Concise report

Comparison of joint destruction between standard- and low-dose etanercept in rheumatoid arthritis from the Prevention of Cartilage Destruction by Etanercept (PRECEPT) study

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Abstract

Objective. To evaluate the prevention of joint destruction and clinical efficacy of low-dose etanercept (ETN) (25 mg/week) compared with standard-dose ETN (50 mg/week) in RA.

Methods. In this prospective, randomized, open-label study, 70 patients were assigned to receive ETN at either 50 or 25 mg/week for 52 weeks. The primary endpoint was the variation in modified total Sharp score (mTSS), and secondary endpoints were variations in disease activity score in 28 joints (DAS-28), modified HAQ and adverse event rate. Values of mTSS were calculated at baseline and after 52 weeks. Non-progression was estimated as $\Delta mTSS \leq 0.5$, and the non-progression rate was compared between groups.

Results. Mean values at baseline were as follows: disease duration 9.2 years; DAS-28 5.45; and annual progression of mTSS 26.1. No significant differences in background were seen between groups. At 52 weeks, the non-progression rate was significantly less in the 25 mg/week group (36.7%) than in the 50 mg/week group (67.7%) ($P = 0.041$). Mean $\Delta mTSS$ was higher at 25 mg/week (1.03) than at 50 mg/week (−0.13). DAS-28 was significantly improved at 4 weeks, and the effect of treatment lasted for 52 weeks in both groups. No differences in adverse event rates were seen between groups.

Conclusion. Low-dose ETN is not inferior to standard-dose ETN in terms of effects on clinical manifestations. However, in terms of the radiographic non-progression rate, the effects of low-dose ETN may be inferior to the effects of standard-dose ETN.


Key words: rheumatoid arthritis, etanercept, radiographic outcome, safety, low-dose treatment, total modified Sharp score, efficacy, randomized controlled trial, radiographic progression, anti-tumour necrosis factor.

Introduction

RA is a systemic autoimmune disease characterized by persistent synovitis and destruction of bone and cartilage in multiple joints. The efficacy and safety of etanercept (ETN), a fully human soluble TNF receptor–Fc fusion protein [1], in RA patients have been demonstrated in clinical trials [2–4]. Combination therapy with ETN and MTX could inhibit the progression of joint destruction and repair bone erosion [5, 6]. However, therapy with biologics...
forces a significant economic burden on patients. To reduce the treatment cost of biologic agents, low-dose ETN has been administered in clinical practice without evidence. Although clinical symptoms might be improved by low-dose ETN, whether low-dose ETN can inhibit joint destruction remains unclear.

Dosages of biologic agent differ according to the kind of agent. The dosage of intravenously injected agent is determined by the weight of the patient, whereas that of subcutaneous injection agent is constant regardless of weight. The global standard dosage of ETN is 50 mg/week by s.c. injection. This dosage might be excessive for Japanese individuals, who generally show a lower weight than individuals from Western countries. Low-dose ETN treatment at 25 mg/week might be selected to reduce adverse events or the economic burden of patients.

We initiated the Prevention of Cartilage Destruction by Etanercept (PRECEPT) study to address differences in radiographic progression and clinical activity between standard- and low-dose ETN therapies for RA patients. We report the 52-week results, focusing on radiographic progression measured by van der Heijde’s modified total Sharp score (mTSS) [7], variation in disease activity according to DAS in 28 joints (DAS-28) [8] and functional disability as evaluated by the modified HAQ (mHAQ) [9].

Patients and methods

Patients

Eligible patients were >20 years old, fulfilled the ACR 1987 revised criteria for the classification of RA [10] and required treatment with biologics. Exclusion criteria were pregnancy, breastfeeding, Steinbrocker class IV, active infection or significant concomitant disease. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of Osaka City University Medical School and the entry hospital. All patients provided written informed consent prior to participation.

Study protocol

This study was registered with the UMIN Clinical Trials Registry [http://www.umin.ac.jp/ctr/ (UMIN000001798) and conducted at seven sites in Japan between July 2008 and February 2010. Patients were randomly assigned to receive either standard-dose ETN 50 mg/week or low-dose ETN 25 mg/week for 52 weeks. Randomization was performed by registering patients at the registration centre with a centralized allocation method. Dosage, type and combination of DMARDs could be varied according to disease activity. The primary endpoint was variation in mTSS. The secondary endpoints were the variations in DAS-28 and mHAQ, and the adverse event rate.

Radiographic assessment

Radiographs were taken at baseline and week 52 and scored independently using van der Heijde’s modified Sharp method (0–448) [7] by two trained readers blinded to treatment group and clinical response of each patient. Lack of progression was defined as \( \Delta \text{mTSS} \leq 0.5 \) from baseline, and the non-progression rate was compared between groups [11]. Ten percent of films were re-read to analyse intra-reader variability. Intraclass correlation coefficients (ICCs) of inter-observer and intra-observer agreement were good (ICC 0.981, 95% CI 0.969, 0.988 and ICC 0.983, 95% CI 0.971, 0.992, respectively).

Clinical assessment

Disease activity was evaluated using the DAS-28 for ESR and CRP, simplified disease activity index (SDAI) [12] and clinical disease activity index (CDAI) [13] at baseline and after 4, 8, 12, 24 and 52 weeks. We also calculated mHAQ to evaluate improvements in activities of daily living. Safety assessments were performed throughout the study.

Statistical analyses

A sample size of 35 patients per treatment group was calculated to provide >80% power for detecting a significant \( (P < 0.05) \) difference in mean changes in scores of clinical findings between groups. The significance of differences in baseline characteristics between groups was tested using the Mann–Whitney test and Fisher’s exact probability test. The significance of changes in laboratory, DAS-28 and mHAQ values at each time point was tested using the Wilcoxon signed-rank test. Mean DAS-28 and mHAQ values in both groups were compared using the Mann–Whitney U test. Significant differences in radiographic progression were tested using rank-transformed analysis of covariance (ANCOVA). The non-progression rate for radiographic changes was analysed using Fisher’s exact probability test. Multivariate logistic regression analysis was performed to test radiographic progression \( (\Delta \text{mTSS} > 0.5) \) with putative predictive factors. All statistical analyses were two-sided and values of \( P < 0.05 \) were considered significant using StatView version 5.0J software (SAS Institute Japan, Tokyo, Japan).

Results

Baseline characteristics of patients

A total of 70 patients were enrolled in the PRECEPT study and randomly allocated to the ETN 50 mg/week group \( (n = 35) \) and the ETN 25 mg/week group \( (n = 35) \). Discontinuation occurred in eight patients \( (n = 4 \) in each group: adverse events, \( n = 6 \); ineffective, \( n = 1 \); cost, \( n = 1 \).

Baseline characteristics did not differ between groups (Table 1). RF results were positive for 82.8% with ETN 50 mg/week and 80.0% with 25 mg/week. Mean mTSS was very high, at 159.9, and annual progression rate was 26.1.

Radiographic evaluation

Baseline annual mTSS progression tended to be slightly lower in the ETN 25 mg/week group than in the ETN...
However, no significant differences were identified between groups (P = 0.60). Fig. 1A shows the cumulative probability plots of changes from baseline to week 52 for mTSS. Overall radiographic progression tended to be slightly less in the ETN 50 mg/week group than in the ETN 25 mg/week group (P = 0.148).

Mean mTSS and progression in erosion score were negative in the ETN 50 mg/week group (−0.13 and −0.26, respectively), and mean progression in joint space narrowing score was 0.13. Mean ΔmTSS and progression in erosion score and joint space narrowing score in the ETN 25 mg/week group tended to be slightly higher (1.03, 0.47 and 0.56, respectively). However, no significant differences were identified between groups. At 52 weeks the non-progression rate was significantly higher in the ETN 50 mg/week group (67.7%) than in the ETN 25 mg/week group (36.7%; P = 0.041) (Fig. 1A).

Predictive factors for radiographic progression (ΔmTSS >0.5) were analysed using multiple logistic regression analysis, identifying low-dose ETN (25 mg/week) (P = 0.022), RF-positive status (P = 0.017) and age (P = 0.042) as the only variables associated with significantly increased risk of radiographic progression. Odds ratios (ORs) for radiographic progression were 4.63 (95% CI 1.25, 17.13) for low-dose ETN, 27.08 (95% CI 1.82, 403.19) for RF-positive status and 1.08 (95% CI 1.01, 1.17) for age.

Clinical efficacy
At 4 weeks, DAS-28-ESR was significantly improved compared with baseline in both groups (Fig. 1B). However, no significant difference was apparent between groups (P = 0.322) (Fig. 1B). The treatment effect continued in both groups for the full 52 weeks. SDAI and CDAI showed the same tendencies. At 52 weeks, SDAI was 9.2 ± 6.1 for the ETN 50 mg/week group and 9.6 ± 7.3 for the ETN 25 mg/week group (P = 0.994).

Low disease activity rate and remission rate for the ETN 25 mg/week group were 37% and 20%, respectively, at 52 weeks. These rates were identical to those in the ETN 50 mg/week group.

Quality of life and safety
In both groups, mHAQ scores began to decrease at 4 weeks. MHAQ scores for the ETN 50 mg/week group were significantly improved at 12 weeks, but for the ETN 25 mg/week group at 52 weeks (Fig. 1C). MHAQ scores for the ETN 25 mg/week group improved more slowly than those for the ETN 50 mg/week group (Fig. 1C).

Adverse events were reported in six patients overall. In the ETN 50 mg/week group, adverse events were reported in two patients, in the form of pneumonia and emesis. In the ETN 25 mg/week group, adverse events were reported in four patients, comprising three cases of pneumonia and one case of itching. Although none of the

### Table 1 Patient demographics and clinical characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>ETN 50 mg/week (n = 35)</th>
<th>ETN 25 mg/week (n = 35)</th>
<th>Total (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.6 (10.0)</td>
<td>61.7 (11.8)</td>
<td>60.7 (11.0)</td>
</tr>
<tr>
<td>Female, %</td>
<td>85.7</td>
<td>74.3</td>
<td>80.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>51.9 (10.1)</td>
<td>55.3 (9.0)</td>
<td>53.6 (9.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.4 (3.0)</td>
<td>22.8 (2.7)</td>
<td>22.1 (2.9)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>9.3 (6.5)</td>
<td>9.0 (8.0)</td>
<td>9.2 (7.3)</td>
</tr>
<tr>
<td>MTX usage rate, %</td>
<td>80.0</td>
<td>82.9</td>
<td>81.4</td>
</tr>
<tr>
<td>MTX dosage, mg/week</td>
<td>7.8 (2.6)</td>
<td>8.2 (2.5)</td>
<td>8.0 (2.6)</td>
</tr>
<tr>
<td>Steroid dosage, mg/day</td>
<td>4.6 (1.4)</td>
<td>4.1 (1.4)</td>
<td>4.4 (1.4)</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>8.3 (6.6)</td>
<td>7.9 (6.7)</td>
<td>8.1 (6.6)</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>5.5 (5.1)</td>
<td>5.3 (5.2)</td>
<td>5.4 (5.2)</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>2.2 (1.7)</td>
<td>1.8 (2.3)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>52.1 (31.9)</td>
<td>44.5 (28.2)</td>
<td>48.3 (30.0)</td>
</tr>
<tr>
<td>MMP-3, ng/ml</td>
<td>275.6 (251.6)</td>
<td>195.7 (144.1)</td>
<td>235.7 (207.5)</td>
</tr>
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<td>Global VAS, 0–100 mm</td>
<td>62.1 (26.6)</td>
<td>59.7 (25.1)</td>
<td>60.9 (25.7)</td>
</tr>
<tr>
<td>DAS-28-CRP</td>
<td>4.87 (1.18)</td>
<td>4.71 (1.14)</td>
<td>4.79 (1.15)</td>
</tr>
<tr>
<td>DAS-28-ESR</td>
<td>5.53 (1.25)</td>
<td>5.36 (1.24)</td>
<td>5.45 (1.24)</td>
</tr>
<tr>
<td>SDAI</td>
<td>25.7 (12.9)</td>
<td>23.9 (13.5)</td>
<td>24.8 (13.1)</td>
</tr>
<tr>
<td>CDAI</td>
<td>23.5 (11.9)</td>
<td>22.1 (12.3)</td>
<td>22.8 (12.0)</td>
</tr>
<tr>
<td>mTSS</td>
<td>183.2 (102.6)</td>
<td>136.5 (107.2)</td>
<td>159.9 (106.8)</td>
</tr>
<tr>
<td>Erosion score</td>
<td>99.3 (64.4)</td>
<td>74.2 (65.4)</td>
<td>86.8 (65.7)</td>
</tr>
<tr>
<td>JSN score</td>
<td>83.9 (39.3)</td>
<td>62.3 (43.2)</td>
<td>73.1 (42.4)</td>
</tr>
<tr>
<td>Annual mTSS progression</td>
<td>27.5 (21.0)</td>
<td>24.6 (23.4)</td>
<td>26.1 (22.1)</td>
</tr>
</tbody>
</table>

Except where indicated otherwise, values represent mean (S.D.). No significant differences were seen between groups at baseline. VAS: visual analogue scale; JSN: joint space narrowing.
six adverse events were serious, all patients decided to withdraw from ETN treatment.

Discussion

The reason for beginning this study was that the BMI and weight of Japanese individuals tend to be lower than those in Caucasians, so low-dose ETN may be sufficient for treating Japanese patients. Wada et al. [14] reported that low-dose ETN offered the same clinical efficacy as standard-dose ETN, but radiographic joint damage was significantly progressive with low-dose ETN compared with standard-dose ETN among Japanese RA patients. Meanwhile, the clinical effects of high-dose ETN (100 mg/week) have been reported by Weinblatt et al. [15]. They carried out a multicentre, randomized, double-blind, active drug-controlled study and documented that the clinical effects of high-dose ETN were the same as those for standard-dose ETN.

The predictive factors for radiographic progression (∆mTSS > 0.5) were low-dose ETN, RF-positive status and age in multiple regression analysis. We analysed predictive factors for radiographic progression in the low-dose ETN group. RF-positive status, age and SDAI were chosen as predictive factors and only RF-positive status significantly increased the risk of radiographic progression (P = 0.017), with an OR of 22.92 (95% CI 1.77, 297.31) by multiple logistic regression model. Smolen et al. [16] recently reported better clinical, functional and radiographic outcomes for continuing and reducing ETN rather than eliminating ETN in the PRESERVE trial. That trial compared the efficacy and safety of continuing ETN 50 mg/week, reducing ETN from 50 to 25 mg/week and withdrawing ETN while maintaining background MTX over 52 weeks after sustained low disease activity had been induced during 9 months of ETN 50 mg/week with MTX treatment. The purpose of that trial was to clarify whether reduction or elimination of ETN was possible after achieving sustained low disease activity. On the other hand, the purpose of the present PRECEPT study was to determine whether control of disease activity by low-dose ETN was possible from the initiation of treatment. Other than Smolen et al., Raffeiner et al. reported the efficacy of low-dose ETN in maintaining clinical and radiological remission after the achievement of remission by standard-dose ETN in a prospective observational study [17, 18].

From the viewpoint of reducing economic burden, low-dose ETN therapy is a reasonable option if sufficient clinical and radiographic efficacy has been obtained. However, the low dose showed significant inferiority to the standard dose in this study. With the exception of using low-dose ETN therapy to maintain remission after initial standard-dose therapy, prevention of joint destruction may not be maintained with low-dose ETN therapy.

Several limitations must be considered with the present study. First, the study was not double-blinded. As a result, some bias may have been present in clinical evaluations by physicians and patients. However, the evaluation of radiography was performed in a blinded manner. Second, the dosage of MTX in this study was low (mean 8.0 mg/week), because the dosage of MTX approved for use in Japan was only 8 mg/week throughout most of this study. Conversely, the dosage of MTX has been very high in some previous articles [2, 15, 19] that have reported the efficacy of combination ETN and MTX. Third, the sample size was small, as obtaining consent for this randomized study was difficult and delayed recruitment of patients. Further studies may include the long-term results of radiographic progression, comparing standard- and low-dose ETN.
Our study demonstrated that low-dose ETN therapy offered equivalent efficacy to standard-dose ETN therapy in terms of clinical results. However, low-dose ETN therapy was significantly inferior to standard-dose ETN therapy in terms of the radiographic non-progression rate. By the time satisfactory clinical efficacy has been achieved with low-dose ETN, joint destruction might have progressed for 1 year. In particular, RF-positive RA patients who take low-dose ETN therapy have increased potential for radiographic progression and are encouraged to use standard-dose ETN therapy.

### Rheumatology key messages
- Clinically, low-dose etanercept was not inferior to standard-dose etanercept for the treatment of RA.
- Radiographically, low-dose etanercept was inferior to standard-dose etanercept for the treatment of RA.
- RF-positive status was a predictor for radiographic progression in low-dose etanercept RA therapy.

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### References

Clinical vignette

Recurrent parotid pseudogout

A 74-year-old woman with hypertension, diabetes and mild chronic renal insufficiency presented to the emergency department with an acute painful swelling of the right parotid gland. Blood tests showed high ESR (52 mm/h), CRP (5.9 mg/dl), uric acid (5 mg/dl), creatinine (1.8 mg/dl) and urea 124 (mg/dl); results were otherwise normal. CT of the neck and face revealed a homogeneous enlargement of the right parotid gland with a nodular heterogeneous hyperdense centre of 3 cm × 3 cm (Fig. 1A). Fine-needle aspiration revealed an inflammatory reaction and deposits of calcium pyrophosphate dihydrate crystals (Fig. 1B); Gram’s stain and aerobic–anaerobic cultures were negative. Six months after resolution of this first episode she was admitted to hospital due to an ischaemic stroke and on day 3 of hospitalization she developed a new episode of acute pseudogout of the left parotid gland. Fine-needle aspiration showed inflammatory reaction and calcium pyrophosphate dihydrate crystals with negative bacteriological studies, which resolved with colchicine and sulindac. At follow-up 12 months later, the patient has not suffered new episodes under therapy with prophylactic colchicine [1].

Disclosure statement: The authors have declared no conflicts of interest.

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Reference


Fig. 1 CT and microscopy images of atypical parotid pseudogout.

Scale: bar 10 μm = 833 pixels.