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ORIGINAL ARTICLE

A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis

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Abstract
Objectives The aim of this phase 3, double-blind study was to compare the radiographic and clinical effects of etanercept (ETN) versus methotrexate (MTX) over 52 weeks in Japanese subjects with active rheumatoid arthritis.
Methods The study population comprised 550 subjects with inadequate response to ≥1 disease-modifying anti-rheumatic drugs who were randomized to treatment groups of ETN 25 mg twice weekly (BIW; $n = 182$), ETN 10 mg BIW ($n = 192$), or MTX (≤8.0 mg/week; $n = 176$).
Results Of the 550 subjects initially enrolled in the three treatment groups, 21.6 % discontinued the study; a significantly higher proportion of those who withdrew from the study due to lack of efficacy were in the MTX (21.6 %) group compared with the ETN 25 mg (3.3 %) and ETN 10 mg (6.8 %) groups ($P < 0.001$). Mean change from baseline in the modified total Sharp score at week 52 (primary endpoint) was significantly lower in the ETN 25 mg [3.33; standard error (SE), 0.73] and ETN 10 mg (5.19; SE 0.93) groups than in the MTX group (9.82; SE 1.16; $P < 0.0001$ vs. either ETN group). Compared with subjects receiving MTX, significantly higher percentages of subjects treated with ETN 25 and 10 mg achieved American College of Rheumatology (ACR) ACR20 and ACR50 response rates at all time points ($P < 0.01$). ETN was well-tolerated, with no unexpected safety findings.
Conclusions ETN 25 mg BIW and ETN 10 mg BIW slowed radiographic progression and improved clinical outcomes more effectively than MTX in this Japanese population.

Keywords Etanercept · Methotrexate · Randomized controlled trial · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic disease that is characterized by joint inflammation that often leads to bone destruction. The resulting structural damage to bones can severely affect the functional ability of patients with RA [1, 2]. Regardless of the disease duration, radiographic progression tends to occur at a constant rate [3] and can continue to progress even in patients whose disease activity seems to be under control [4, 5].

Therapeutic targets for patients with RA are increasingly being defined by improvements in both clinical and radiographic outcomes; therefore, new treatment strategies are needed that aim to achieve these goals [6]. Although conventional disease-modifying anti-rheumatic drugs (DMARDs) may show improvements in clinical and functional outcomes of subjects with active RA, they may not be sufficiently efficacious in slowing joint destruction [7–9]. Previous studies have demonstrated that tumor necrosis factor inhibitors (TNFi) improve outcomes in terms of both clinical disease activity and radiographic

progression [10–16]. Etanercept (ETN), a TNFi, has been shown to delay joint destruction in European and North American populations and has since been approved for this indication in the USA and European Union (in 2000 and 2002, respectively) [17, 18]. Here, we report our phase 3, double-blind study which was undertaken to compare the effects of ETN with that of the DMARD, methotrexate (MTX), on radiographic progression, disease activity, and safety over 52 weeks in Japanese subjects with active RA.

Subject and methods

Study design and population

This was a phase 3, randomized, controlled, double-blind, parallel-group, outpatient study in which individuals with active RA across 40 sites in Japan were enrolled. All such individuals of Japanese ancestry aged 20 through 75 years and living in Japan at the time of written consent were eligible. Study subjects had to meet the American Rheumatism Association 1987 Revised Criteria for Classification of RA [19]: ≥6 swollen joints, ≥6 tender/painful joints, and either elevated erythrocyte sedimentation rate (ESR) ≥28 mm/h, or C-reactive protein (CRP) ≥2.0 mg/dL, or a morning stiffness duration of ≥45 min. Only those RA patients who had a diagnosis of ≤10 years from screening and less than satisfactory response to at least one DMARD were included in this study.

Subjects were excluded from participating in the study if they had: (1) previously received ETN or any other TNFi; (2) received any DMARDs, changed their oral corticosteroid doses (up to 10 mg/day prednisone allowed), or received corticosteroid injections within 4 weeks of the baseline visit; (3) received >1 non-steroidal anti-inflammatory drug (NSAID), changed dose, or exceeded the maximum recommended dose within 2 weeks of the baseline visit; (4) received investigational drugs or biologics within 3 months of the baseline visit; (5) received cyclophosphamide within 6 months of the baseline visit; (6) had a history of MTX treatment associated with clinically significant toxicity or a worsening of RA symptoms while receiving MTX; (7) showed contraindications for ETN or MTX treatment, including serious active infection, active tuberculosis (TB), demyelinating disorders or history of such disorders, or significant concurrent medical diseases.

Upon enrollment, subjects were randomly assigned to one of three treatment groups (1:1:1 ratio) to receive either monotherapy ETN 25 mg twice weekly (BIW), ETN 10 mg BIW, or MTX (up to 8.0 mg) once weekly (QW). The allocation of eligible subjects to the treatment groups was performed through the computerized randomization/enrollment (CORE) system. The initial dose of MTX was 6 mg/week (divided into three doses each, administered at 12 ± 2-h intervals over a 2-day period) at baseline and was increased to 8 mg/week if an inadequate response was reported at week 8. ETN was administered subcutaneously (SC), and MTX was given as oral capsules. For study blinding, subjects randomized to ETN received placebo capsules and subjects randomized to MTX received SC placebo injections. Subjects participated in this study for approximately 60 weeks, which included a screening period of up to 4 weeks, a 52-week treatment period, and a 4-week follow-up period. During the first 24 weeks of the study, subjects were allowed to receive a stable dose of ≤10 mg/day of prednisone or equivalent and/or one NSAID at no greater than the maximum recommended dose. After week 24, corticosteroid and NSAID dosing could be adjusted.

This study was conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. Independent Ethics Committee (IEC) approval of the protocol was obtained. All subjects signed and dated an IEC-approved informed consent form before study screening.

Study endpoints and assessments

The primary efficacy endpoint was the change in modified total Sharp score (mTSS; using the modified Sharp/van der Heijde scoring system [20]) from baseline to week 52. Secondary radiographic efficacy endpoints included changes in mTSS from baseline to week 24 and changes in erosion score and joint space narrowing (JSN) from baseline to weeks 24 and 52, as well as the percentages of subjects with no progression of joint destruction [mTSS change ≤0.0, ≤0.5, ≤3.0, or ≤smallest detectable difference (SDD), respectively] at week 52.

Radiographs of the hands, wrists, and forefeet were taken at baseline and at weeks 24 and 52. Subjects who discontinued before the final scheduled visit had radiographs taken at the time of discontinuation if the timing was >30 days since the prior radiographs were taken. Two blinded independent readers viewed and scored the digitalized X-ray images for erosions and JSN, and these data were used to calculate a total joint erosion score (0–280) and a total JSN score (0–168). The total mTSS score (0–448) was defined as the total joint erosion score plus the total JSN score. In addition, analyses were performed to examine the relative efficacy of the treatments on mTSS change at week 52 in clinically relevant subgroups. These subgroups included prior MTX use (yes or no), baseline progression rate of mTSS (quartiles: ≤8.6, >8.6 and ≤15.6,

>15.6 and ≤28.8, >28.8), tender joint count (quartiles: ≤9.0, >9.0 and ≤14.0, >14.0 and ≤22.0, >22.0), CRP (mg/dL quartiles: ≤0.3, >0.3 and ≤1.5, >1.5 and ≤3.0, and >3.0), and duration of disease (by ≤3 vs. >3 years).

Clinical efficacy endpoints included the number (%) of subjects achieving American College of Rheumatology (ACR) 20/50/70 response rates over 52 weeks, and the mean change from baseline over 52 weeks for the following: (1) disease activity score [DAS, 4 domains-ESR; calculated using the Ritchie Articular Index (53 joints in 26 units for tenderness), swollen joints (44 joints), ESR, and general health score]; (2) disease activity score in 28 joints [DAS28, 4 domains-ESR; tender joints (0–71), swollen joints (0–68), and physician and patient global assessment (0–10); (3) patient general health visual analog scale (VAS; 0–100 mm); (4) pain VAS (0–100 mm); (5) CRP levels; (6) ESR levels. Functional ability was assessed by the change from baseline at week 52 in the Health Assessment Questionnaire-Disability Index (HAQ-DI).

After the protocol was finalized, the analysis was expanded to include additional endpoints: the number of subjects (%) achieving DAS28 remission (DAS28 <2.6) and the number of subjects (%) achieving DAS28-based European League Against Rheumatism (EULAR) good/moderate/no response over 52 weeks.

Safety assessments included complete medical history and physical examination, vital sign measurements, chest X-ray, 12-lead electrocardiogram, and laboratory evaluations (the National Cancer Institute criteria for determining laboratory results of potential clinical importance were used and included blood chemistry, hematology, urinalysis, and autoantibodies). Physician and subject reports of adverse events (AEs) were collected throughout the study. An AE was defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations that occurred in a person given a test article or in the clinical study. An AE was deemed serious (SAE) if it resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, or resulted in persistent or significant disability or incapacity, cancer, congenital anomaly or birth defect, or any important medical event that jeopardized the subject and required medical or surgical intervention. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA; ver. 13) and classified by treatment relationship and severity.

Blood samples for ETN serum concentrations were collected for pharmacokinetic evaluation at weeks 12, 24, and 52 and analyzed using a validated enzyme-linked immunosorbent assay method (range of quantitation 78.1–5000 pg/mL).

Statistical analysis

The radiographic efficacy analysis was based on the radiographic intent-to-treat (rITT) population which included all subjects who received at least one dose of the assigned test article and provided radiographic data for the baseline and at least one post-baseline visit and did not include subjects who withdrew from the study within 1 month of the baseline visit. The clinical efficacy analysis was based on a modified intent-to-treat (mITT) population that included all subjects who received at least one dose of the assigned test article. The safety population included all subjects who received at least one dose of test article.

The primary efficacy endpoint, the change in mTSS from baseline to 52 weeks, and other radiographic variables were analyzed using the analysis of covariance (ANCOVA) model based on rank transformed data, adjusting for rank baseline, with study center, prior MTX use, and treatment group as the factors in the model. The primary radiographic efficacy analysis was based on a 52-week annualized change in mTSS score. Radiographic nonprogression using different cut-offs (mTSS change ≤0.0, ≤0.5, ≤3.0, and ≤SDD) and ACR20/50/70 response rates were analyzed using the Cochran–Mantel–Haenszel approach, stratified by study center and prior MTX use, as were the evaluation of DAS28 remission and EULAR response rates. For continuous clinical efficacy endpoints, changes from baseline were analyzed using an ANCOVA model, with baseline values as a covariate and study center, prior MTX use, and treatment as factors. For missing radiographic data, the linear interpolation or extrapolation method was used for the primary radiographic efficacy analysis. For missing clinical data, the last observation carried forward method was used for the primary clinical efficacy analyses. Descriptive statistics, such as means and standard deviations (SD), were provided for demographic data and baseline characteristics. Safety data during the study were compared between treatment groups using Fisher's exact test procedures for categorical endpoints and the ANCOVA model with a baseline value as covariate for continuous endpoints.

For the subgroup analyses, subgroup-by-treatment interactions were tested for each group individually by adding a subgroup main effect and subgroup-by-treatment interaction term to the primary analysis model. Tables of means by treatment and subgroup were produced with pairwise comparisons.

Sample size was determined based on the results of the U.S. [17] and European studies [18]. A total of 540 subjects were deemed necessary to show a difference between the ETN 25 mg and MTX treatment groups, the primary comparison of interest. This sample size did not afford significant power to detect differences for the secondary

comparisons of ETN 25 versus 10 mg, or ETN 10 mg versus MTX.

Results

Subject disposition and baseline characteristics

All 550 randomized study subjects ($n = 182$, ETN 25 mg; $n = 192$, ETN 10 mg; $n = 176$, MTX) received at least one dose of study drug and were included in the mITT and safety populations (Fig. 1). Of these, 542 subjects were included in the rITT population; eight subjects with no post-baseline radiographic data were excluded. Overall, 431 (78.4 %) subjects completed the study. Over the 52-week period, subjects in the MTX arm received a median weekly dose of 6.0 mg (mean 6.54 mg, SD 0.83). The rate of study discontinuation was significantly higher in the MTX treatment group than in the ETN treatment groups ($P \leq 0.01$), with 38 (21.6 %) subjects in the MTX group withdrawing due to lack of efficacy compared with six (3.3 %) in the ETN 25 mg group and 13 (6.8 %) subjects in the ETN 10 mg group (overall $P < 0.001$). The number of subjects who withdrew due to AEs was comparable between groups (overall $P = 0.173$).

Demographics and baseline disease characteristics in the mITT population were comparable among the ETN 25 mg, ETN 10 mg, and MTX groups with the exception of the mean body mass index (BMI; $P = 0.019$; Table 1); pairwise ANOVA showed that the ETN 25 mg and MTX groups were significantly different. Prior to study initiation, all subjects (100 %) had received DMARD treatment, including MTX.

At baseline, the mean mTSS was 41.98 (SD 41.51) in the ETN 25 mg, 45.17 (SD 38.75) in the ETN 10 mg, and 43.01 (SD, 46.78) in the MTX groups and did not differ significantly between groups ($P = 0.760$). The mTSS progression rates [calculated by dividing the baseline mTSS by the duration of disease (years)] was similar across all three treatment groups ($P = 0.322$), with progression rates of 25.11 (SD 34.20), 31.42 (SD 45.47), and 27.82 (SD 40.65) in the ETN 25 mg, ETN 10 mg, and MTX groups, respectively.

Concomitant therapy

Concomitant use of NSAIDs and corticosteroids was common among the subjects during the study. In the ETN 25 mg, ETN 10 mg, and MTX groups, 158 (86.8 %), 161 (83.9 %), and 149 (84.7 %) subjects, respectively, received oral NSAIDs (overall $P = 0.719$). Concomitant oral corticosteroid use was reported by 104 (57.1 %), 124 (64.6 %), and 94 (53.4 %) subjects in the ETN 25 mg, ETN 10 mg and MTX groups, respectively (overall $P = 0.086$).

Efficacy

Radiographic outcomes

For the primary efficacy endpoint, the change from baseline at week 52 in mTSS was significantly less in subjects

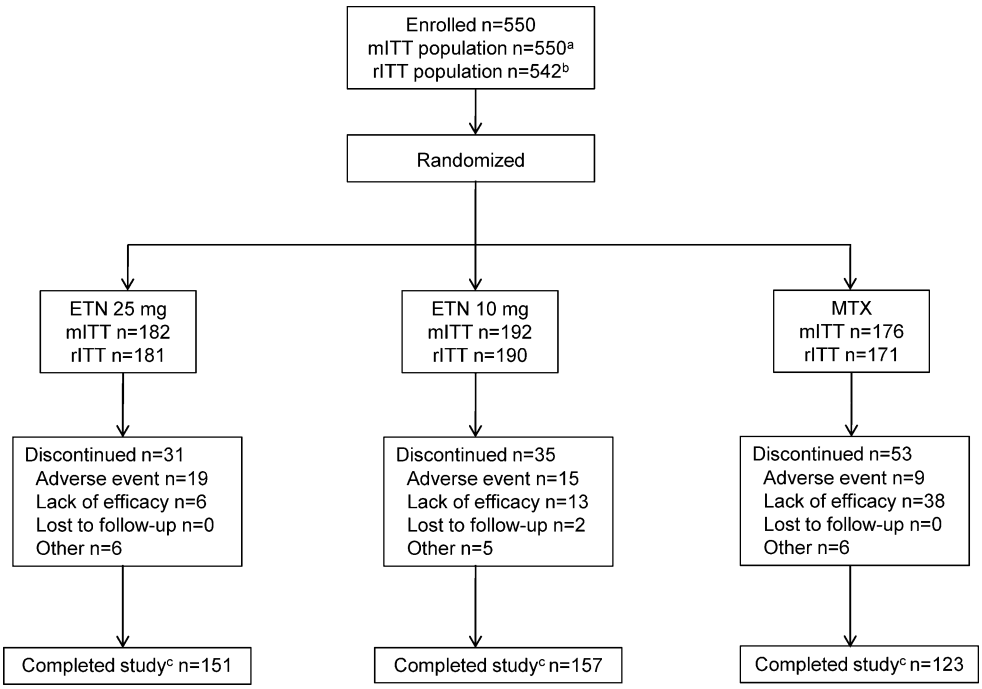

Fig. 1 Subject disposition. [a] All subjects in the modified intent-to-treat (*mITT*) population were also in the safety population, [b] 8 subjects did not have baseline or post-baseline radiographic data and were not included in the radiographic intent-to-treat (*rITT*) population, [c] all subjects who completed the 52-week treatment phase also completed the 4-week follow-up period. *ETN* Etanercept, *MTX* methotrexate

Table 1 Baseline demographics and disease characteristics

	ETN 25 mg ($n = 182$)	ETN 10 mg ($n = 192$)	MTX ($n = 176$)
Demographic characteristics[a]			
Age, years, mean (SD)	51.8 (11.1)	51.5 (12.2)	50.4 (11.9)
Sex, *n* (%)			
Male	37 (20.3)	38 (19.8)	36 (20.5)
Female	145 (79.7)	154 (80.2)	140 (79.6)
BMI, kg/m^2, mean	22.8	22.1	21.7
Prior corticosteroid use, *n* (%)	109 (59.9)	129 (67.2)	105 (59.7)
Prior NSAID use, *n* (%)	169 (92.9)	173 (90.1)	164 (93.2)
Prior MTX use, *n* (%)	122 (67.0)	123 (64.1)	108 (61.4)
Prior DMARD use including MTX, *n* (%)	182 (100.0)	192 (100.0)	176 (100.0)
Prior DMARD use excluding MTX, *n* (%)	154 (84.6)	155 (80.7)	148 (84.1)
Baseline disease characteristics, mean (SD)[a]			
Duration of disease, years	3.0 (2.6)	2.9 (2.7)	3.0 (2.7)
RF+, *n* (%)	142 (78.0)	147 (75.6)	133 (75.6)
DAS	4.1 (0.9)	4.0 (0.9)	4.1 (1.0)
DAS28	5.8 (1.0)	5.7 (1.2)	5.8 (1.1)
Tender joint count	17.5 (11.2)	16.3 (10.6)	17.1 (10.8)
Swollen joint count	14.0 (8.8)	14.2 (9.0)	13.8 (7.8)
Physician global assessment	6.2 (1.9)	6.2 (1.8)	6.3 (2.0)
Patient global assessment	6.0 (2.0)	6.1 (2.2)	6.0 (2.3)
Patient General Health VAS	55.7 (21.7)	58.7 (23.1)	58.4 (24.0)
Pain VAS	52.6 (21.5)	54.4 (23.1)	54.9 (23.6)
CRP, mg/L	22.1 (24.2)	22.9 (29.8)	21.1 (22.3)
ESR, mm/h	43.7 (27.6)	42.0 (29.4)	42.6 (28.2)
HAQ-DI	1.1 (0.7)	1.2 (0.7)	1.0 (0.7)
Baseline disease characteristics, mean (SD)[b]	ETN 25 mg ($n = 181$)	ETN 10 mg ($n = 190$)	MTX ($n = 171$)
mTSS, mean (SD)	41.98 (41.51)	45.17 (38.75)	43.01 (46.78)
mTSS progression rate[c], mean (SD)	25.11 (34.20)	31.42 (45.47)	27.82 (40.65)
Erosion score, mean (SD)	25.23 (23.88)	26.66 (22.11)	25.09 (26.30)
JSN score, mean (SD)	16.75 (19.11)	18.50 (19.14)	17.92 (21.93)

ETN etanercept, *MTX* methotrexate, *SD* standard deviation, *BMI* body mass index, *NSAID* non-steroidal anti-inflammatory drugs, *DMARD* disease-modifying anti-rheumatic drugs, *RF+* rheumatoid factor positive, *DAS* disease activity score, 4 variables-ESR, *DAS28* disease activity score in 28 joints, *VAS* visual analogue scale, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire Disability Index, *mTSS* modified total Sharp score, *JSN* joint space narrowing, *mITT* modified intent-to-treat, *rITT* radiographic intent-to-treat

[a] mITTpopulation

[b] rITT population

[c] The baseline progression rate of mTSS was calculated by dividing the baseline mTSS by the duration of disease

receiving ETN 25 mg [3.33; standard error (SE) 0.73] and ETN 10 mg (5.19; SE 0.93) than in subjects in the MTX group (9.82; SE 1.16; $P < 0.0001$ vs. either ETN group; Fig. 2a). Significant differences in mTSS change from baseline were also observed at week 24 (ETN 25 mg: 1.74, SE 0.45; ETN 10 mg: 2.42, SE 0.48; MTX group: 5.11, SE 0.58; $P < 0.0001$ for MTX vs. either ETN group). For the secondary radiographic endpoints at week 52, the mean change from baseline in the erosion score paralleled that of the mTSS and was significantly lower in the ETN 25 mg (2.03; SE 0.48) and ETN 10 mg (2.75; SE 0.57) groups than in the MTX group (5.43; SE 0.64; $P < 0.0001$ vs. either ETN group; Fig. 2b). Similarly, the mean change from baseline in the JSN score was significantly lower in the ETN 25 mg (1.31; SE 0.33) and ETN 10 mg (2.44; SE 0.42) groups than in the MTX group (4.39; SE 0.66;

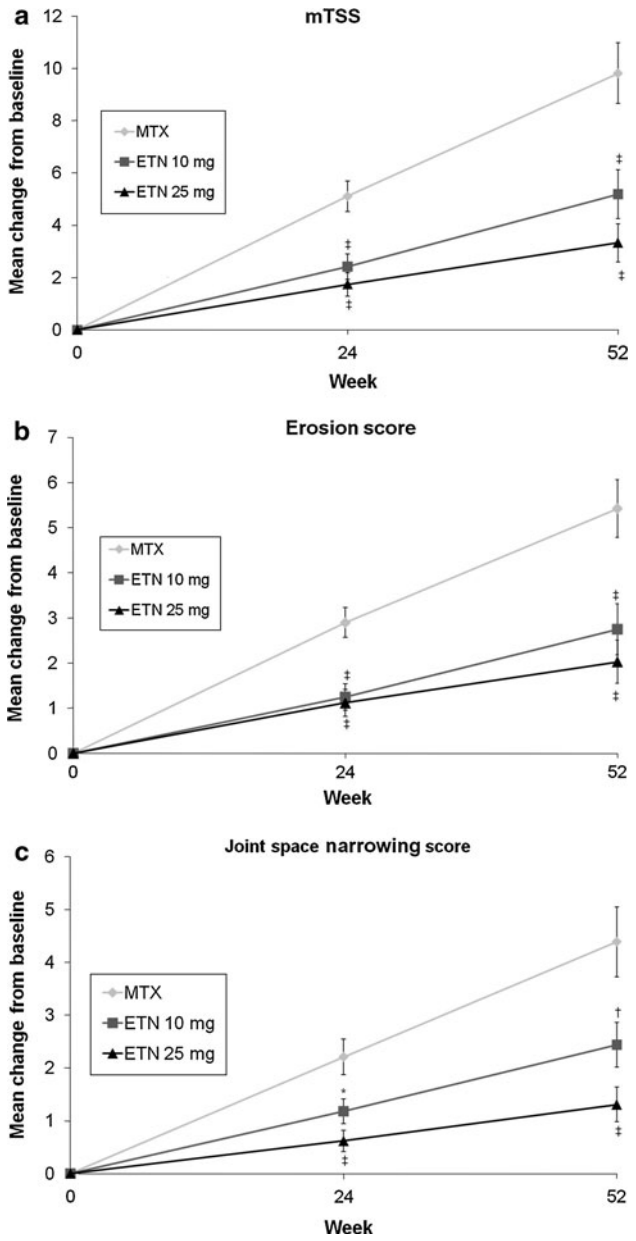

Fig. 2 Mean change from baseline in the modified total Sharp score (mTSS), erosion, and joint space narrowing (JSN) scores at weeks 24 and 52 for subjects with rheumatoid arthritis (RA) after treatment. Analyses were performed on the rITT population. *Error bars* SE. $^{*}P = 0.0013$ vs. MTX and $P = 0.0186$ vs. ETN 25 mg; $^{\dagger}P < 0.001$ vs. MTX; $^{\ddagger}P < 0.0001$ vs. MTX

$P < 0.0001$ vs. ETN 25 mg group; $P = 0.0006$ vs. ETN 10 mg group; Fig. 2c). Significantly more subjects achieved mTSS changes of ≤0, ≤0.5, ≤3.0, and ≤SDD in the ETN 25 mg (43.6, 49.2, 68.0, and 94.5 %, respectively) and ETN 10 mg (41.6, 45.3, 64.2, and 88.9 %, respectively) treatment groups than in the MTX group (22.8, 25.7, 46.8, and 81.9 %, respectively) at week 52 ($P < 0.05$ for ETN 25 and 10 mg groups vs. MTX for all comparisons; Table 2).

The subgroup analyses of this population of subjects found no statistically significant main effect of prior MTX use, tender joint count, or swollen joint count on the change from baseline in mTSS. However, there was a statistically significant main effect of CRP levels ($P < 0.0001$), baseline progression rate of mTSS ($P < 0.0001$), and disease duration ($P < 0.0004$). Higher CRP, higher baseline progression rate of mTSS, lower disease duration associated with greater radiographic progression. No significant subgroup-by-treatment interaction for any subgroup factor was found. In addition, on pairwise comparison, patients with high baseline tender joint counts of ≥22 at week 24 ($P = 0.0275$) and a high baseline CRP level of >3.0 mg/L at week 24 ($P = 0.0324$) and 52 ($P = 0.0345$) showed less mean change in mTSS with ETN 25 mg than with ETN 10 mg.

Clinical and functional outcomes

At week 52, the ACR20, ACR50, and ACR70 rate responses were achieved by a significantly greater percentage of subjects receiving ETN 25 and 10 mg compared with MTX (Table 2). The mean improvement in DAS at week 52 was significantly higher in the ETN 25 mg (49.3 %) and ETN 10 mg (46.6 %) groups than in the MTX group (34.8 %; $P < 0.0001$ vs. either ETN group). Similarly, the improvement in DAS28 was higher in the ETN 25 mg (42.9 %) and ETN 10 mg (39.0 %) groups than in the MTX group (29.1 %; $P < 0.0001$ vs. either ETN group). The proportions of subjects achieving DAS28 remission were 34.1, 31.9, and 19.3 % in the ETN 25 mg, ETN 10 mg, and MTX groups, respectively ($P < 0.01$ for MTX vs. either ETN group).

A EULAR good response was achieved at week 52 by 50.0, 44.2, and 29.7 % of subjects in the ETN 25 mg, ETN 10 mg, and MTX groups, respectively, and a EULAR moderate response was achieved by 39.0, 35.8, and 40.0 % of subjects in the ETN 25 mg, ETN 10 mg, and the MTX treatment groups, respectively. A statistically significantly greater proportion of subjects in both the ETN 25 mg and ETN 10 mg treatment groups achieved a EULAR response compared with the MTX treatment group ($P < 0.0001$ for ETN 25 mg vs. MTX; $P = 0.0009$ for ETN 10 mg vs. MTX).

At week 52, the tender joint count, swollen joint count, physician global assessment, patient global assessment, patient general health VAS, pain VAS, CRP levels, and ESR levels had all significantly improved from baseline in both the ETN 25 mg and ETN 10 mg groups compared with the MTX treatment group (Table 2). In addition, there was a significantly greater improvement in physician global assessment scores and tender joint counts in the ETN 25 mg group versus the ETN 10 mg group ($P < 0.05$).

Table 2 Summary of efficacy responses at week 52 by treatment group

Efficacy endpoint	Proportions of subjects achieving endpoint, *n*/*N* (%)		
	ETN 25 mg	ETN 10 mg	MTX
mTSS change ≤0	79/181 (43.6)*	79/190 (41.6)*	39/171 (22.8)
mTSS change ≤0.5	89/181 (49.2)‡	86/190 (45.3)*	44/171 (25.7)
mTSS change ≤3.0	123/181 (68.0)*	122/190 (64.2)*	80/171 (46.8)
mTSS change ≤SDD	171/181 (94.5)†,§	169/190 (88.9)#	140/171 (81.9)
ACR20	143/182 (78.6)*	145/191 (75.9)†	110/176 (62.5)
ACR50	113/182 (62.1)‡	114/192 (59.4)‡	65/176 (36.9)
ACR70	66/182 (36.3)‡	65/192 (33.9)‡	28/176 (15.9)
DAS28 remission	62/182 (34.1)†	61/191 (31.9)†	34/176 (19.3)
EULAR good response[a]	91/182 (50.0)‡,§	84/190 (44.2)*	52/175 (29.7)
EULAR moderate response[a]	71/182 (39.0)‡,§	68/190 (35.8)*	70/175 (40.0)
Assessment	Mean score (% improvement from baseline)		
	ETN 25 mg ($n = 182$)	ETN 10 mg ($n = 192$)	MTX ($n = 176$)
DAS	2.1 (49.3)‡	2.2 (46.6)‡	2.7 (34.8)
DAS28	3.3 (42.9)‡	3.5 (39.0)‡	4.1 (29.1)
Tender joint count	4.3 (74.2)‡,§	5.6 (67.6)	6.9 (57.2)
Swollen joint count	3.5 (74.5)‡	4.4 (68.1)*	6.3 (52.1)
Physician global assessment	2.1 (64.9)‡,§	2.6 (57.7)‡	3.6 (41.8)
Patient global assessment	3.0 (44.5)‡	3.1 (46.0)‡	4.0 (24.3)
Patient General Health VAS	24.6 (46.5)‡	26.3 (51.0)*	35.0 (31.4)
Pain VAS	24.3 (51.4)‡	25.2 (49.7)‡	34.9 (28.7)
CRP, mg/L	7.0 (83.3)‡	10.0 (78.2)*	15.9 (50.0)
ESR, mm/h	24.8 (38.9)‡	27.3 (25.3)#	32.3 (11.0)
HAQ-DI	0.5 (58.1)‡	0.6 (53.7)†	0.7 (29.2)

* $P < 0.001$ vs. MTX, † $P < 0.01$ vs. MTX, ‡ $P < 0.0001$ vs. MTX, § $P < 0.05$ vs. ETN 10 mg, # $P < 0.05$ vs. MTX

SDD Smallest detectable difference, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism

Based on the last observation carried forward method of analysis and mITT population unless otherwise stated

[a] Statistical test (Cochran–Mantel–Haenszel test) based on overall difference between groups

Functional ability, as measured by HAQ-DI, significantly improved from baseline to week 52 in the ETN 25 mg (58.1 %) and ETN 10 mg (53.7 %) groups versus the MTX (29.2 %) group ($P < 0.0001$ vs. ETN 25 mg; $P = 0.0040$ vs. ETN 10 mg).

Safety

A total of 403 (73.3 %) subjects reported treatment-emergent adverse events (TEAEs), excluding infections, and 300 (54.5 %) subjects reported treatment-emergent infections (Table 3). Seventeen subjects (9.3 %) in the ETN 25 mg group, 14 subjects (7.3 %) in the ETN 10 mg group, and eight subjects (4.5 %) in the MTX group withdrew from the study due to an AE, but the difference was not statistically significant among the treatment groups ($P = 0.208$).

Table 4 presents the TEAEs and treatment-emergent infections reported in ≥5 % of subjects; the rates of both were generally similar among the three treatment groups. The most common TEAEs were increased liver enzymes, rash, eczema, and constipation. Notably, the rate of increased liver enzymes was significantly higher in the MTX treatment group. The most common treatment-emergent infections were nasopharyngitis, upper respiratory tract infection, and pharyngitis. With regards to differences in treatment-emergent infections between the three treatment groups, a significantly higher rate of pneumonia was observed in the ETN 10 mg group (3.1 %) than the ETN 25 mg (1.1 %) and MTX treatment groups (0.0 %; $P = 0.032$). Significantly more subjects reported periodontitis in the ETN 25 mg group (2.7 %) than the ETN 10 mg (0.5 %) and MTX (0.0 %; $P = 0.033$) groups.

Table 3 Safety summary by treatment group

System organ class	No. of subjects (%)				
	ETN 25 mg ($n = 182$)	ETN 10 mg ($n = 192$)	MTX ($n = 176$)	Total ($n = 550$)	*P* value
Any TEAE (excluding infections)	128 (70.3)	150 (78.1)	125 (71.0)	403 (73.3)	0.164
Injection site reactions ≥1	37 (20.3)	40 (20.8)	3 (1.7)	–	–
Treatment-emergent infections	102 (56.0)	106 (55.2)	92 (52.3)	300 (54.5)	0.757
Any SAE (excluding infections)	11 (6.0)	8 (4.2)	10 (5.7)	29 (5.3)	0.701
Serious infections	0	2 (1.0)[b]	1 (0.6)[c]	3 (0.5)	0.656
Demyelinating disease	0	0	0	0	–
Malignancy	2 (1.1)[a]	0	2 (1.1)[d]	4 (0.7)	0.399
Deaths	0	0	0	0	–

Overall *P* value: comparison among treatment arms

TEAE Treatment-emergent adverse event, *SAE* serious adverse event

[a] 2 cases of breast cancer

[b] 1 case each of pneumonia and urinary tract infection

[c] Appendicitis

[d] 1 case of each of breast cancer and prostate cancer

Table 4 Treatment-emergent adverse events and treatment-emergent infections occurring in ≥5 % of subjects

System organ class: preferred term	No. of subjects (%)				
	ETN 25 mg ($n = 182$)	ETN 10 mg ($n = 192$)	MTX ($n = 176$)	Total ($n = 550$)	*P* value
TEAEs					
Alanine aminotransferase, increased	10 (5.5)	12 (6.3)	22 (12.5)	44 (8.0)	0.034
Aspartate aminotransferase, increased	8 (4.4)	8 (4.2)	18 (10.2)	34 (6.2)	0.035
Rash	10 (5.5)	10 (5.2)	8 (4.5)	28 (5.1)	0.941
Constipation	7 (3.8)	6 (3.1)	9 (5.1)	22 (4.0)	0.632
Insomnia	2 (1.1)	9 (4.7)	9 (5.1)	20 (3.6)	0.055
Pruritis	5 (2.7)	12 (6.3)	3 (1.7)	20 (3.6)	0.063
Diarrhea	10 (5.5)	5 (2.6)	5 (2.8)	20 (3.6)	0.291
Treatment-emergent infections					
Nasopharyngitis	37 (20.3)	45 (23.4)	43 (24.4)	125 (22.7)	0.620
Upper respiratory tract infection	21 (11.5)	20 (10.4)	20 (11.4)	61 (11.1)	0.941
Pharyngitis	15 (8.2)	18 (9.4)	12 (6.8)	45 (8.2)	0.687

Overall *P* value: comparison among treatment arms

TEAE Treatment-emergent adverse event, *ETN* etanercept, *MTX* methotrexate

SAEs (excluding infections) were reported in 11 (6.0 %) subjects in the ETN 25 mg group, eight (4.2 %) in the ETN 10 mg group, and 10 (5.7 %) in the MTX group. No particular patterns were present among the reported SAEs, and no statistically significant differences were observed among treatment groups in the incidence of any individual SAE. Serious infections were observed in only three subjects (0.5 %): one (0.6 %, appendicitis) in the MTX group and two (1.0 %, urinary tract infection and pneumonia, respectively) in the ETN 10 mg group. Medically important infections (those requiring hospitalization or use of parenteral antimicrobials) were experienced by four (2.2 %), 10 (5.2 %), and three (1.7 %) subjects in the ETN 25 and 10 mg and MTX treatment groups, respectively ($P = 0.140$). The most common medically important infection was pneumonia.

No significant differences were observed among treatment groups for individual liver-related laboratory tests. Aspartate transaminase (AST) increases of more than threefold the upper limit of normal (ULN) were reported in 3.3, 2.1, and 1.1 % of subjects in the ETN 25 mg, ETN 10 mg, and MTX treatment groups, respectively. Alanine

aminotransferase (ALT) increases of more than threefold the ULN were reported in 4.4, 2.6, and 4.5 % of subjects in the ETN 25 mg, ETN 10 mg, and MTX groups, respectively. Of the 13 subjects who were receiving ETN 25 or 10 mg and developed ALT elevations of more than threefold the ULN, seven were discontinued from the study. In the MTX group, eight subjects had ALT elevations of more than threefold the ULN, and two of these withdrew from the study. Of the subjects with ALT or AST levels of more than threefold the ULN and withdrawn from the study, three still had elevated levels at the last available assessment (1 subject receiving ETN 10 mg and 2 subjects receiving MTX). No patients were reported to have had clinical symptoms related to elevated liver enzyme-related tests, and none of the elevations of ALT and/or AST were reported as SAEs. Similarly to the liver-related laboratory tests, there were no statistically significant differences in the incidence of any grade 3 or 4 laboratory test results among treatment groups for any individual blood chemistry test. No cases of TB or other opportunistic infections, demyelinating diseases, or deaths were reported.

Pharmacokinetics

The mean ETN concentrations observed throughout the study were dose-proportional and remained relatively constant over time.

Discussion

We have shown both ETN 25 mg BIW and ETN 10 mg BIW to be more efficacious than MTX at slowing joint damage in this Japanese population of subjects with active RA. In addition, a dose-response to ETN over the 52 weeks was evident in the mTSS scores and its component erosion and JSN scores. Although the differences between the ETN 25 and 10 mg groups were not statistically significant, the study design was not powered to detect such differences and, therefore, this result was not unexpected. Considering subjects with RA may be treated over a number of years, the magnitude of the differences in mTSS between the ETN 25 mg and ETN 10 mg groups observed in this study could be viewed as clinically important. Additionally, in the subgroup analyses, subjects with factors indicating high disease activity showed less radiographic progression on ETN 25 mg than on ETN 10 mg over the 52-week study period.

In addition to improving radiographic outcomes, ETN 25 mg and ETN 10 mg were more efficacious than MTX in achieving control of disease activity and improving functional ability. In terms of clinical outcomes, there were some statistically significant differences in favor of ETN 25 mg BIW over ETN 10 mg BIW, including improvements in physician global assessment scores, this added proportion of subjects achieving EULAR response, and improvement in tender joint counts at week 52. After the study was complete, a post hoc analysis was conducted to explore the effects of ETN using HAQ-DI remission (<0.5) and the new ACR/EULAR Boolean-based definition of remission (where all of the following must be satisfied: tender joint count of ≤1, swollen joint count of ≤1, CRP of ≤1 mg/dL, and patient global assessment score of ≤1) [21, 22]. HAQ-DI remission (<0.5) was achieved by 63.3 % of subjects receiving ETN 25 mg, 52.4 % of those receiving ETN 10 mg, and 47.2 % of those receiving MTX ($P = 0.0027$ for ETN 25 mg vs. MTX; $P = 0.2874$ for ETN 10 mg vs. MTX; $P = 0.0124$ for ETN 25 vs. 10 mg). In all, 18.7 % of subjects receiving ETN 25 mg, 10.4 % of those receiving ETN 10 mg, and 8.0 % of those receiving MTX achieved the Boolean-based remission criteria ($P = 0.0007$ for ETN 25 mg vs. MTX; $P = 0.0179$ for ETN 25 vs. 10 mg; $P = 0.3648$ for ETN 10 mg vs. MTX). These post hoc analyses further support the superiority of the ETN 25 mg dose to treat this population of subjects.

The results presented here are consistent with those reported from similar etanercept studies performed outside of Japan, namely trial of etanercept and methotrexate with radiographic subject outcomes (TEMPO) [23] and early rheumatoid arthritis (ERA) [18]. In the international TEMPO study, performed in subjects with active RA who had previously failed DMARD treatment other than MTX, the radiographic efficacy of ETN 25 mg BIW was shown to be superior to MTX (≤20 mg/week) over 52 weeks (mTSS change from baseline: 0.5 in ETN 25 mg group and 2.8 in MTX group). The ERA study, performed in MTX-naïve North American subjects with a mean RA duration of <3 years, showed that ETN 25 mg BIW was superior to both ETN 10 mg BIW and MTX QW (mean dosage 19 mg/week) at slowing the radiographic progression rate (mTSS change from baseline: 1.00 in ETN 25 mg group, 1.59 in MTX group, and 1.44 in the ETN 10 mg group over 52 weeks.

The 52-week radiographic progression rate in all three treatment groups was substantially higher in our study than in both TEMPO (mTSS 21.8–26.8, yearly mTSS progression rate 8.4–11.0) and ERA (mTSS 2.5–12.9, yearly mTSS progression rate 8.0–9.0) which is not surprising considering the advanced level of structural damage in our patients at baseline. The ERA study found ETN 10 mg to have similar radiographic efficacy to MTX, whereas our results showed ETN 10 mg to be significantly more effective than MTX. These differences could be explained by the low dose of MTX (up to 8 mg/week) used in our trial—the dose that was approved by the Japanese Ministry of Health, Labour, and Welfare (JMHLW) at the time of

this study, which is far lower than the typical dose of 15–25 mg/week used globally outside Japan [24]. As of February 2011, the JMHLW increased the recommended MTX dose to 16 mg/week.

The recent JESMR (Efficacy and Safety of Etanercept on Active Rheumatoid Arthritis Despite Methotrexate Therapy in Japan) study [25] investigated the radiographic efficacy of ETN 25 mg BIW versus ETN 25 mg plus MTX in Japanese subjects with RA. Subjects who continued MTX treatment in combination with ETN had significantly less radiographic progression and better clinical outcomes at weeks 24–52 than subjects receiving ETN alone. Consequently, these results support the treatment strategy of continuing MTX when ETN 25 mg BIW therapy is initiated.

The radiographic efficacy of etanercept in our study is comparable to that observed with tocilizumab, an inhibitor of interleukin-6 (IL-6), in Japanese subjects in the Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis (SAMURAI) study [26]. In SAMURAI, subjects who were randomized to receive tocilizumab 8 mg/kg intravenously every 4 weeks exhibited significantly less radiographic change from baseline over 52 weeks (mean mTSS change 2.3) than conventional DMARD therapy (mean mTSS change 6.1). This is comparable to the change exhibited in our results with ETN 25 mg; however, subjects in the SAMURAI study had a far lower mean mTSS score (29.4) and estimated yearly mTSS progression rate (13.3) at baseline.

Etanercept was well-tolerated, and no unexpected safety findings were reported. The numbers of subjects reporting TEAEs, SAEs, and serious infections were generally similar among the three treatment groups. Additionally, no safety differences were observed between the two ETN groups, suggesting an optimal benefit risk balance associated with the ETN 25 mg BIW dose, particularly in subjects with factors indicating higher disease activity.

One major limitation of this study was the number of subjects in the MTX group who withdrew, mainly due to lack of efficacy. As discussed previously, the MTX dose administered here was far lower than the typical global dose and could be the reason for the higher discontinuation rate due to lack of efficacy in the MTX treatment arm.

In conclusion, the results of this study show ETN 25 mg BIW and ETN 10 mg BIW to be superior to MTX in slowing radiographic progression and treating the clinical symptoms of RA in this Japanese population of subjects with moderate-to-severe active RA.

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