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

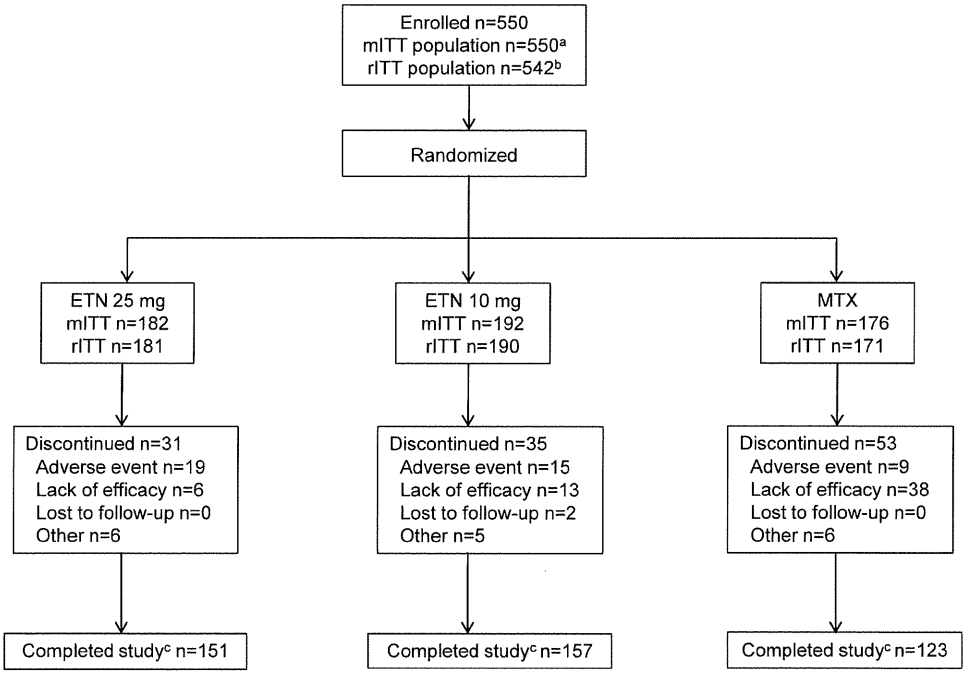

Fig. 1 Subject disposition. [a] All subjects in the modified intent-to-treat (*mITT*) population were also in the safety population, [b] 8 subjects did not have baseline or post-baseline radiographic data and were not included in the radiographic intent-to-treat (*rITT*) population, [c] all subjects 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;

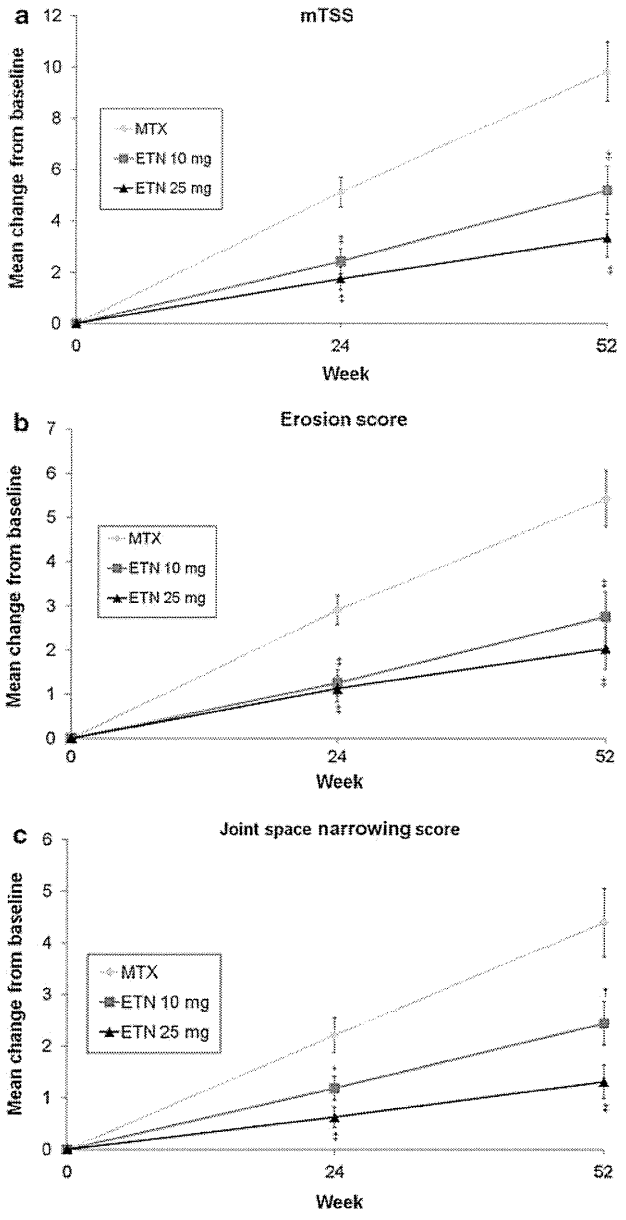

Fig. 2 Mean change from baseline in the modified total Sharp score (mTSS), erosion, and joint space narrowing (JSN) scores at weeks 24 and 52 for subjects with rheumatoid arthritis (RA) after treatment. Analyses were performed on the rITT population. *Error bars* SE. *$P = 0.0013$ vs. MTX and $P = 0.0186$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

A comparison of incidence and risk factors for serious adverse events in rheumatoid arthritis patients with etanercept or adalimumab in Korea and Japan

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Abstract

Objective. To compare the incidence and risk factors of serious adverse events (SAEs) in rheumatoid arthritis (RA) patients treated with etanercept (ETN) or adalimumab (ADA) between Korean and Japanese registries.

Methods. We recruited 416 RA patients [505.2 patient-years (PYs)] who started ETN or ADA from Korean registry and 537 RA patients (762.0 PY) from Japanese registry. The patient background, incidence rate (IR) of SAE in 2 years, and risk factors for SAEs were compared.

Results. Korean patients were younger and used more nonbiologic DMARDs, higher doses of methotrexate, and lower doses of prednisolone (PSL). The IR of SAEs (/100 PY) was higher in the Japanese registry compared to the Korean [13.65 vs. 6.73]. In both registries, infection was the most frequently reported SAE. The only significant risk factor for SAEs in Korean registry was age by decade [1.45]. In Japanese registry, age by decade [1.54], previous use of nonbiologic DMARDs ≥ 4 [1.93], and concomitant use of oral PSL ≥ 5 mg/day [2.20] were identified as risk factors for SAEs.

Conclusions. The IR of SAE in Japan, especially infection, was higher than that of Korea, which was attributed to the difference of demographic and clinical characteristics of RA patients and treatment profiles.

Keywords

Epidemiology, Registry, Rheumatoid arthritis, Safety

History

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Introduction

The introduction of biologic disease-modifying antirheumatic drugs (biologic DMARDs) in the past decade has revolutionized treatment of rheumatoid arthritis (RA). Efficacy and safety of treatment with biologic DMARDs have been demonstrated in a number of clinical trials, but cost and long-term effectiveness of treatment with biologic DMARDs and safety in older patients or those with comorbidities, who are generally excluded from clinical trials, have been of concern [1]. To complement the evidence obtained from clinical trials, observational cohorts for RA patients treated with biologic DMARDs have been established in many countries, and have provided indispensable evidence for the safety and effectiveness of biologic DMARDs in clinical practice. However, some cohorts have reported results with differing magnitudes or even discordance of risk for the same adverse events [2]. For example, the incidence of serious infections in European RA registries was comparable [3,4], whereas in the US, lower rates have been reported in some studies [5]. These discrepant results arise from methodological differences, such as case definition for adverse events, length of follow-up, or selection and structure of a comparator group. Difference in treatment profile and ethnics may also account for the discrepancy. Therefore, a careful comparison of registries from various point of views including methodology is

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imperative to understand similarities and differences in the results obtained from each registry [6].

Through international collaborations among countries, the comparison of data from RA patients treated with biologic DMARDs will allow us to investigate the impact of differences in patients' characteristics and health care systems on efficacy and safety of the treatment. Curtis et al. [2] have conducted the qualitative comparison of RA biologics registries in US and Europe and reported that different patients' demographics, patterns of comorbidities, and sociodemographic characteristics provide valuable information to address the comparative safety of treatments for RA. However, no international collaborative studies have yet been reported to investigate the same outcomes using harmonized methodologies. In Korea, the effectiveness and safety of biologic DMARDs in clinical practice have been reported using a retrospective biologic DMARDs registry (REtrospective study for Safety and Effectiveness of Anti-RA treatment with biologiCs, RESEARCh) [7]. In Japan, the REgistry of Japanese rheumatoid Arthritis patients on Biologics for Long-term safety (REAL) has provided evidence about safety of biologic DMARDs in Japanese RA patients [8,9]. Taking advantage of these established cohorts for patients with RA, we conducted the first epidemiological study to compare data from two countries where biologic DMARDs are widely used for treatment of RA.

For this study, we carefully scrutinized features of Korean and Japanese registries and considered standardization of methodological approaches. We conducted this study to reveal the factors influencing safety of adalimumab (ADA) or etanercept (ETN) by comparing RA patients treated with these drugs from Korean and Japanese registries in terms of retention rates and reasons for discontinuation of biological DMARDs, incidence rates (IR) of serious adverse events (SAEs), and factors influencing their development.

Patients and methods

Database and patients

RESEARCh

The retrospective registry of Korean patients with RA, the RESEARCh, was established to evaluate the safety and effectiveness of biologic DMARDs by Clinical Research Center of Rheumatoid Arthritis (CRCRA) funded by Ministry of Health and Welfare, Republic of Korea [7]. All patients meeting the 1987 American College of Rheumatology criteria for RA who had ever been treated with biologic DMARDs from December 2000 to June 2011were identified from the medical records of Hanyang University Hospital for Rheumatic Diseases. The RESEARCh study was approved by the ethics committees of the Hanyang University Hospital, and informed consent was not required because the data was deidentified and collected retrospectively.

Comprehensive chart reviews for all patients were undertaken by well-trained health professionals; and demographics, disease activity, comorbidities, medications, and laboratory data during the use of biologic DMARDs and their SAEs were collected. For the patients who were in use of biologic DMARDs at the time of data collection, the observational period was defined from starting point of current agent to assessment date. For the other patients who had stopped biologic DMARDs before data collection, the agent with longest use for each patient was included in this database. Demographic features of RA patients and the persistence of TNF inhibitors in the RESEARCh database were quite similar to those of a previously reported study using nation-wide claims database of Korea; mean age (50.5 ± 13.2 in the RESEARCh vs. 50.6 ± 14.9 in the nation-wide database), proportion of female (86.1% vs. 84.9%), and persistence of TNF inhibitors during one year (74% vs. 73%) [7,10].

REAL

REAL is a prospective cohort established to investigate the long-term safety of biologic DMARDs in RA patients. Twenty-seven institutions participate, including 16 university hospitals and 11 referring hospitals. Details of the REAL have been previously described [9,11]. Briefly, the criteria for patient enrollment in the REAL include meeting the 1987 American College of Rheumatology criteria for RA, written informed consent, and starting or switching treatment with biologic DMARDs or starting, adding, or switching nonbiologic DMARDs at the time of enrollment in the REAL. Demography, disease activity, comorbidities, treatments, and laboratory data at the time of enrollment in the REAL were recorded. A follow-up form was submitted every 6 months by participating physicians to the REAL Data Center at the Department of Pharmacovigilance of Tokyo Medical and Dental University to report the occurrence of SAEs, current RA disease activity, treatments, and clinical laboratory data. Each patient is followed for 5 years. Enrollment in the REAL database was started in June 2005 and closed in January 2012. Data were retrieved from the REAL database on August 24, 2011 for this study. The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and other participating institutions. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Patients and follow-up

We first identified 416 Korean RA patients whose registered biologic DMARDs in the RESEARCh database were ADA or ETN and 537 Japanese patients with RA who used ADA or ETN as the first biologic DMARDs in the REAL database, and enrolled themselves in this study. The reason for selecting ADA and ETN for this study is that these two biologics were approved within two calendar years in both countries. The observation period for this study started at the first dose of one of these biologic DMARDs. Observation of each patient was stopped either 2 years after the start of the observation period, or on the date of discontinuation of these biologic DMARDs, switching to other biologic DMARD, death, loss-to-follow up, or enrollment in clinical trials, whichever came first. We defined discontinuation of treatment with ADA or ETN as stopping administration of these agents for more than 90 days. Reasons for discontinuation of these biologic DMARDs were retrieved from medical records and classified into adverse events (AEs), Lack of efficacy (LOE), or miscellaneous. When a patient had two or more reasons for drug discontinuation, site investigators assigned precedence and the primary reason contributing to drug discontinuation for the patient was used.

Definition for comorbidity

For qualitative comparison, comorbidity was defined as cardiovascular and cerebrovascular diseases, including angina, myocardial infarction, heart failure, and strokes; pulmonary diseases, including interstitial lung diseases, chronic obstructive pulmonary diseases, and asthma; or liver diseases, including abnormalities in liver function tests, liver cirrhosis, hepatitis B, and hepatitis C. Renal dysfunction was defined using the estimated glomerular filtration rate (eGFR). We used a modification of diet in renal disease (MDRD) formula to calculate eGFR and categorized according to the stage of chronic kidney disease (CKD) [12]. Anemia was defined using the WHO criteria (hemoglobin level < 13 g/dl for men and < 12 g/dl for women) [13].

Definition of SAEs

Our definition of a SAE, including serious infection (SI), was based on the report by the International Conference on Harmonization. In addition, bacterial infections that required intravenous administration of antibiotics, as well as opportunistic infections, were also regarded as SAEs. SAEs were classified using the System Organ Class (SOC) of the medical dictionary for regulatory activities (MedDRA version 11.1). SAEs were attributed to ETN or ADA when they developed during treatment with these biologics and no risk window was applied.

Statistical analysis

The chi-square test was used for comparison of categorical variables and the Mann–Whitney test for continuous variables. Drug retention rates were compared using the Kaplan–Meier method and the log-rank test. Crude IRs per 100 PY and crude incidence rate ratios (IRRs) with their 95% confidence intervals (CI) comparing Japan to Korea were calculated for all SAEs occurring from the first dose of ADA or ETN to the end of the observation period. For multivariate analysis, the Cox regression model with the forced entry method was employed. These statistical analyses were performed using SPSS (version 20.0, SPSS Inc., Chicago, IL USA). All p values were 2-tailed and $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical baseline characteristics of patients from the two registries

We first compared baseline demographic and clinical characteristics of RA patients who used ADA or ETN in each registry (Table 1 and Figure 1). Patients in the RESEARCh were younger (47.5 ± 15.8 vs. 58.9 ± 13.3 years-old, $p < 0.001$) and had shorter disease duration (8.5 ± 6.7 vs. 9.9 ± 9.0, years $p = 0.009$) than those in the REAL. The proportions of patients without previous exposure to biologic DMARDs (i.e., biologic DMARD-naïve patients) did not differ between the two registries, while 60.0% of the patients in the RESEARCh, but only 29.4% in the REAL, experienced four or more nonbiologic DMARDs ($p < 0.001$). The mean numbers of previous nonbiologic DMARDs were 4.1 in the RESEARCh and 2.6 in the REAL; the distribution is shown in Figure 1A. The mean Disease Activity Score calculated based on three variables including 28-swollen and tender joints count and C-reactive protein at starting biologic DMARDs did not differ between the registries. Patients in the RESEARCh used concomitant methotrexate (MTX) more frequently and at higher dosage than those in the REAL (75.9% and 13.3 ± 3.2 mg/week vs. 54.2% and 7.7 ± 2.4 mg/week, $p < 0.001$ for both) (Table 1 and Figure 1B). On the other hand, patients in the REAL used concomitant corticosteroids (CSs) more frequently and at higher dosage than those in the RESEARCh (PSL-equivalent dose, 6.0 ± 3.5 mg/day vs. 4.5 ± 3.1 mg/day, $p < 0.001$) (Table 1 and Figure 1C).

The rates for comorbidities differ significantly between the two registries. The rates for patients with peptic ulcer (6.0% for the RESEARCh vs. 0.7% for the REAL), liver disease (10.8% vs. 6.7%), hypertension (21.9% vs. 15.8%), and anemia (73.8% vs. 60.5%) were significantly higher in the RESEARCh compared to the REAL. However, the rates for pulmonary disease (5.3% vs. 20.3%) and diabetes mellitus (9.4% vs.13.6%) were significantly higher in the REAL than in the RESEARCh (Table 1).

Table 1. Demographic and clinical characteristics of patients with RA treated with ETN or ADA from Korean (RESEARCh) and Japanese (REAL) registries.

	RESEARCh ($n = 416$)	REAL ($n = 537$)	p value
Age (years-old) mean ± SD	47.5 ± 15.8	58.9 ± 13.3	<0.001
>65, n (%)	57 (13.7)	201 (37.4)	<0.001
Gender (female), %	84.3	79.0	0.067
Disease duration (years), mean ± SD	8.5 ± 6.7	9.9 ± 9.0	0.009
DAS28(3)/CRP*, mean ± SD	4.4 ± 0.9	4.5 ± 1.3	0.973
Unexposed to biological DMARDs, (%)	333 (80.0)	440 (81.9)	0.505
Number of previous nonbiologic DMARDs† ≥4, (%)	249 (60.0)	158 (29.4)	<0.001
MTX, mg/week (%)	13.3 ± 3.2 (75.9)	7.7 ± 2.4 (54.2)	<0.001
Corticosteroid**, mg/week (%)	4.5 ± 3.1 (72.1)	6.0 ± 3.5 (67.6)	<0.001
Cardiovascular disease, n (%)	11 (2.6)	30 (5.6)	0.026
Pulmonary disease‡, n (%)	22 (5.3)	109 (20.3)	<0.001
Liver disease, n (%)	45 (10.8)	36 (6.7)	0.024
Peptic ulcer, n (%)	25 (6.0)	4 (0.7)	<0.001
Diabetes mellitus, n (%)	39 (9.4)	73 (13.6)	0.045
Hypertension, n (%)	91 (21.9)	85 (15.8)	0.017
Anemia¶, n (%)	307 (73.8)	325 (60.5)	<0.001
Renal dysfunction§, n (%)			
Advanced staged CKDs (CKD3, 4 or 5), n (%)§	23 (5.5%)	14 (2.6%)	0.021

SD, standard deviation; DAS28, disease activity score including 28-joint count; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; PSL, prednisolone; CKD, chronic kidney disease; GFR, glomerular filtration rate

*DAS 28(3)/CRP was calculated based on three variables; swollen and tender joint counts and CRP.

**The oral corticosteroid dose was converted to the equivalent PSL dosage.

†Nonbiologic DMARDs included MTX, hydroxycholoroquine, sulfasalazine, leflunomide, bucillamine, mizoribine, tacrolimus, azathioprine, cyclosporin.

‡Pulmonary disease included interstitial lung disease, chronic obstructive pulmonary disease, and asthma.

¶Anemia was defined using WHO criteria.

§Renal dysfunction was defined using GFR calculated by modification of diet in renal disease. GFR was categorized according to the staging of CKD.

MTX and corticosteroid doses are shown as the mean ± SD among users of these drugs.

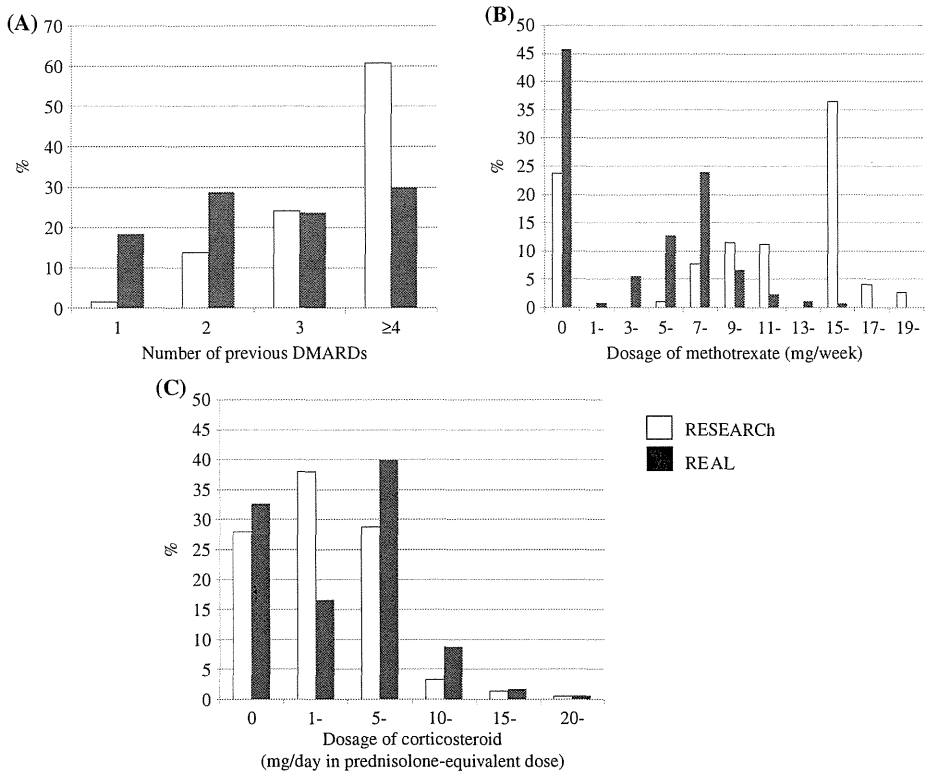

Figure 1. Comparison of RA-related medication usage between two registries, RESEARCh (Korea) and REAL (Japan). For all graphs, the white columns indicate the rates in RESEARCh and the black columns indicate the rates in REAL.
(A) Comparison of the numbers of previous nonbiologic DMARDs between the two registries.
(B) Comparison of baseline MTX dosage between the two registries.
(C) Comparison of baseline corticosteroid dosage between the two registries.

Reasons for drug discontinuation and retention rates for ADA and ETN

The median interquartile range treatment period for each registry was 1.3 (0.5–2.0) years for the RESEARCh and 2.0 (0.8–2.0) years for the REAL. The numbers of patients who discontinued ADA or ETN for any reasons during the observation period were 124 (29.8%) for the RESEARCh and 144 (26.8%) for the REAL ($p = 0.308$ by chi-square). The reasons for discontinuation of ETN or ADA in each registry are shown in Table 2. The development of AEs was the most frequent reason for the discontinuation in both the RESEARCh ($n = 41$, 33.1%) and the REAL ($n = 56$, 38.9%). The two major AEs leading to discontinuation of the biologic DMARDs were infection and allergic reaction for both registries. There was no significant difference in the retention rates of ETN and ADA for 2 years between the registries (64.6% in the RESEARCh, 70.1% in the REAL, $p = 0.060$ by Kaplan–Meier analysis and log-rank test [supplementary Figure 2A available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695]), and no significant differences for treatment discontinuation due to AEs ($p = 0.848$ by log-rank test [supplementary Figure 2B available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695]).

Types and occurrence of SAEs

Among 416 patients with 505.2 PY in the RESEARCh, 34 SAEs were reported during the observation period, while 104 SAEs in 537 patients with 762.0 PY were found in the REAL. Based on the SAE categories classified using the SOC, 'infection and infestations' was the most common category in both registries (15 cases for the RESEARCh and 38 for the REAL) and 'respiratory, thoracic and mediastinal disorders' was the second most common category (5 cases for the RESEARCh and 13 for the REAL).

Pulmonary infection was the most frequent site-specific infection in both registries (9 cases for the RESEARCh and 22 cases for the REAL), followed by skin infection, including herpes zoster and cellulitis (4 cases for the RESEARCh and 8 cases for the REAL). Other infections included one bone and joint infection and one subcutaneous tuberculosis in the RESEARCh, and two urinary infections, four sepses, one infectious gastroenteritis, and one infection not otherwise specified in the REAL. The IR for SAEs

Table 2. Reasons for drug discontinuation of patients with RA treated with ETN or ADA in Korean (RESEARCh) and Japanese (REAL) registries.*

Reasons for drug discontinuation	RESEARCh ($n = 124$)†	REAL ($n = 144$)†
Adverse events, n (%)	41 (33.1)	56 (38.9)
Infection, n (%)	11 (8.9)	19 (13.2)
Pulmonary disease except infection‡, n (%)	4 (3.2)	6 (4.2)
Allergy reaction, n (%)	10 (8.1)	12 (8.3)
Malignancy, n (%)	0 (0)	4 (2.8)
Cardiovascular system disease, n (%)	2 (1.6)	3 (2.1)
Others, n (%)	14 (11.3)	12 (8.3)
Lack of efficacy, n (%)	31 (25.0)	53 (36.8)
Miscellaneous§, n (%)	52 (41.9)	35 (24.3)

Chi-square test was applied to assess differences in the proportion of causes for discontinuation (i.e., adverse event, lack of efficacy, and miscellaneous), and the adjusted residuals were calculated. A significant difference among the two groups ($p = 0.007$) was observed. The adjusted residuals indicated that significantly higher percentage of patients in the REAL stopped the treatment due to lack of efficacy compared to the RESEARCh and significantly more patients in the RESEARCh stopped the treatment due to miscellaneous.

*Values are the number (percentage) of patients who discontinued ETN or ADA because of each reason.

†Number of patients who discontinued ETN or ADA for any reason.

‡Pulmonary diseases except for infection included interstitial pneumonia and other pulmonary diseases.

§Miscellaneous included good control, patients' preference, financial reasons, and pregnancy. Among 52 cases in the RESEARCh, 14 cases discontinued for financial reasons, 6 cases for patients' refusal, 7 cases for procedure, 5 cases for good control, 4 cases for transfer to local clinic, 1 case for pregnancy, 15 cases for other reasons. In the REAL, among 35 cases, 20 cases for good control, 10 cases for patients' preferences, and 5 cases for financial reasons.

Table 3. Occurrence of SAEs in patients with RA treated with ETN or ADA in Korean (RESEARCh) and Japanese (REAL) registries.*

	RESEARCh 505.2 PY IR (/100 PY)	REAL 762.0 PY IR (/100 PY)	REAL vs. RESEARCh Crude IRR (95% CI)
Total SAEs†	6.73 (4.74–9.29)	13.65 (11.21–16.47)	2.03 (1.38–2.99)
Blood and lymphatic system disorders	0	0.52 (0.18–1.25)	NA
Cardiac disorders	0	0.66 (0.25–1.44)	NA
Endocrine disorders	0	0.26 (0.05–0.84)	NA
Eye disorders	0	0.13 (0.01–0.61)	NA
Gastrointestinal disorders	0	0.79 (0.33–1.62)	NA
General disorder and administration site conditions	0.20 (0.02–0.92)	0.39 (0.11–1.05)	1.99 (0.21–19.12)
Hepatobiliary disorders	0.79 (0.26–1.88)	0.26 (0.05–0.84)	0.33 (0.06–1.81)
Infections and infestations	2.97 (1.73–4.77)	4.99 (3.58–6.77)	1.68 (0.92–3.05)
Injury, poisoning, and procedural complications	0.99 (0.38–2.17)	1.31 (0.67–2.33)	1.33 (0.45–3.88)
Investigations	0	0.39 (0.11–1.05)	NA
Musculoskeletal and connective tissue disorders	0.40 (0.08–1.27)	0.79 (0.33–1.62)	1.99 (0.40–9.85)
Nervous system disorders	0.20 (0.02–0.92)	0.39 (0.11–1.05)	1.99 (0.21–19.12)
Renal and urinary disorders	0	0.39 (0.11–1.05)	NA
Reproductive system and breast disorders	0	0.26 (0.05–0.84)	NA
Respiratory, thoracic and mediastinal disorders	0.99 (0.38–2.17)	1.71 (0.96–2.83)	1.44 (0.55–3.78)
Skin and subcutaneous tissue disorders	0.20 (0.02–0.92)	0.26 (0.05–0.84)	1.33 (0.12–14.62)
Vascular disorders	0	0.13 (0.01–0.61)	NA

PY, patient-year; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NA, not applicable
*Crude IR per 100 PY and crude IRR with their 95% CI were calculated for each category of SAEs occurring from the first to the last dose of ETN or ADA.
†SAEs were classified using the SOC of the MedDRA version 11.1.

are summarized in Table 3. The crude IRR comparing the REAL with the RESEARCh for all SAEs was 2.03 (95% CI, 1.38–2.99). The IRR for infections and respiratory diseases were 1.68 (95% CI, 0.92–3.05) and 1.44 (95% CI, 0.55–3.78), respectively (Table 3).

Factors influencing development of SAEs

To determine factors influencing development of SAEs, we compared patients who had and had not experienced SAEs using a univariate analysis and selected variables with p value < 0.05 or those with medical importance for the multivariate analysis. In the RESEARCh, age per decade (hazard ratio [HR] 1.45, 95% CI 1.10–1.91) was identified as the only risk factor for development of SAEs using the multivariate Cox regression model. In the REAL, age per decade (HR 1.54, 95% CI 1.22–1.93), previous use of nonbiologic DMARDs ≥ 4 (HR 1.93, 95% CI 1.20–3.10), concomitant use of oral CSs (PSL-equivalent dose) ≥ 5 mg/day (HR 2.20, 95% CI 1.11–4.35) were identified as risk factors for SAEs using the multivariate Cox regression model. We then combined the patients from the two registries and performed the multivariate Cox regression analysis. In this analysis, the risk for SAEs was significantly higher in older patients (HR 1.47 per decade, 95% CI 1.23–1.74), and with previous use of nonbiologic DMARDs ≥ 4 (HR 1.64, 95% CI 1.09–2.47) and concomitant use of oral CSs (0 < PSL-equivalent dosage < 5 mg/day; HR 1.91, 95% CI 1.04–3.49, ≥ 5 mg/day; HR 2.04, 95% CI 1.18–3.53) (Table 4).

Discussion

This is the first study to directly compare safety of biologic DMARDs using harmonized methods between two registries from two

Table 4. Factors influencing development of SAEs in patients with RA treated with ETN or ADA in Korean (RESEARCh) and Japanese (REAL) registries.*

	RESEARCh		REAL		Data combined	
Variables at baseline	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age by decade	1.48 (1.15–1.89)	1.45 (1.10–1.91)	1.57 (1.27–1.95)	1.54 (1.22–1.93)	1.52 (1.31–1.77)	1.47 (1.23–1.74)
Gender (female)	0.77 (0.33–1.76)	0.75 (0.32–1.76)	0.67 (0.40–1.13)	0.87 (0.51–1.49)	0.68 (0.44–1.05)	0.82 (0.52–1.28)
Previous nonbiological DMARDs ≥ 4	1.50 (0.72–3.14)	1.14 (0.53–2.43)	2.20 (1.39–3.47)	1.93 (1.20–3.10)	1.64 (1.12–2.40)	1.64 (1.09–2.47)
Concomitant use of MTX						
0 mg/week	1	1	1	1	1	1
0 < MTX < median value† (mg/week)	0.42 (0.18–1.01)	0.40 (0.17–0.97)	0.70 (0.37–1.32)	0.90 (0.46–1.76)	0.60 (0.38–0.95)	0.78 (0.48–1.27)
MTX ≥ median value (mg/week)	0.46 (0.21–0.99)	0.49 (0.22–1.08)	0.56 (0.32–0.97)	1.00 (0.55–1.83)	0.44 (0.27–0.72)	0.67 (0.37–1.21)
Concomitant use of corticosteroid						
0 mg/day	1	1	1	1	1	1
0 < PSL < 5 mg/day	1.94 (0.76–4.96)	2.01 (0.78–5.20)	2.20 (1.00–4.84)	1.85 (0.82–4.17)	1.98 (1.09–3.60)	1.91 (1.04–3.49)
≥ 5 mg/day	1.77 (0.66–4.71)	1.60 (0.60–4.33)	2.66 (1.38–5.11)	2.20 (1.11–4.35)	2.47 (1.44–4.23)	2.04 (1.18–3.53)
Chronic pulmonary disease‡	1.84 (0.56–6.03)	1.17 (0.35–3.98)	2.51 (1.56–4.04)	1.66 (0.97–2.83)	2.58 (1.69–3.93)	1.56 (0.97–2.50)
Chronic renal disease§	0.53 (0.07–3.89)	0.35 (0.05–2.61)	2.33 (0.85–6.39)	1.55 (0.55–4.37)	1.29 (0.53–3.17)	0.91 (0.36–2.27)
Nationality (Japan)					1.52 (1.01–2.29)	0.95 (0.55–1.64)

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; PSL, prednisolone
*Cox regression model analysis, adjusted for the variables included in the table.
†Median value of each registry; 15 mg/week for the RESEARCh, 8 mg/week in the REAL, 10 mg/week in the data combined.
‡Chronic pulmonary disease included interstitial lung disease, chronic obstructive pulmonary disease, and asthma.
§Chronic renal disease means chronic kidney stages 3, 4, or 5.

countries in Asia. This study provides unique findings about safety of ADA and ETN because the two registries have different demographic and clinical characteristics of patients, as well as treatment profiles before starting biologic DMARDs. Some of these differences are identified as factors influencing the development of SAEs.

We found significant differences in demographic and clinical characteristics of RA patients between the two registries. First, in the RESEARCh, significantly more patients had experienced four or more nonbiologic DMARDs before starting ETN or ADA than the REAL, although patients in the RESEARCh were significantly younger with shorter disease durations than the REAL. In Korea, according to strict reimbursement guidelines, rheumatologists are required to treat a patient with at least two nonbiologic DMARDs, including MTX, for six months before confirming inadequate response to the treatment and starting TNF inhibitors. Japanese guidelines in 2007 recommend treatment with TNF inhibitors for patients who had inadequate response to treatment with at least one DMARD for 3 months [14]. Second, patients in the RESEARCh used concomitant MTX more frequently and higher dosages than those in the REAL. The maximum approved dosage for MTX in these countries apparently affects the use of the anchor drug in the two registries; i.e., 8 mg/week until February 2011, allowed up to 16 mg/week now in Japan and 20 mg/week in Korea.

The unadjusted IR of overall SAEs in the REAL was significantly higher than in the RESEARCh (IRR 2.03, 95% CI 1.38–2.99), explained at least in part by the numerically higher IR of SI in the REAL compared to the RESEARCh. The incidence of SIs in the REAL of 4.99/100 PY was comparable to Western registries incidence of 5.4–6.6/100 PY, whereas a lower incidence in the RESEARCh of 2.97/100 PY was observed [3,4,15]. We suppose that demographic features including age structure and comorbidity profiles of the two cohorts contributed to the difference. The proportion of elderly (≥65) in the general population in Japan was higher than in Korea in 2009 (22.7% in Japan vs. 10.4% in Korea) [16,17]. Compatible with these figures, the prevalence of elderly RA (≥65-year-olds) was 36.2% in a Japanese RA cohort [18] and 21.8% in Korean RA cohort [19]. Increased percentage of patients with pulmonary comorbidities, cardiovascular diseases, and diabetes mellitus in Japan may be explained by higher prevalence of elderly RA patients and longer disease duration. The prevalence of infection-related comorbidities such as pulmonary diseases, diabetes mellitus, and renal dysfunction is significantly higher in the REAL compared to the RESEARCh. It is plausible that the higher prevalence of comorbidities could be associated with the higher IR of SIs in the REAL. This association was supported by a previous comparative study showing that the difference in incidence of SIs between the American and European registries could be derived from differing comorbidity profiles of the registries [2].

Difference in the use of CSs between the two countries needs to be mentioned. It has been reported that the frequent usage of CSs at higher dosages was significantly associated with development of SIs in cohort studies from Western countries [20–22]. Japanese post marketing surveillance for ETN (HR 2.03, 95% CI 1.46–2.84) [23] and tocilizumab [24] (odds ratio 2.17, 95% CI 1.25–3.74) also revealed that concomitant use of CSs was one of the risk factors for SIs. Moreover, higher dosages of CSs significantly increased the risk for SIs in the REAL and its relative risk was the highest among the identified risk factors (2.49, 95% CI 1.08–5.50) [9]. Overall, it is apparent that use of CSs leads to a higher risk for SIs. In this study, the mean dosage of CSs at baseline was significantly higher in the REAL compared to the RESEARCh, which also explains the difference in incidence of SIs between the two registries. Furthermore, frequent usage of CSs at higher dosages may also be responsible for the higher prevalence of diabetes mellitus in Japanese RA patients, which in turn makes them more susceptible to infection. These data emphasize the importance of minimizing exposure to CSs in RA patients to decrease the risk for SIs.

Age, previous use of nonbiologic DMARDs ≥ 4, and concomitant use of CSs were significantly associated with occurrence of SAEs in the REAL as well as in the combined data, while the latter two factors were not in the RESEARCh. It has been reported that RA patients with larger number of previously used DMARDs have increased risk for SIs [20,22], which could explain the association between nonbiologic DMARDs ≥ 4 and SAE in this study because SIs account for about 40% of the SAEs (Table 3). In general, larger numbers of previously used DMARDs suggest long-standing and/or intractable disease. This may not be the case, however, for Korean patients given biologics because the patients have to be treated at least with DMARDs ≥ 2 beforehand by strict reimbursement guidelines. Such difference could lead to lack of association between previous use of nonbiologic DMARDs ≥ 4 and SAE in the RESEARCh. Weak trend toward positive association between the concomitant use of CS and SAE was observed in the RESEARCh. The small number of SAEs in the RESEARCh probably contributed to wide 95% confidence interval of the HR for the concomitant use of CS (Table 4) and the factor did not reach statistical significance.

There are certain limitations in our study. First, the difference of study design between the two registries should be mentioned. The data were obtained retrospectively from the RESEARCh registry and prospectively from the REAL registry [25], which could affect the results of this comparative study. To compensate for this difference in collecting data, we standardized the definition of SAEs, reasons for drug discontinuation, and variables such as comorbidities in two registries in this study as described in Patients and Methods. We discussed ambiguous SAE cases through regular meetings as well. A second limitation is that we did not investigate the patients with other biologics except for ETN and ADA. The safety and tolerance of a biologic DMARD can be affected by the approval status of other biologic and nonbiologic DMARDs [26]. The difference in approval status of biologic and nonbiologic DMARDs should be considered when we compare the use of biologic DMARDs between two countries. In this study, therefore, we focused on ADA and ETN, which were approved for treatment of RA within two calendar years in Korea and Japan (see Supplementary Figure S1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695). Third limitation is that RESEARCh was performed in a single institution, whereas REAL is comprised of 27 institutions, which may create selection bias in the study.

In conclusion, the differences in the demographic and clinical characteristics such as age structures, patterns of comorbidity, and treatments profile for RA between the two countries affect types and incidences of SAEs. This international collaborated study facilitates our understanding of similarity and discrepancy in the results from various biological registries, and may help applying the evidence to clinical management of patients with RA.

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Supplementary material available online

Supplementary Figures 1 and 2.

Clinical Investigations

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Serodiagnosis of *Mycobacterium avium* Complex Pulmonary Disease in Rheumatoid Arthritis

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Key Words
Glycopeptidolipid · *Mycobacterium avium* complex pulmonary disease · Rheumatoid arthritis · Sensitivity · Specificity

Abstract
Background: *Mycobacterium avium* complex (MAC) pulmonary disease (PD) is often difficult and complicated to diagnose or to discriminate from follicular bronchitis, bronchiectasis, or other conditions associated with rheumatoid arthritis (RA) lung in the clinical setting. ***Objective:*** We investigated whether a serologic test for anti-glycopeptidolipid (GPL) antibody was useful for distinguishing MAC-PD from RA lung in diagnosis. ***Methods:*** Serum IgA antibody to MAC-specific GPL core antigen was measured by an enzyme immunoassay. Antibody levels were measured in sera from 14 RA patients with MAC-PD (RA + MAC), 20 RA patients with bronchial or bronchiolar lesions without MAC-PD (RA w/o MAC), 20 RA patients without pulmonary lesions (RA only), and 25 healthy volunteers (HV). ***Results:*** The levels of serum anti-GPL antibodies were higher in the RA + MAC group than in the RA w/o MAC, RA-only, and HV groups (2.87 ± 2.83 vs. 0.50 ± 0.45, 0.31 ± 0.24, and 0.38 ± 0.10 U/ml, respectively; $p < 0.001$). With the cutoff point in receiver-operating characteristic analysis set at 0.7 U/ml, the serologic test differentiated RA + MAC from RA w/o MAC with a sensitivity of 100% and specificity of 90%. ***Conclusions:*** This serologic test for anti-GPL antibody is useful for diagnosing MAC-PD in RA.

Introduction

Recent reports have shown a rising prevalence of disease caused by nontuberculous mycobacteria (NTM) [1–5]. Seventy percent of patients with NTM disease in Japan are diagnosed with *Mycobacterium avium* complex (MAC) [6]. MAC causes chronic and progressive pulmonary disease (PD) in immunosuppressed patients and immunocompetent patients alike. Chest computed tomography (CT) of patients with rheumatoid arthritis (RA) reveals bronchial and/or lung abnormalities along with various other distinguishing features [7]. While only 1–3% of RA patients exhibit bronchiectasis clinically, as many as 30% manifest bronchiectasis in high-resolution CT [8]. MAC-PD is therefore difficult to diagnose or to differentiate from follicular bronchitis, bronchiectasis, or other conditions associated with RA lung in the clinical setting.

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The tumor necrosis factor (TNF)-α antagonists infliximab and etanercept are used for the treatment of RA, as well as sarcoidosis and other collagen diseases and inflammatory conditions that interfere with granuloma formation [9]. Infections with intracellular pathogens such as NTM have been exacerbated in patients treated with TNF-α antagonists [10]. Because TNF-α antagonists pose a high risk for NTM-infected patients, they are not indicated for NTM under the guidelines from the American College of Rheumatology 2008. Whether TNF-α antagonists can be administered for RA remains an important issue [10, 11]. For this reason, we normally expect to conduct specific screening tests whenever we plan to administer anti-TNF-α drugs to RA patients.

In this study, we investigated whether a serologic test for anti-glycopeptidolipid (GPL) antibody was useful for distinguishing MAC-PD from RA lung in diagnosis.

Materials and Methods

Subjects

All subjects were enrolled between April 2009 and September 2011. Serum samples were collected from 14 RA patients with MAC-PD (RA + MAC), 20 RA patients with bronchial or bronchiolar lesions without MAC-PD (RA w/o MAC), 20 RA patients without pulmonary lesions (RA only), and 25 healthy volunteers (HV). Blood was collected from 11 of the 14 RA + MAC patients after the start of the MAC-PD treatment. Three of the 14 RA + MAC patients were treated with a 3-drug regimen, 3 received no drugs, and 8 were treated with a 1-drug treatment. Among the 8 RA + MAC patients treated with the 1-drug treatment, they received the single drugs for the following reasons: 4 were diagnosed after blood collection, 2 failed to properly comply with the multidrug regimen, 1 was elderly, and 1 had been treated with the 3-drug regimen but required dose reduction. The Research and Ethics Committees of the Tokyo Medical and Dental University approved the study as a study on human subjects (identification No. 984), and all of the subjects provided written informed consent.

Criteria

Our study subjects were selected retrospectively from patients who regularly visited our hospital because of RA and/or abnormal chest shadows. First, the RA patients were divided into two groups, namely patients without abnormal shadows on chest X-ray (RA only) and patients with abnormal shadows. Then, in the latter group, the patients with radiologic findings compatible with MAC-PD were divided into two subgroups: those in whom MAC was detected by sputum culture or bronchoscopy (RA + MAC) and those in whom no MAC was detected (RA w/o MAC). All patients with MAC-PD met the diagnostic criteria of the American Thoracic Society (ATS) guideline [1]. Clinical criteria included: (1) pulmonary symptoms, nodular or cavitary opacities on chest radiograph or a high-resolution CT scan manifesting multifocal bronchiectasis with multiple small nodules, and (2) appropriate exclusion of other diagnoses. Microbiologic criteria included: (1) positive culture results from at least two sputum samples, (2) positive culture results from at least one bronchial wash or lavage, or (3) transbronchial or other lung biopsy with mycobacterial histopathological features. All cases of RA + MAC and RA w/o MAC underwent chest CT, and the findings were compatible with MAC-PD.

Enzyme Immunoassay for Anti-GPL Antibody

All serum samples were measured by an enzyme immunoassay (EIA) kit for anti-GPL antibody (Tauns Laboratories, Inc., Shizuoka, Japan). All sera were stored at −20°C until assayed for IgA antibodies to GPL antigen according to the manufacturer's instructions [12]. The interfering substance, rheumatoid factor (RF), was <500 IU/ml, a level too low to affect the EIA, in every sample.

Radiological Analysis

The patients with MAC-PD were classified into two groups, namely fibrocavitary (FC) disease and nodular-bronchiectatic (NBE) disease, based on the chest radiographic findings [1]. FC disease was defined as the presence of cavitary forms in the upper lobes. NBE disease was defined as the presence of bronchiectasis and multiple nodular shadows on chest CT. Disease conforming to neither of these types was considered unclassifiable. To localize the infection, the lungs of each patient were divided into 10 fields (right lung, S^{1+2}, S^{3}, S^{4+5}, S^{6}, and $S^{7+8+9+10}$, and left lung, S^{1+2}, S^{3}, S^{4+5}, S^{6}, and S^{8+9+10}) according to Moore's [13] definition. Each field was evaluated with reference to the presence of bronchiectasis, centrilobular nodules, air space disease, cavities, and nodules >10 mm in diameter. The extent of disease was expressed as the number of MAC-involved segments, as described in previous studies [14, 15]. Chest CT findings were assessed by a consensus reading by two respiratory physicians and one radiologist (Y.M., Y.K., and Y.M.).

Statistical Analysis

All statistical analyses were performed using SPSS version 19 (IBM Japan Inc., Tokyo, Japan). Antibody levels in all groups were expressed as means ± SD. To compare mean values of multiple groups, data were compared using the Kruskal-Wallis test. The Steel-Dwass test, a nonparametric post hoc multiple comparison test, was used to evaluate differences between the groups when appropriate. Spearman's rank correlation coefficient was used for correlation analysis and the χ^2 test was used to assess the degree of compatibility. A probability value of $p < 0.05$ was regarded as significant.

Results

Characteristics of the Study Subjects

Table 1 summarizes the characteristics of the study subjects at blood sampling. None of the patients was seropositive for HIV type 1 or type 2, and none of the patients was suspected of MAC colonization. Among the 14 patients in the RA + MAC-PD group, 1 patient had diabetes mellitus, 2 had sequelae of pulmonary tuberculosis,