick up pen</td>
<td>57.33 ± 29.93</td>
</tr>
<tr>
<td>Helping hand</td>
<td>54.70 ± 32.03</td>
</tr>
<tr>
<td>Armless chair</td>
<td>55.24 ± 32.05</td>
</tr>
<tr>
<td>Floor lying on back</td>
<td>60.67 ± 28.35</td>
</tr>
<tr>
<td>Standing unsupported</td>
<td>58.43 ± 30.66</td>
</tr>
<tr>
<td>Climbing 12–15 steps</td>
<td>50.67 ± 32.38</td>
</tr>
<tr>
<td>Looking over shoulder</td>
<td>70.20 ± 27.44</td>
</tr>
<tr>
<td>Physically demanding activity</td>
<td>58.85 ± 28.55</td>
</tr>
<tr>
<td>Full day’s activities</td>
<td>63.85 ± 26.64</td>
</tr>
</tbody>
</table>

**Table 6** Acute-phase reactant changes before and after etanercept treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of study (week 12)</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>p value</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.37 ± 1.76</td>
<td>0.51 ± 0.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>35.28 ± 23.08</td>
<td>7.76 ± 7.95</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table 7** Drug-related adverse events after 12 weeks etanercept treatment in 46 patients with AS

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>6 (13.0%)</td>
</tr>
</tbody>
</table>

**Fig. 3** Patient and physician global assessment before and at 12 weeks etanercept treatment

Acute-phase reactants

Drug-related adverse events were those adverse events assessed by investigators to be related to study medication. Table 7 summarizes incidence of all reported drug-related adverse events during the 12 weeks treatment period. Overall incidence of drug-related adverse events was 20%. The most frequently reported adverse event was liver function impairment (6 patients, 13.0%). All of these
events of liver disorder were recovered at the end of the study or poststudy follow-up.

**Clinical laboratory tests**

All changes after etanercept including in hematology [white blood cells (WBC), Hgb, platelet], biochemistry (BUN, creatinine, AST, ALT, etc.), and urine analysis were minor, and none were clinically significant.

**Discussion**

AS primarily affects sacroiliac joint and the axial skeleton, although peripheral joint involvement may also be an important feature. Common clinical manifestations include low back pain, chest pain, extra-articular tenderness due to enthesitis, uveitis, and joint pain and effusion [1, 2]. Comparatively, there was no significant difference in clinical features, including prevalence of peripheral arthritis, uveitis, enthesitis, and age at onset, between Caucasian and Chinese patients [28, 29]. However, the therapeutic response to either nonsteroidal anti-inflammatory agents (NSAIDs), disease-modifying antirheumatic drug (DMARD) or TNF-α blocker in Chinese patients with AS has been less well studied to date [30, 31]. Therapeutic options for AS are limited. The main targeting therapy is use of NSAIDs. Mild to moderate benefits are shown in AS patients who receive either NSAIDs or DMARDs [5, 6]. Elevation of TNF in serum and biopsy samples of inflamed joints of patients with AS provides the rationale for study of TNF-α inhibitors to reduce clinical symptoms and signs of AS [7–9].

Since 2000, biological therapy with TNF-α inhibitor has been increasingly used in patients with severe AS. Early studies showed that either infliximab or etanercept was successful in treating the limited number of intractable AS patients [11, 12]. The Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) was a large (279 patients) infliximab trial for AS. The results showed that ASAS20 was achieved by 61.2% of the infliximab group versus 19.2% of the control group \(p < 0.001\) [32]. Other parameters including BASDAI, BASFI, CRP, Short-Form 36 (SF-36), and Bath AS Metrology Index (BASMI) were also significantly improved. Gormen et al. [12] reported that 80% of AS patients had good clinical response after 4 months etanercept treatment. A large cohort study (277 patients) in AS patients treated with etanercept showed that ASAS20 was achieved by 59% of patients in the etanercept group and 28% of patients in the placebo group \(p < 0.001\) [13]. A long-term study with etanercept (54 weeks) in 30 patients with active AS showed that 88% were still on treatment with etanercept and 58% of the patients achieved 50% improvement of BASDAI at week 54 [16]. Spinal mobility (BASMI), function (BASFI), and quality of life (SF-36) also improved significantly. Davis et al. [33] in a recent study showed that etanercept significantly improved quality of life and function in AS patients. Similarly, 58.2% of adalimumab-treated patients achieved ASAS20 response, compared with 20.6% of placebo-treated patients, at week 12. Partial remission was 22.1% in the adalimumab-treated group [18].

In this 12-week, prospective, open-label study, etanercept demonstrated rapid and significant improvement in the validated measure, the ASAS20 responsive criteria, at as early as 2 weeks after initiation of therapy. Improvements in these responsive criteria and high levels of ASAS response (ASAS50, ASAS70) continued throughout the study. Consistent with Western reports, all clinical parameters, including BASDAI, BASFI, BASGI, and spinal mobility tests (BASMI), in our 46 patients with active AS also showed remarkable improvement after etanercept. BASDAI and ASAS are the 2 most important tools to evaluate clinical manifestation and disease activity. In this study, BASDAI decreased from 6.8 (baseline) to 2.1 (week 12), which was comparatively superior to the data from 6.4 (baseline) to 3 (week 12) that was recently reported by Brandt et al. [16] and to 3.3 by Choi et al. [20]. Moreover, the partial remission rate at week 12 after etanercept treatment was 49.3%, which was higher when compared with the 31% at week 54 in a German study [16] and 6.5% at week 12 in a Korean study [20]. More importantly, in this study, high early response (71.7%) was observed after 2 weeks of treatment, which was similar to other studies [13, 14]. Better clinical response to TNF-α blocker in Chinese than in Caucasian patients may be due to the easy access to health care in Taiwanese (98% Taiwanese are covered by National Health Insurance) and early management of those critical AS patients who are indicated for TNF-α blocker. Further evidence to correlate with the clinical response at week 2 was the laboratory data for matrix metalloproteinase 3 (MMP3) and interleukin (IL)-6, which were also significantly reduced in serum at week 2 after starting etanercept treatment (data not shown), similar to the report that greater reduction of IL-6, vascular endothelial growth factor (VEGF), and CRP was observed after week 2 of infliximab treatment in patients with AS [34].

We did not perform magnetic resonance imaging (MRI) examination in patients before and after etanercept. Study by German investigators has demonstrated that spinal inflammation was persistently reduced in all AS patients treated with infliximab, etanercept or adalimumab [17, 19, 21, 35]. However, inflammation in some areas of the MRI still remained, and this is why disease may relapse after discontinuation of TNF blockade [7, 19, 35].
Laboratory tests showed, in comparison with baseline, that mean CRP and ESR concentration fell significantly after 2 weeks etanercept treatment. These results correlate well with the clinical response in our patients and with other studies [15–18].

In this study, adverse events observed at a higher rate in etanercept-treated recipients were abnormal liver function tests (13.0%). No serious adverse events including malignancy, sepsis, tuberculosis (TB) or pneumonia were found in this 3 months trial. In fact, long-term use (2–3 years) of either infliximab or etanercept can maintain both efficacy and safety in AS patients [16, 17].

In conclusion, etanercept is generally safe, well tolerated, and effective in Chinese patients with severe AS. Efficacy of short-term etanercept treatment in AS is even better in our Chinese patients than in Caucasian patients. Further studies are needed to determine long-term efficacy and safety of etanercept in Chinese patients with AS.

Acknowledgments Thanks are due to Wyeth Company, which provided us with etanercept samples for this open-label, postmarketing clinical trial.

Conflict of interest statement None.

References