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;

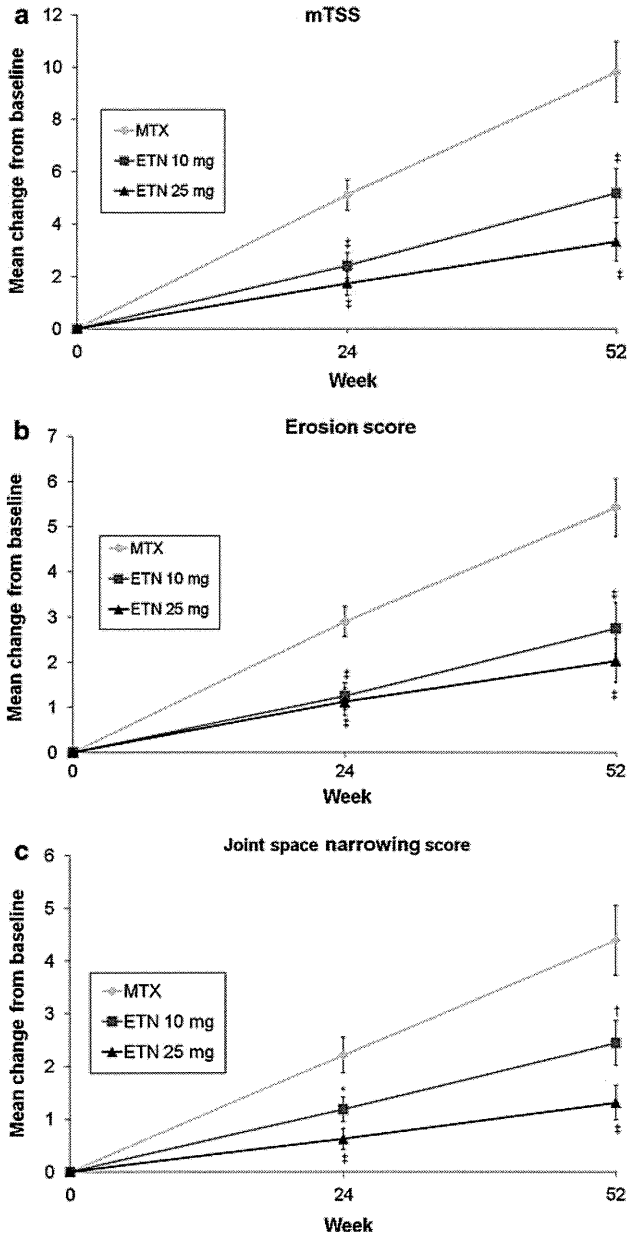

Fig. 2 Mean change from baseline in the modified total Sharp score (mTSS), erosion, and joint space narrowing (JSN) scores at weeks 24 and 52 for subjects with rheumatoid arthritis (RA) after treatment. Analyses were performed on the rITT population. *Error bars* SE. $^{*}P = 0.0013$ vs. MTX and $P = 0.0186$ 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 $\leq$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 $\leq$1, swollen joint count of $\leq$1, CRP of $\leq$1 mg/dL, and patient global assessment score of $\leq$1) [21, 22]. HAQ-DI remission (<0.5) was achieved by 63.3 % of subjects receiving ETN 25 mg, 52.4 % of those receiving ETN 10 mg, and 47.2 % of those receiving MTX ($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 ($\leq$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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EXTENDED REPORT

Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study

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ABSTRACT

Objectives To evaluate the efficacy and safety of adalimumab+methotrexate (MTX) in Japanese patients with early rheumatoid arthritis (RA) who had not previously received MTX or biologics.

Methods This randomised, double-blind, placebo-controlled, multicentre study evaluated adalimumab 40 mg every other week+MTX 6–8 mg every week versus MTX 6–8 mg every week alone for 26 weeks in patients with RA (≤2-year duration). The primary endpoint was inhibition of radiographic progression (change (Δ) from baseline in modified total Sharp score (mTSS)) at week 26.

Results A total of 171 patients received adalimumab+MTX (mean dose, 6.2±0.8 mg/week) and 163 patients received MTX alone (mean dose, 6.6±0.6 mg/week, p<0.001). The mean RA duration was 0.3 years and 315 (94.3%) had high disease activity (DAS28>5.1). Adalimumab+MTX significantly inhibited radiographic progression at week 26 versus MTX alone (ΔmTSS, 1.5±6.1 vs 2.4±3.2, respectively; p<0.001). Significantly more patients in the adalimumab+MTX group (62.0%) did not show radiographic progression (ΔmTSS≤0.5) versus the MTX alone group (35.4%; p<0.001). Patients treated with adalimumab+MTX were significantly more likely to achieve American College of Rheumatology responses and achieve clinical remission, using various definitions, at 26 weeks versus MTX alone. Combination therapy was well tolerated, and no new safety signals were observed.

Conclusions Adalimumab in combination with low-dose MTX was well tolerated and efficacious in suppressing radiographic progression and improving clinical outcomes in Japanese patients with early RA and high disease activity.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that is associated with joint damage and progressive disability, an increased risk of morbidity related to comorbid conditions, and substantial socioeconomic costs.[1–3] Given the significant impact biologic therapies have had in the treatment of RA, a paradigm shift has emerged toward earlier inclusion of these therapies in the management of RA.[3 4] Furthermore, international guidelines published in 2010 recommend a treat-to-target goal of remission for patients with early RA in order to mitigate radiographic progression and long-term disability.[5] The efficacy and safety of adalimumab, a tumour necrosis factor (TNF)-α inhibitor, administered as monotherapy or in combination with methotrexate (MTX) for the treatment of RA has been well established in clinical trials conducted in Western countries.[6–12] In early RA, the PREMIER and OPTIMA studies demonstrated that initial combination therapy with adalimumab and MTX was superior to MTX alone in inhibiting radiographic progression and improving clinical symptoms.[6 7 12]

Translating efficacy and safety results of RA Western-based studies to an Eastern populace can be potentially misleading given the genetic, medical and environmental differences (eg, body weight) observed between the two populations.[13] A limited number of studies have evaluated the efficacy or effectiveness and safety of adalimumab in Japanese patients. However, these studies either assessed adalimumab monotherapy in moderate-to-severe RA[14] or were retrospective[15] or postmarketing surveillance studies[16] of adalimumab monotherapy or combination therapy in a population with a wide range of RA duration and prior biologic and MTX experience. Thus, a randomised, placebo-controlled study of adalimumab +MTX combination therapy in MTX-naive Japanese patients with early RA was lacking.

The current study, called adalimumab, a human anti-TNF monoclonal antibody, outcome study for the persistent efficacy under allocation to treatment strategies in early RA, or HOPEFUL 1, was conducted to compare the efficacy and safety of early intervention with adalimumab+MTX versus MTX alone for 26 weeks in inhibiting radiographic progression in MTX-naive Japanese patients with RA.

PATIENTS AND METHODS

Patients aged ≥20 years were evaluated during March 2009 and November 2010 from 94 centres. Eligible patients had RA (1987-revised American College of Rheumatology (ACR) criteria),[17] of ≤2-year duration, a tender joint count ≥10, a swollen joint count ≥8, a C reactive protein (CRP) level ≥1.5 mg/dl or erythrocyte sedimentation rate

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(ESR) ≥28 mm/h, and had ≥1 joint erosion or were rheumatoid factor positive. Patients had not previously received MTX, leflunomide or >2 other disease-modifying antirheumatic drugs (DMARDs). Patients who had previously received cyclophosphamide, cyclosporine, azathioprine, tacrolimus or biologic DMARDs (eg, anti-TNF-α therapy) and patients with a chronic infection, interstitial pneumonia, or a history of tuberculosis or malignancy were excluded from the study.

The phase III trial consisted of a randomised, double-blind, placebo-controlled, 26-week phase followed by a 26-week open-label extension phase (clinicaltrials.gov identifier, NCT00870467; only 26-week double-blind data presented). After a 4-week washout period for patients taking eligible DMARDs and a >2-week screening period for all patients, participants were randomised (1 : 1) to receive subcutaneous adalimumab 40 mg or placebo every other week, both administered in combination with oral MTX 6–8 mg/week (adalimumab +MTX vs MTX alone) for 26 weeks. Treatment with MTX was initiated at 6 mg/week and increased to 8 mg/week in patients who did not experience ≥20% decrease from baseline in tender or swollen joint counts on or after week 8, unless investigators indicated a safety concern. In addition, reduction of the MTX dose to 4 mg/week was permitted at the investigator's discretion. All patients received concomitant oral folic acid 5 mg/week. Patients who experienced a >20% increase from baseline in tender and swollen joint counts at weeks 12, 16 or 20 were to discontinue blinded treatment with adalimumab or placebo and were eligible for open-label rescue treatment with adalimumab 40 mg every other week.

The primary endpoint was inhibition of radiographic progression assessed as the change from baseline (Δ) in modified total Sharp score (mTSS) at week 26. All single-emulsion radiographs of the hands (posteroanterior view) and feet (anteroposterior view) obtained from a patient were scored by two independent readers blinded to patient and treatment, as previously described,[6] with the exception that the triquetrum/pisiform joint was not scored for erosions and the first interphalangeal joint was not scored for joint-space narrowing (range, 0–380) (see online supplementary text for more information).

Secondary efficacy endpoints included ACR responses[18 19] by visit; clinical remission (the 28-joint disease activity score with ESR (DAS28-ESR)<2.6) at week 26;[20 21] and change from baseline in the Health Assessment Questionnaire disability index (HAQ-DI)[22] at week 26. Several additional post hoc analyses were conducted, including assessments of the DAS28-CRP, simplified disease activity index (SDAI)[23] and clinical disease activity index (CDAI) scores[24] over time; clinically relevant radiographic progression (ΔmTSS>3); European League Against Rheumatism responses[25] at week 26; and clinical remission, defined as DAS28-CRP<2.6,[26] SDAI≤3.3,[27 28] CDAI≤2.8[28] or meeting Boolean remission criteria,[27] at week 26. Low, medium and high disease activity was also determined using DAS28-ESR, DAS28-CRP, SDAI and CDAI. Adverse events (AEs) and clinical laboratory parameters were routinely monitored during the study. A 28-day follow-up after the completion of or discontinuation from the study and a 70-day follow-up after the last dose of adalimumab administration were conducted to evaluate safety.

Statistics

The primary endpoint was analysed using the Wilcoxon rank sum test for observed data with a separate supportive analysis using linear extrapolation (LE) to impute missing values. Secondary endpoints were analysed using the Fisher's exact test and Wilcoxon rank sum test for discrete variables and continuous variables, respectively. Non-responder imputation was used for binary variables, and the last-observation-carried-forward approach was applied for continuous variables. The safety population included all randomised patients who received ≥1 dose of study medication and had ≥1 efficacy assessment.

To identify baseline predictors of no radiographic progression (mTSS≤0.5) and clinical remission (DAS28-ESR<2.6),

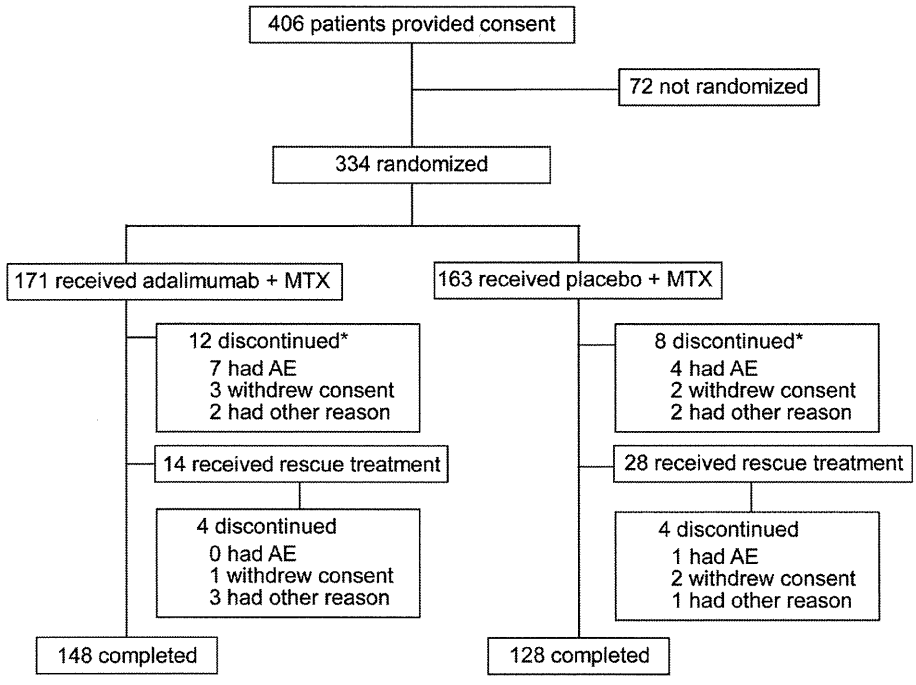

Figure 1 Patient disposition through week 26. *Three adalimumab+MTX patients and one MTX alone patient discontinued from the study by week 26; however, they were included in the efficacy analyses at week 26. AE, adverse event; MTX, methotrexate.

univariate logistic regression analysis was performed, applying 24 baseline demographics and disease characteristics. Significant ($p<0.1$) variables in univariate were included in multivariate models. Last, multivariate models were selected based on model fit statistics (Akaike information criterion and r^2) and clinical significance. Adjusted OR and 95% CIs for selected baseline variables were calculated.

RESULTS

Overall, 334 patients were randomised to treatment and received adalimumab+MTX (n=171) or MTX alone (n=163), and 148 (86.5%) and 128 (78.5%) patients completed the double-blind portion of the study, respectively (figure 1). Demographics and baseline characteristics were well matched between treatment groups (table 1). The mean RA disease duration was 0.3 years, and the majority of patients had ≥1 erosion at baseline and high disease activity. The mean MTX dose during the 26-week study was 6.2±0.8 mg/week in the adalimumab+MTX group and 6.6±0.6 mg/week in the MTX alone group ($p<0.001$). After 26 weeks of treatment, 34.5% (59/171) of adalimumab+MTX patients were receiving MTX 8 mg/week versus 65.0% (106/163) of MTX alone patients ($p<0.001$).

Radiographic progression

Treatment with adalimumab+MTX significantly inhibited radiographic progression (figure 2A) at week 26 versus MTX alone (mean change±SD, 1.5±6.1 vs 2.4±3.2, respectively; $p<0.001$). Results were confirmed by an LE analysis (figure 2A). Changes in radiographic progression during 26 weeks of treatment were also assessed by a cumulative probability plot of ΔmTSS (figure 2B). Fewer adalimumab+MTX patients exhibited radiographic progression (ΔmTSS>0.5), with 62.0% (106/171) of patients showing no radiographic progression versus 35.4% (57/161) of MTX alone patients ($p<0.001$). Furthermore, only 14.0% (24/171) of adalimumab+MTX patients exhibited clinically relevant radiographic progression (ΔmTSS>3) versus 37.3% (60/161) of MTX alone patients ($p<0.001$). In addition, a significantly higher percentage of adalimumab+MTX patients did not experience worsening (≤0.5) in erosion score (73.7% (126/171)) versus MTX alone patients (42.2% (68/161); $p<0.001$). In patients who lacked baseline erosive damage, the continued absence of erosions was reported in more adalimumab+MTX patients versus MTX alone patients (9/9 vs 2/6 patients, respectively; $p=0.01$).

Clinical response

A significantly higher percentage of adalimumab+MTX patients achieved ACR responses versus MTX alone patients at each assessment (figure 3A–C). Significant differences between treatment groups, observed as early as week 2, were maintained through week 26. At week 26, a significantly larger percentage of adalimumab+MTX patients versus MTX alone patients achieved ACR20, ACR50 and ACR70 (figure 3A–C) and ACR90 (12.9% vs 5.5%; $p=0.02$) responses. Significant differences in favour of adalimumab+MTX were also observed from week 2 to 26 for DAS28-ESR, DAS28-CRP, SDAI and CDAI (see online supplementary figure 1A–D). A larger percentage of adalimumab+MTX patients than MTX alone patients demonstrated good or moderate European League Against Rheumatism responses (figure 3D) and were in states of low disease activity or remission after 26 weeks of treatment (figure 3E). Furthermore, a significantly larger percentage of adalimumab+MTX patients versus MTX alone patients satisfied Boolean remission criteria (19.3% vs 8.6%, $p=0.007$). Adalimumab+MTX achieved a 1.8- to 2.2-fold increase in the percentage of patients achieving clinical remission, across all definitions of clinical remission evaluated, versus MTX alone.

Table 1 Demographics and baseline characteristics

Parameter*	Adalimumab+MTX (n=171)	MTX (n=163)
Age±SD (year)	54.0±13.1	54.0±13.2
Females (n (%))	144 (84.2)	128 (78.5)
RA duration±SD (year)	0.3±0.4	0.3±0.4
Weight±SD (kg)	54.4±9.7	56.1±12.3
Previous DMARD use (n (%))	74 (43.3)	87 (53.4)
1 DMARD	57 (33.3)	69 (42.3)
2 DMARDs	17 (9.9)	18 (11.0)
Corticosteroid use at baseline (n (%))	58 (33.9)	49 (30.1)
RF positive (n (%))	146 (85.4)	136 (83.4)
Mean titre±SD (IU/ml)	154.5±202.3	163.7±362.8
Anti-CCP positive (n (%))	145 (84.8)	136 (83.4)
Mean titre±SD (U/ml)	386.2±694.2	241.3±367.2
ESR (mm/h)	59.9±30.1	61.8±29.0
CRP (mg/dl)	2.9±3.0	3.1±3.3
Swollen joint count (n±SD)		
0–28	11.5±4.7	11.8±5.3
0–66	16.5±6.2	17.3±7.7
Tender joint count (n±SD)		
0–28	13.2±5.8	13.2±6.1
0–68	20.7±9.4	21.1±10.2
mTSS	13.6±22.3	13.6±17.4
Erosion score	7.5±11.6	7.3±9.2
Joint space narrowing score	6.2±11.4	6.2±9.4
DAS28-ESR	6.6±0.9	6.6±1.0
DAS28-CRP	5.8±1.0	5.9±1.0
HAQ-DI score	1.1±0.7	1.3±0.8
SDAI score	40.7±12.0	41.4±13.8
CDAI score	37.8±10.9	38.3±12.4
Physician's global assessment of disease activity±SD (mm)	65.8±18.4	66.2±18.8
Patient's global assessment of disease activity±SD (mm)	64.1±24.8	66.4±23.7

*Data are mean±SD unless otherwise indicated.
CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; CRP, C reactive protein; DAS28-CRP, disease activity score using a 28-joint count and CRP level; DAS28-ESR, disease activity score using a 28-joint count and ESR; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire disability index; mTSS, modified total Sharp score; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simplified disease activity index.

A significantly larger decrease from baseline in mean HAQ-DI score, indicative of an improvement in physical function, was observed for adalimumab+MTX patients versus MTX alone patients at week 26 (−0.6±0.6 vs −0.4±0.6; $p<0.001$). Although the significant difference between the two groups was small (0.2 units), the percentage of patients achieving normal functionality (HAQ-DI score<0.5) after 26 weeks of treatment was also significantly higher with adalimumab+MTX (figure 3F).

Factors associated with the absence of radiographic progression or with clinical remission

Disease activity or function baseline variables generally were associated with the absence of radiographic progression (ΔmTSS≤0.5) and with clinical remission (DAS28-ESR<2.6) in both treatment groups (see online supplementary text and online supplementary table 1).

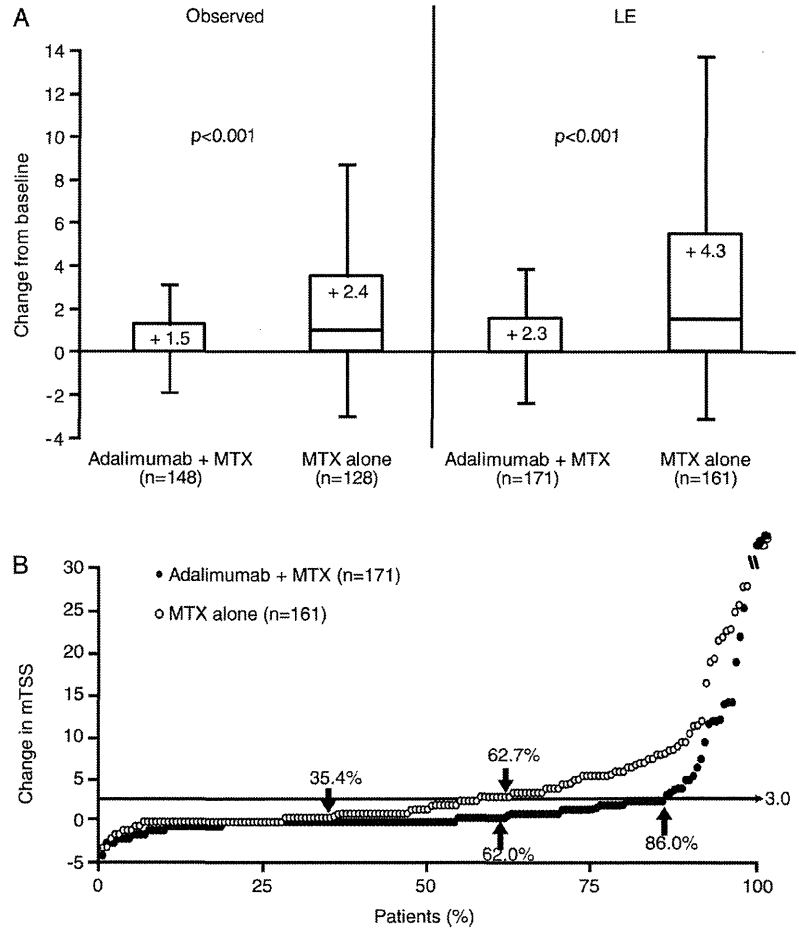

Figure 2 (A) Box plot of change from baseline in mTSS at week 26 with adalimumab+MTX versus MTX alone and (B) cumulative probability plot of mean change from baseline to week 26 in mTSS score (LE). Thickened horizontal lines in (A) indicate median values, the boxes mark the interval between the 25th and 75th percentiles, whiskers indicate the IQR and mean values are reported in the boxes. No radiographic progression (change from baseline in mTSS≤0.5) was reported in 62.0% (106/171) of adalimumab+MTX patients versus 35.4% (57/161) of MTX alone patients (p<0.001). No clinically relevant radiographic progression (change from baseline mTSS≤3) was reported in 86.0% (147/171) of adalimumab+MTX patients versus 62.7% (101/161) of MTX alone patients (p<0.001) (B). LE, linear extrapolation; mTSS, modified total Sharp score; MTX, methotrexate. p Value determined using Wilcoxon rank sum test.

Safety

The mean treatment duration during the double-blind phase was 168.7±36.6 days for adalimumab+MTX patients (mean cumulative adalimumab dose, 477.4±104.5 mg) and 162.8±38.6 days for MTX alone patients. Overall, there were 376 and 302 AEs reported in the adalimumab+MTX group and the MTX alone group, respectively. There were no significant differences in the percentage of patients with AEs in the adalimumab+MTX group (80.7% (138/171)) versus the MTX alone group (71.8% (117/163)), and the incidence of severe AEs was rare (table 2). No significant differences in the incidence of AEs of interest were observed between the two groups, with the exception of injection-site reactions, which were reported in 10.5% of adalimumab+MTX patients and 3.7% of MTX alone patients (p=0.02; table 2). Serious infections were observed in two adalimumab+MTX patients (one case each of pneumonia and infectious enteritis) and one MTX alone patient (*Pneumocystis jiroveci* pneumonia), occurring at rates of 2.5 and 1.4 events per 100 patient-years, respectively. There were no reports of demyelination, tuberculosis or malignancy during the study. One death, due to worsening of interstitial lung disease, occurred in the MTX alone group.

DISCUSSION

The HOPEFUL 1 study was designed to evaluate the efficacy and safety of adalimumab in combination with MTX in Japanese patients with early RA. This is the first description of a clinical trial of anti-TNF therapy+MTX versus MTX alone in MTX-naive Japanese patients with early RA and high disease activity. It is also the first randomised trial evaluating the efficacy of anti-TNF therapy+low-dose MTX versus low-dose MTX alone for the inhibition of radiographic progression in any patient population. This study extends observations from Western studies of adalimumab by demonstrating the superiority of adalimumab+MTX to MTX alone for the inhibition of radiographic progression and improvement in clinical outcomes in Japanese patients with early RA. Moreover, the combination of adalimumab+MTX significantly improved a wide array of clinical and functional disease activity measures and responses versus MTX alone, with improvements observed as early as the first assessment (week 2) and maintained through the 26-week double-blind trial.

Following 26 weeks of treatment, the mean ΔmTSS (primary endpoint) in adalimumab+MTX patients (1.48) in the current study was significantly smaller than observed in MTX alone patients (2.38). In addition, a similar trend in inhibition of radiographic progression in patients with early RA was observed in the OPTIMA study, with a smaller mean ΔmTSS in adalimumab+MTX patients (0.15) versus MTX alone patients (0.96; p<0.001).[12] The difference between the two treatment groups (0.8) at week 26 was similar to the difference observed in the current study (0.9 (observed)).[12] Furthermore, baseline characteristics, including RA duration, in the two studies were generally similar, but the OPTIMA study had a lower percentage of previous DMARD use.

A similar trend in inhibition of radiographic progression in the current study was observed in the PREMIER study, with a

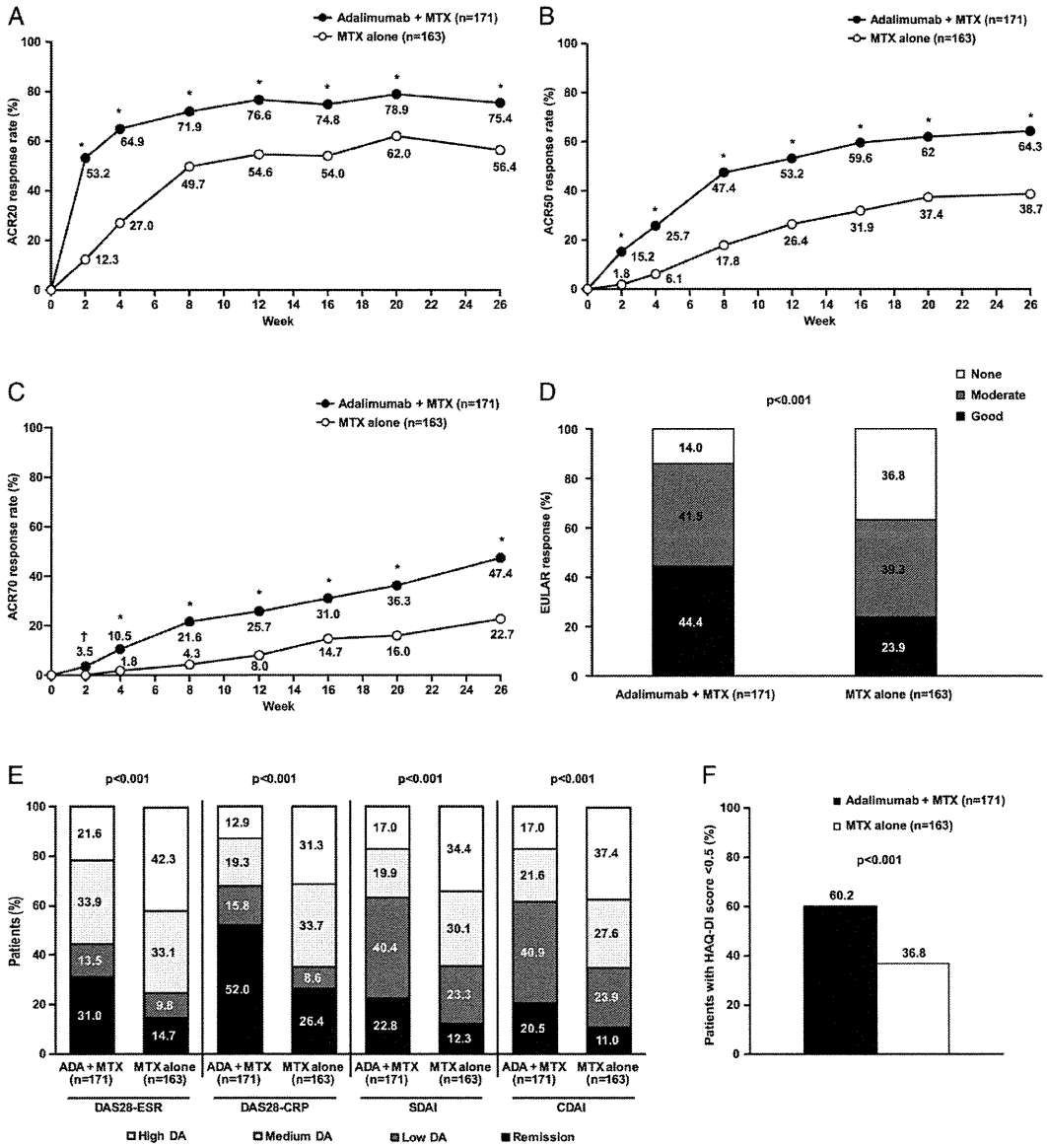

Figure 3 Percentage of patients with an (A) ACR20 response, (B) ACR50 response or (C) ACR70 response over time; (D) the percentage of patients with a EULAR response at week 26; (E) the percentage of patients with low, medium or high disease activity at week 26; and (F) the percentage of patients achieving functional remission (HAQ-DI score<0.5) at week 26. The following values were used to identify remission, low, medium and high disease activity for each clinical assessment in (E): DAS28-ESR or DAS-CRP (<2.6, ≥2.6–<3.2; ≥3.2–≤5.1, >5.1, respectively), SDAI (≤3.3, >3.3–≤11.0, >11.0–≤26.0, >26.0, respectively), and CDAI (≤2.8, >2.8–≤10.0, >10.0–≤22.0, >22.0, respectively). *p<0.001 versus MTX alone. †p=0.03 versus MTX alone. ACR, American College of Rheumatology; ADA, adalimumab; CDAI, clinical disease activity index; DA, disease activity; DAS28-CRP, disease activity score using a 28-joint count and C reactive protein level; DAS28-ESR, disease activity score using a 28-joint count and erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire disability index; MTX, methotrexate; SDAI, simplified disease activity index.

smaller mean ΔmTSS in adalimumab+MTX patients (0.8) versus MTX alone patients (3.5; p<0.001). However, the mean difference in radiographic progression between the two treatments groups, although statistically significant, was smaller in the current study (0.9 (observed); 2.0 (LE)) than in the PREMIER study (2.7).

In the current study, the SD for the mean ΔmTSS at week 26 was generally high. When the median ΔmTSS was compared using observed data, results were in good agreement between the PREMIER study (0.0 (adalimumab+MTX) vs 1.3 (MTX alone); data on file) and the current study (0.0 (adalimumab +MTX) vs 1.0 (MTX alone)). Alternatively, the smaller difference in improvement observed in the current study may also be related to the mTSS scoring method used, but this seems unlikely because only two joints assessed in PREMIER were omitted from scoring in the present analysis. The mean duration of RA was also shorter in the current study (0.3 years) versus the PREMIER study (0.7–0.8 years), although the percentage of patients who had previously taken DMARDs was higher (43.3–53.4% vs 31.5–32.5%). There were also slight differences in mean baseline tender and swollen joint counts and CRP levels, which were higher in the PREMIER study and considered

Table 2 Adverse events (AEs)

Parameter	Patients (n (%)) Adalimumab+MTX (n=171)	MTX (n=163)
Any AE	138 (80.7)	117 (71.8)
Severe AE	1 (0.6)	1 (0.6)
Serious AE	7 (4.1)	4 (2.4)
Infectious AE	59 (34.5)	48 (29.4)
Serious infection	2 (1.2)	1 (0.6)
AEs leading to study drug discontinuation	7 (4.1)	6 (3.7)
AEs of interest		
Elevated liver function test level	32 (18.7)†	21 (12.9)†
Injection-site reaction	18 (10.5)*	6 (3.7)
Haematological event	7 (4.1)	8 (4.9)
Allergic reaction	1 (0.6)	2 (1.2)
Interstitial lung disease	1 (0.6)	1 (0.6)
Lupus-like syndrome	0	1 (0.6)
Opportunistic infection	0	1 (0.6)

*p=0.02 versus MTX.
†≥94% of events were mild in severity.
MTX, methotrexate.

related to the longer duration of RA at baseline versus the current study. Furthermore, the MTX dose of 6–8 mg/week, although consistent with the dosage commonly administered in Japan at the time the study was conducted, was substantially lower than that commonly administered in Western countries (eg, 15–20 mg/week). In the PREMIER study, MTX was initiated at 7.5 mg/week, increased to 15 mg/week during weeks 4–8, and increased to 20 mg/week starting at week 9. In addition, the mean MTX dose during the 26 weeks of the current study was significantly lower in the adalimumab+MTX group (6.2±0.8 mg/week) versus the MTX alone group (6.6±0.6 mg/week; $p<0.001$), thereby potentially impacting the ΔmTSS and thus the maximal difference observed between the two treatment groups. Therefore, these multiple differences may have contributed to the small difference in radiographic outcomes between the current study and the PREMIER study. Whether the difference in radiographic outcomes can be explained by differences between Japanese and Western populations remains unclear, although this seems unlikely. Longer-term studies may help elucidate potential differences in outcomes.

Since this study was conducted, the maximum approved MTX dosage in Japan has been increased from 8 to 16 mg/week in patients with RA. Therefore, this study provides important information on the efficacy of low-dose MTX and anti-TNF therapy versus low-dose MTX alone for the inhibition of radiographic progression. Data suggest that patients with early RA who may not tolerate higher doses of MTX will likely benefit from adalimumab+low-dose MTX combination therapy.

Given the lower MTX dose prescribed, one could question whether we might only be seeing natural progression in the MTX only arm. It is ethically difficult to include a true placebo arm in clinical trials of ≥6 months duration for early active RA, particularly when MTX is recommended as first-line therapy to achieve clinical remission/low disease activity. Although an important question to ponder, a placebo arm in long-term clinical trials in early active RA appears to be unrealistic, and further research using highly sensitive and reproducible imaging techniques during a short-term placebo-treatment period in early active RA is warranted.

It is also important to note that the current patient population had severe baseline symptoms, including baseline erosions, despite only several months since RA onset. This scenario is becoming increasingly less common in Western populations due to treat-to-target recommendations and earlier intervention. In Japan, general practitioners are still seeing many early RA patients and referrals to rheumatologists are often delayed. In addition, the diagnosis of RA in this trial was based upon 1987 classification criteria. Thus, these factors may have played a role in the conundrum of more severe baseline clinical symptoms yet shorter mean disease duration.

The clinical results of the current study are supported by the HARMONY study, which retrospectively determined the effectiveness and safety of adalimumab 40 mg every other week with or without MTX (mean dose, 8.5 mg/week) in Japanese patients with RA (mean RA duration, 9.0±9.5 years) with or without prior biologic treatment.[15] Although patients in the HARMONY study had more established disease and the study design was retrospective, adalimumab+MTX patients (n=143) had an improvement from baseline in DAS28-ESR score at week 24 (baseline, 5.3; week 24, 3.3), which was within the range but slightly smaller than the improvement observed in the current study at week 26 (baseline, 6.6; week 26, 3.7; see online supplementary figure 1A). Clinical remission rates for adalimumab+MTX patients were also comparable between the HARMONY study (week 24, 35.0%) and the current study (week 26, 31.0%).

The safety profile of the current study was generally consistent with those in previous clinical studies of adalimumab in patients with RA conducted in Japan.[14–16] There were no reports of demyelination, tuberculosis or malignancy, and there were no statistically significant differences in the incidence of serious AEs, serious infections, opportunistic infections or lupus-like reactions between adalimumab+MTX patients versus MTX alone patients. There was a significantly higher incidence of injection-site reactions for adalimumab+MTX patients versus MTX alone patients, but the incidence (10.5%) was similar to that reported for the 167 adalimumab±MTX patients in the HARMONY study (12.0%). The incidence of injection-site reactions in both of these studies was lower than the 30.8% reported for the 91 adalimumab monotherapy patients (40 mg every other week) in the CHANGE study,[14] possibly related to the immunosuppressive effects of concomitant MTX in the current study and in some of the patients in the HARMONY study.

In the multivariate regression analyses (see online supplementary table 1), lower baseline CRP level was identified as a predictor of radiographic non-progression in adalimumab+MTX patients, whereas normal baseline CRP level (≤0.3 mg/dl) appeared to have an increased likelihood of radiographic non-progression. However, no baseline predictors appeared to predict both the lack of progression and clinical remission. Furthermore, baseline mTSS was not an independent predictor for either treatment group in this study.

Overall, adalimumab+MTX was well tolerated in Japanese patients with early RA with no new safety signals and with a safety and tolerability profile similar to that observed in Western populations. Administration of adalimumab in combination with MTX was efficacious in improving radiographic and clinical responses in MTX-naive patients with early RA, high disease activity and poor prognostic factors (eg, rheumatoid factor positive or with baseline erosive damage) through week 26. Given its radiographic, clinical and functional superiority versus MTX monotherapy, consideration should be given to administration

of anti-TNF-α and MTX combination therapy in patients with early RA and high disease activity.

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ORIGINAL ARTICLE

Efficacy of weekly mizoribine pulse therapy in refractory lupus nephritis

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Abstract
Objective We investigated the efficacy of a high-dose intermittent dosing treatment method (weekly mizoribine pulse therapy) conceived in the hope of achieving better efficacy by increasing the peak blood levels of mizoribine in patients with refractory lupus nephritis.
Methods Seventeen patients with lupus nephritis who had been resistant to corticosteroid and immunosuppressant therapy received weekly mizoribine pulse therapy. Mizoribine (350 mg) was administered three times at 12 h intervals over 2 consecutive days (700 mg for day 1 and 350 mg for day 2), followed by a washout period from day 3 to day 7.
Results This therapeutic strategy enabled the peak blood levels of mizoribine to be increased to more than 3 μg/mL in most of the patients. Although SLEDAI, anti-ds-DNA antibody titer, CH-50, and serum albumin level did not significantly improve, urinary protein levels decreased, and it was possible to taper the dose of concomitant steroids. Using our definition of clinical response, 10 of the 17 patients were responders and 4 of them were nonresponders. The average peak serum mizoribine concentration of the responders was as high as 3.5 μg/mL. Elevation of serum liver enzymes was seen in 1 patient, and hyperuricemia occurred in 4 cases, but none of these adverse events were serious.
Conclusion Intermittent administration of mizoribine can increase blood levels and may be effective for refractory lupus nephritis.

Keywords Lupus nephritis · Mizoribine

Introduction

Despite recent improvements in therapeutic outcomes for lupus nephritis, a form of nephropathy associated with systemic lupus erythematosus (SLE), the prognosis remains unsatisfactory. Lupus nephritis is primarily treated with corticosteroids, but treatment with corticosteroids alone is often insufficient [1]. In some cases, corticosteroids cannot be used at sufficient doses because of adverse reactions (such as diabetes mellitus, osteoporosis, and avascular necrosis of the femoral head). Therefore, a variety of immunosuppressants are used [2–4], but there have been problems with adverse reactions such as suppression of gonadal function, hemorrhagic cystitis, and renal impairment.

Mizoribine is an immunosuppressant [5] that inhibits inosine monophosphate dehydrogenase (IMPDH) in the same manner as mycophenolate mofetil (MMF) [6, 7]. In Japan, mizoribine has been approved for renal transplant rejection reactions and lupus nephritis, rheumatoid arthritis and nephrotic syndrome. However, in the clinical setting, mizoribine is often ineffective at the approved dose rate

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(50 mg three times a day) for lupus nephritis and rheumatoid arthritis.

Recently, mizoribine doses have been increased in the hope of achieving higher efficacy, and doses of 6 mg/kg or more per day have sometimes been used in transplant patients [8]. It is therefore possible that dosage and administration have not been adequately studied in the area of collagen vascular diseases.

Here, we investigated the efficacy of a high-dose intermittent dosing treatment method (weekly mizoribine pulse therapy) conceived in the hope of achieving better efficacy by increasing the peak blood levels (C_{max}) of mizoribine in patients with refractory lupus nephritis, with reference to the use of methotrexate (MTX) in the treatment of rheumatoid arthritis.

Materials and methods

Patients

Seventeen patients with refractory lupus nephritis who met the revised classification criteria for SLE (1997) during their whole disease courses were enrolled in this study. All subjects had been resistant to conventional treatment with corticosteroids with or without immunosuppressants at the Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, over a 7-year period from May 2003 to April 2009. Patients had been treated for at least 6 consecutive weeks with prednisolone (PSL) $\geq$30 mg/day with little or no response, or needed to reduce the dose of PSL because of adverse reactions or complications. The following patients were excluded: patients with a creatinine clearance $\leq$40 mL/min or serum creatinine $\geq$3.0 mg/dL; patients who were nursing, pregnant, or trying to become pregnant; patients with serious complications such as bone marrow suppression, infections, or peptic ulcers; and patients with hypersensitivity to mizoribine. This study was initiated with the approval of the Ethics Board of Saitama Medical University (approval no. 117/117-II). Written informed consent was obtained in all patients.

Weekly mizoribine pulse therapy

Seven tablets (350 mg) of mizoribine were administered three times at 12 h intervals over 2 consecutive days (700 mg for day 1 and 350 mg for day 2), followed by a washout period from day 3 to day 7. The weekly dose was same as the approved dose (1,050 mg/week).

Clinical assessment was done at 24 months, and the results were compared to the baseline data based on the SLE disease activity index (SLEDAI [9]), serum biochemical analysis, urinalysis, and PSL dose. Missing clinical data were substituted using the last observation carried forward (LOCF) method and employed for statistical analysis (paired t test).

Patients who fulfilled at least one of the following two criteria were considered to be responders: (1) SLEDAI score decreased without increasing the corticosteroid dose; (2) the daily dose of corticosteroid decreased without any elevation in the SLEDAI score. Similarly, nonresponders were defined as patients whose SLEDAI scores and corticosteroid doses were unchanged from the baseline, patients whose SLEDAI scores increased without tapering the dose of corticosteroid, and patients who received an increased corticosteroid dose.

The types of adverse reactions and the actions taken were documented.

To measure the mizoribine blood levels, blood samples were taken 5 times during the treatment course in 10 patients; 2 h after the first dose, immediately before the second dose, and 2 h after the second dose on day 1, and immediately before the third dose and 2 h after the third dose on day 2. Serum samples separated from blood were measured by HPLC at Asahi Kasei Pharma [10].

Results

Demographic features of the 17 patients were as follows: male:female ratio was 4:13; mean age was 33.3 $\pm$ 12.2 years; mean duration of illness was 8.2 $\pm$ 6.6 years. Renal biopsy revealed type II in 2 cases, type II/III in 1 case, type III/IV in 1 case, type IV in 10 cases, and type V in 2 cases. One case was not tested. Previously used immunosuppressants were cyclophosphamide in 5 cases, cyclosporine in 6 cases, tacrolimus in 5 cases, and azathioprine in 5 cases. At the start of treatment with mizoribine, all of the subjects had been using PSL with a mean dose of 27 $\pm$ 17 mg/day (Table 1).

Blood level profiles are shown for the 10 cases in which blood levels were measured over time during the weekly mizoribine pulse therapy (Fig. 1). Mean mizoribine concentrations were 2.4 μg/mL at 2 h after the first dose, 3.3 μg/mL at 2 h after the second dose, and 3.0 μg/mL at 2 h after the third dose.

Changes in clinical parameters at baseline and after 3, 12, and 24 months in subjects undergoing mizoribine pulse therapy are shown in Table 2. Missing clinical data were substituted using the LOCF method and used for statistical analysis (paired t test). The mean SLEDAI score was significantly decreased at 12 months but not at 24 months. Although anti-ds-DNA antibody titer and CH50 did not improve, both urinary protein and the dose of PSL decreased significantly at 24 months. These results suggest

Table 1 Patient demographics

Case	Sex	Age (years)	Duration of illness (years)	Renal biopsy (WHO)	Prior treatment	Mizoribine start date	PSL dose (mg/day)	Concomitant immunosuppressant	Mizoribine treatment time (months)	Mizoribine pulse therapy stopped/continued (reason)
1	F	38	24	V	AZ, POCY	2003.5.12	30	–	80	Continued
2	F	45	4	II/III	–	2005.12.13	30	2009.7.4 ~ CsA	48	Continued
3	F	20	3	IV	CsA, FK-506, AZ, IVCY	2006.10.24	30	–	4	Stopped (liver disorder)
4	F	38	3	III/IV	–	2006.12.11	30	–	36	Continued
5	F	42	8	IV	IVCY, POCY + FK-506	2007.1.15	10	–	22	Continued
6	F	42	8	Not tested	CsA, FK-506	2007.2.9	20	–	4	Stopped (no response)
7	M	25	4	IV	CsA, AZ	2007.5.23	60	–	32	Continued
8	M	29	9	IV	mPSL pulse	2007.6.4	5	2008.5.1 ~ FK-506	30	Continued
9	F	22	5	II	CsA	2007.7.7	10	–	28	Continued
10	F	40	10	IV	CsA, FK-506	2007.2.9	10	–	10	Stopped (no response)
11	F	25	6	V	FK, CsA	2008.7.25	10	2009.5.2 ~ FK-506	16	Stopped (no response)
12	F	56	2	IV	PSL	2008.4.2	40	FK-506	1	Stopped (death by SAH)
13	M	56	11	IV	AZ, POCY	2008.6.30	17.5	–	18	Continued
14	M	21	10	IV	MMF, IVCY, AZ, mPSL pulse	2008.7.4	30	–	9	Stopped (no response)
15	F	23	9	II	AZ, FK-506	2008.9.11	30	2009.9.15 ~ FK-506	15	Continued
16	F	18	1	IV	–	2008.9.29	60	2009.10.7 ~ FK-506	18	Stopped (no response)
17	F	27	24	IV	AZ, FK-506, PE	2009.3.26	50	–	9	Continued

Patient demographics are shown for patients undergoing weekly mizoribine pulse therapy

mPSL methyl prednisolone, *PSL* prednisolone, *CY* cyclophosphamide, *AZ* azathioprine, *CsA* cyclosporine A, *FK-506* tacrolimus, *PE* plasma exchange

the efficacy of concomitant mizoribine pulse therapy. Serum albumin levels increased after 24 months of treatment, but this was not a statistically significant increase.

According to the criteria mentioned above, there were 10 responders and 4 nonresponders (Table 3). Three patients (case nos. 2, 7, and 10) whose SLEDAI scores elevated after successfully reducing the corticosteroid dose could not be classified as either responders or nonresponders. The average peak mizoribine level of the 7 responders was as high as 3.54 μg/mL. One of the 17 subjects undergoing mizoribine pulse therapy experienced liver disorder, resulting in the discontinuation of therapy. Hyperuricemia occurred in four cases. Concomitant treatment with allopurinol was necessary in two of these cases, and this resulted in improvement. Serum creatinine (Cr) levels did not increase in all patients.

Discussion

Mizoribine, a competitive inhibitor of IMPDH, inhibits de novo purine synthesis and reduces the pools of guanine nucleotides, leading to the inhibition of lymphocyte proliferation, like MMF [5]. Mizoribine has been approved for lupus nephritis at a dose of 50 mg three times a day, and enjoys broad clinical use. However, it has been noted clinically that its efficacy is inadequate.

In a placebo-controlled trial on mizoribine in lupus nephritis [11], 6 of the 23 subjects (26.1 %) were rated as "improved or better," although not significantly so, in comparison with the placebo group. Laboratory test results also showed a slight, but not significant, improvement in urinary protein. The incidence of adverse reactions was about the same as for the placebo group. Kuroda et al. [12]

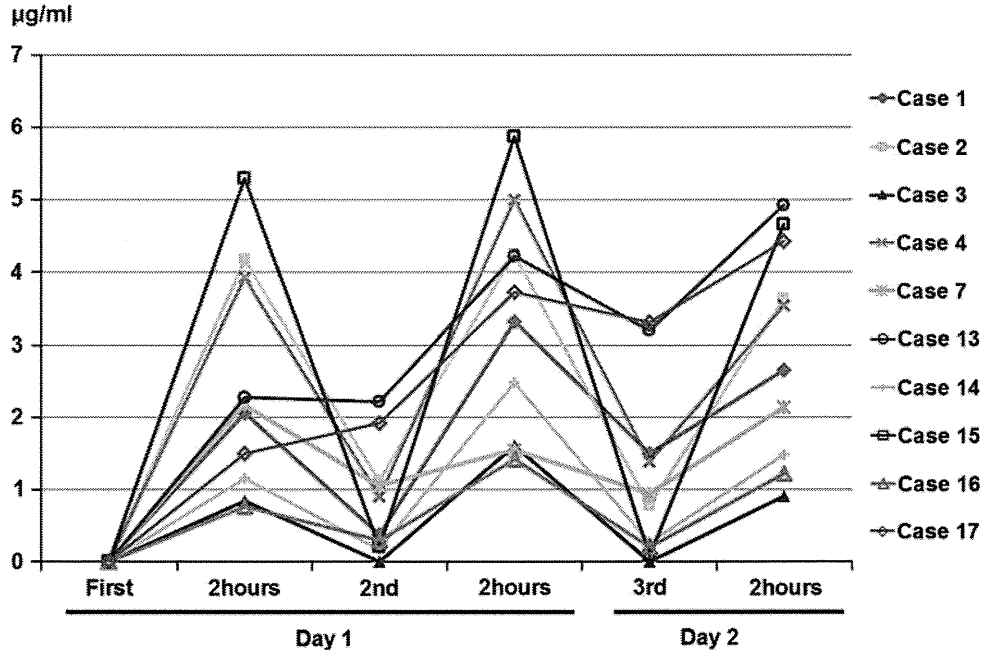

Fig. 1 Blood mizoribine levels in 10 patients Seven tablets (350 mg) of mizoribine were administered three times at 12 h intervals over two consecutive days (700 mg for day 1 and 350 mg for day 2), followed by a washout period from day 3 to day 7. To measure mizoribine blood levels, samples were taken 5 times during the treatment course in 10 patients: 2 h after the first dose, immediately before the second dose and 2 h after the second dose on day 1, and immediately before the third dose and 2 h after the third dose on day 2

Table 2 Clinical assessment of weekly mizoribine pulse therapy

	Baseline (n = 17)	3 months	12 months	24 months
SLEDAI	13 ± 6	10 ± 7	10 ± 7*	10 ± 6
Serum Alb (g/dL)	3.1 ± 0.8	3.4 ± 0.8	3.4 ± 0.9	3.5 ± 0.9
Serum Cr (mg/dL)	1.0 ± 0.5	0.9 ± 0.5	1.2 ± 0.7	1.2 ± 0.7
CH50 (U/mL)	35.4 ± 13.5	37.4 ± 17.4	33.9 ± 18.4	39.7 ± 18.3
Anti-ds-DNA antibody titer (IU/mL)	99 ± 170	89 ± 221	23 ± 27	22 ± 25
Urinary protein (mg/dL)	194 ± 208	157 ± 157	118 ± 108	114 ± 106*
PSL dose (mg/day)	27 ± 17	16 ± 9**	18 ± 12	15 ± 12*

Mean ± SD

CH50 (U/mL), normal = 30–45 U/mL; anti-ds-DNA antibody titer (IU/mL), normal = 0–20 IU/mL

SLEDAI SLE disease activity index

* $p < 0.05$, baseline vs. 24 months; ** $p < 0.01$, baseline vs. 3 months

then studied the association between blood levels and efficacy in patients with lupus nephritis, and showed that the effective range in normal usage is ≥0.66 μg/mL. We therefore suggested that a dose sufficient to enhance efficacy was not established during the development of mizoribine, and it therefore appears that the dose should have been planned accounting for blood levels.

The doses at which mizoribine is used are too low in comparison to MMF. A clinical study was recently conducted in renal transplant patients that used MMF doses as a reference, and high doses of 6–12 mg/kg were shown to be as effective as MMF [8], showing that the effects of mizoribine are related to blood levels. The dose relationship of mizoribine to immunocompetent cells has been studied using various methods, and it has been shown that concentrations of 1–5 μg/mL result in 50 % inhibition of nucleic acid synthesis in human lymphocytes [13–15]. Mizoribine has also been reported to bind to 14-3-3 proteins, enhancing glucocorticoid receptor transcriptional activity, but this effect was significantly enhanced at mizoribine concentrations of ≥10 μM (2.6 μg/mL) [16]. In light of these findings, mizoribine should be administered at a concentration of more than 3 μg/mL [17]. A simulation study of mizoribine in pediatric patients with renal disease showed that the peak serum concentration of mizoribine administered orally once a day at doses of between 2.5 and 13.5 mg/kg (mean 6.14 mg/kg) was as high as 6 μg/mL [17]. Another pharmacokinetic study was done in male healthy volunteers, where 12 mg/kg/day (6 mg/kg twice daily) of mizoribine was well tolerated and C_{max} reached

Table 3 Peak mizoribine concentrations of nonresponder and responder patients

Case no.	PSL	SLEDAI	Mizoribine peak level (μg/mL)
Nonresponders			
6	Increased	Decreased	nd
11	Increased	Unchanged	nd
12	Unchanged	Unchanged	nd
14	Unchanged	Unchanged	2.48
Responders			
1	Decreased	Decreased	3.32
3	Decreased	Unchanged	1.61
4	Decreased	Decreased	3.93
5	Unchanged	Decreased	nd
8	Unchanged	Decreased	nd
9	Unchanged	Decreased	nd
13	Decreased	Decreased	4.23
15	Decreased	Decreased	5.88
16	Decreased	Decreased	1.42
17	Decreased	Decreased	4.42
			(3.54 ± 1.73)

4.6 ± 1.6 μg/mL [18]. The therapeutic window of mizoribine for suppressing acute-phase rejection following transplantation has been defined in terms of the trough concentration as 0.5–3.0 μg/mL. This was achieved using a dosing regimen of 6 mg/kg twice daily [18]. Yumura et al. reported on the pharmacokinetics of mizoribine in patients with lupus nephritis. Blood kinetics were compared at three mizoribine doses: 150 mg once a day, 100 mg twice a day, and 50 mg three times a day. At a dose of 150 mg, the mean peak blood level was 1.8 μg/mL. In contrast, the peak blood level at three doses of 50 mg was less than 1 μg/mL [19].

Recently, the efficacy of mizoribine pulse therapy (500 mg twice a week) has been reported in a patient with focal segmental glomerulosclerosis [20]. Good results have also been reported with mizoribine pulse therapy in pediatric lupus nephritis [21, 22]. A peak mizoribine blood level of 3 μg/mL was targeted in these reports as well. The outcomes were similar to those reported here, and the results fully support our approach.

In light of the fact that weekly administration of MTX at 12 h intervals was widely reported to be effective for rheumatoid arthritis, and considering the previous case reports on the effectiveness of high-dose mizoribine therapies for lupus nephritis, we developed weekly mizoribine pulse therapy, in which the weekly dose would be given over 2 days in order to get sufficient or higher blood levels of mizoribine. Seventeen patients with active refractory lupus nephritis who had been resistant to corticosteroids and immunosuppressants were enrolled in this study. The high doses of mizoribine administered, 350 mg at a time (maximum daily dose of 700 mg), led to peak blood levels of ≥3 μg/mL. Although clinical markers for lupus activity such as SLEDAI, anti-dsDNA titer, and serum complement level did not change, corticosteroid doses were significantly reduced. Ten of the 17 subjects were considered responders with peak blood levels of mizoribine as high as 3.5 μg/mL, which also supports the idea that peak blood levels of mizoribine are an important factor in the efficacious treatment of lupus nephritis. Although the number of patients analyzed was very small, peak mizoribine concentration may be related to clinical response. Some subjects were still on mizoribine monotherapy for more than 2 years after being weaned from corticosteroids (Fig. 2). No serious adverse reactions were observed in our 17 patients. However, mild liver dysfunction occurred in 1 case, and hyperuricemia occurred in 4 cases.

A number of immunosuppressants and a wide range of treatment options that can be used for lupus nephritis are currently available in Japan. Tacrolimus is used to treat refractory lupus nephritis, but is not always effective [23]. Multi-target therapy has recently been proposed, and the results of combination treatment with MMF and tacrolimus have been published [24]. Based on that research, combination therapy with mizoribine and tacrolimus has been studied in Japan, with good results [25]. Such a combination therapy may be a good treatment option for remission induction therapy and lead to better outcomes for lupus nephritis.

Mizoribine is a IMPDH inhibitor that causes the inhibition of purine synthesis by lymphocytes. As shown by the efficacies of various immunosuppressive therapies, such as cyclophosphamide and MMF, it is necessary to suppress lymphocyte function to control lupus nephritis. In this study, immunological markers such as anti-dsDNA titer and serum complement level did not improve significantly. This may be because they were already suppressed by a previous long-term immunosuppressive treatment, including moderate to high dose steroid treatment. Our weekly mizoribine pulse therapy yielded a C_{max} of mizoribine of 3 μg/mL or more, which the approved dose regimen (50 mg three times a day) cannot reach, leading to the suppression of lymphocyte function and enabling us to reduce the dose of concomitant corticosteroid administered to control lupus activity. In this therapeutic strategy, serum mizoribine levels are almost zero from day 4 to day 7. Given that the clinical efficacy of intermittent mizoribine pulse therapy has been demonstrated in previous reports [20, 21] as well as in our 10 responders, it appears to be important to obtain a sufficiently high peak serum level (more than 3 μg/mL), even only transiently.

Concomitant immunosuppressive agents should be used to reduce the risk of adverse effects of long-term steroid