Table 2 Status of the treatment and reasons for discontinuation

Items	Patients (%)
Treatment status at week 24	
Continued	2,213 (69.8)
Discontinued before week 24	883 (27.8)
Lost to follow-up	74 (2.3)
Unknown	2 (0.1)
Reasons for discontinuation (multiple response)	
Adverse events	454 (14.3)
Lack of effectiveness	227 (7.2)
Patient's preference	181 (5.7)
Improvement of symptoms	3 (0.1)
Others	83 (2.6)

patients (4.9 %) developed 194 serious ADRs (Table 3). The most common SOC categories for serious ADRs were infections and infestations in 75 patients (2.4 %), followed by respiratory, thoracic and mediastinal disorders in 21 patients (0.7 %). Of 75 serious infections, 36 were pneumonia-related events (23 pneumonia, 4 *Pneumocystis jiroveci* pneumonia, 3 pneumonia bacterial, 2 bronchopneumonia, 2 pneumonia mycoplasmal, 1 pneumonia fungal, and 1 chlamydia pneumonia), and 5 were bronchitis. Tuberculosis was reported in 3 patients and two of them had been exposed to TNF inhibitors: one had used infliximab and etanercept prior to TAC administration and concomitantly received etanercept with TAC; the other had used infliximab prior to TAC administration. All patients were successfully treated with antibiotics. Serious impaired glucose tolerance-related ADR was reported in 9 patients (0.3 %) and serious renal impairment-related ADR was reported in 5 patients (0.2 %). Of 21 serious respiratory, thoracic and mediastinal disorders, 15 were interstitial pneumonia.

Almost half of the safety population was treated with other DMARDs, and 28.9 % were given MTX. Incidences of total ADRs and infection were 29.1 and 6.9 % in those with concomitant MTX and 38.8 and 6.8 % in those without MTX, respectively. Incidence of total ADRs and infection didn't increase in patients who used concomitant MTX. Incidence of total ADRs and infection in elderly patients didn't differ between those who concomitantly received MTX (34.3 and 7.8 %) and those who did not (42.2 and 7.5 %).

We identified risk factors of ADRs using multivariate Cox proportional hazards models (Table 4). The increased risk for overall ADRs was associated with the following patient characteristics at baseline: age $\geq$65 years, concurrent renal dysfunction, and concurrent diabetes mellitus. Risk factors were also explored for several important ADRs of TAC. For these analyses, we included 243 infectious events, 271 renal impairment events and 183 impaired glucose tolerance events. Definitions for these events are described in the legend of Table 4. Risk factors for infections were Steinbrocker's functional class 3 or 4, and dose of concomitant corticosteroids $\geq$10 mg. Risk factors for renal impairment were age $\geq$65 years, concurrent renal dysfunction, and concomitant use of NSAIDs. Risk factors for impaired glucose tolerance were concurrent diabetes mellitus and dose of concomitant corticosteroids $\geq$10 mg.

The response rate according to the EULAR criteria at week 24 was 65.4 % (good response in 28.1 % and moderate response in 37.4 %) in 680 patients, using the LOCF method (Fig. 1). Stratification of the patients revealed that elderly ($n = 373$) and nonelderly patients ($n = 307$) showed comparable response rates (66.5 vs. 64.2 %) and so did those with ($n = 178$) and without ($n = 502$) concomitant MTX at baseline (64.6 vs. 65.7 %). At baseline, 48.7, 49.4 and 1.9 % of the patients had high, moderate and low disease activity, respectively, whereas at week 24, the rate for high disease activity decreased to 17.8 % and that for low disease activity increased to 33.7 %, including remission in 19.3 % (Fig. 2). Mean ($\pm$SD) DAS28-CRP were 5.1 ($\pm$1.0) at baseline and decreased to 3.9 ($\pm$1.4) at week 24.

Discussion

This is the first report that describes the safety and effectiveness of treatment with TAC in clinical practice using data from a large prospective cohort of RA patients. Safety and effectiveness of TAC in this study exhibited similar profiles to those reported in clinical trial settings in RA patients who had shown insufficient response to conventional treatments [8, 9, 12].

As for drug safety, overall incidence of ADRs in the present study was 36.0 %, which was relatively lower than that reported in clinical trials (36.0–68.4 %) (unpublished data). The lower overall incidence of ADRs compared to clinical trials is mainly attributed to the lower rate of abnormal changes in laboratory test values such as renal functions and glucose tolerance in this study. Possible reasons for this difference include less stringent protocol of the PMS study compared to previous clinical trials in terms of frequency of laboratory examination and lack of direct monitoring by a pharmaceutical company, and lower average dose (1.8 mg/day) and lower starting dose (1.5 mg/day) of TAC.

Since TAC is frequently used in RA patients who had inadequate response to or were intolerant to MTX, we compared the results of this study with those from PMS studies for biological DMARDs in Japanese patients with

Table 3 Incidences of ADRs and serious ADRs by SOC classification

	ADRs	Serious ADRs	ADRs	
			Elderly (≥65 years) (n = 1,506)	Nonelderly (<65 years) (n = 1,666)
Number of patients with ADRs	1,142	157	610	532
Number of ADRs	1,855	194	1,018	837
Incidence of ADRs (%)	36.0	4.9	40.5	31.9
ADR types (system organ class)				
Infections and infestations	185 (5.8)	75 (2.4)	104 (6.9)	81 (4.9)
Bacteremia	2 (0.1)	2 (0.1)	2 (0.1)	0
Bronchopneumonia	3 (0.1)	2 (0.1)	2 (0.1)	1 (0.1)
Herpes zoster	12 (0.4)	2 (0.1)	6 (0.4)	6 (0.4)
Pneumonia	33 (1.0)	23 (0.7)	21 (1.4)	12 (0.7)
Pneumonia chlamydial	1 (0.0)	1 (0.0)	1 (0.1)	0
Pneumonia mycoplasmal	2 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)
Pulmonary tuberculosis	3 (0.1)	3 (0.1)	1 (0.1)	2 (0.1)
Sepsis	4 (0.1)	4 (0.1)	2 (0.1)	2 (0.1)
Pneumonia bacterial	7 (0.2)	3 (0.1)	4 (0.3)	3 (0.2)
Pneumonia fungal	1 (0.0)	1 (0.0)	1 (0.1)	0
Pneumocystis jiroveci pneumonia	4 (0.1)	4 (0.1)	3 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	7 (0.2)	7 (0.2)	3 (0.2)	4 (0.2)
Blood and lymphatic system disorders	21 (0.7)	2 (0.1)	10 (0.7)	11 (0.7)
Immune system disorders	1 (0.0)	1 (0.0)	0	1 (0.1)
Metabolism and nutrition disorders	135 (4.3)	11 (0.4)	87 (5.8)	48 (2.9)
Psychiatric disorders	10 (0.3)	1 (0.0)	3 (0.2)	7 (0.4)
Nervous system disorders	81 (2.6)	14 (0.4)	47 (3.1)	34 (2.0)
Eye disorders	7 (0.2)	0	4 (0.3)	3 (0.2)
Ear and labyrinth disorders	5 (0.2)	2 (0.1)	2 (0.1)	3 (0.2)
Cardiac disorders	31 (1.0)	11 (0.4)	15 (1.0)	16 (1.0)
Vascular disorders	36 (1.1)	1 (0.0)	19 (1.3)	17 (1.0)
Respiratory, thoracic and mediastinal disorders	67 (2.1)	21 (0.7)	29 (1.9)	38 (2.3)
Interstitial pneumonia	17 (0.5)	15* (0.5)	9 (0.6)	8 (0.5)
Gastrointestinal disorders	203 (6.4)	9 (0.3)	111 (7.4)	92 (5.5)
Hepatobiliary disorders	49 (1.5)	4 (0.1)	19 (1.3)	30 (1.8)
Skin and subcutaneous tissue disorders	116 (3.7)	2 (0.1)	57 (3.8)	59 (3.5)
Musculoskeletal and connective tissue disorders	18 (0.6)	0	6 (0.4)	12 (0.7)
Renal and urinary disorders	84 (2.7)	4 (0.1)	57 (3.8)	27 (1.6)
Reproductive system and breast disorders	5 (0.2)	1 (0.0)	1 (0.1)	4 (0.2)
General disorders and administration site conditions	69 (2.2)	4 (0.1)	37 (2.5)	32 (1.9)
Laboratory test abnormal	397 (12.5)	8 (0.3)	219 (14.5)	178 (10.7)
Injury, poisoning and procedural complications	5 (0.2)	2 (0.1)	3 (0.2)	2 (0.1)

SOC system organ class

RA. The incidence rate for ADRs was 27.3 % for tocilizumab, 28.0 % for infliximab, 30.6 % for etanercept, and 35.5 % for adalimumab [13–16]. The incidence of serious ADRs in this study was 4.9 %, which didn't differ from the results of adalimumab (4.1 %), etanercept (5.7 %), infliximab (6.2 %) and tocilizumab (7.2 %) [13–16].

In the present study, metabolism and nutrition disorders, renal and urinary disorders, abnormal laboratory values, gastrointestinal disorders, and infections and infestations were frequently reported. These are known ADRs of TAC when used in transplant recipients [17–19]. Regarding safety in elderly RA patients aged 65 years or older, 1,018 ADRs were reported in 610 out of 1,506 patients (40.5 %). The common ADRs revealed in elderly patients in previous clinical trials of TAC included infections, renal impairment, gastrointestinal disorders, skin disorders and

Table 4 Patient characteristics at baseline as risk factors for ADRs

Factor	Hazard ratio	*p* value	95 % CI
Overall (ADRs)			
Age (≥65 vs. <65 years)	1.21	0.020	1.03–1.42
Concurrent renal dysfunction (presence vs. absence)	1.32	0.007	1.08–1.61
Concurrent diabetes mellitus (presence vs. absence)	1.60	<0.001	1.33–1.93
Infections			
Functional class (≥3 vs. ≤2)	1.45	0.042	1.01–2.08
Dose of concomitant corticosteroids (0–10 vs. 0 mg)	0.99	0.962	0.64–1.53
Dose of concomitant corticosteroids (≥10 vs. 0 mg)	1.68	0.047	1.01–2.80
Renal impairment			
Age (≥65 vs. <65 years)	1.59	0.004	1.16–2.17
Concurrent renal dysfunction (presence vs. absence)	1.90	<0.001	1.36–2.67
Concomitant NSAIDs (use vs. non use)	1.67	0.005	1.17–2.40
Impaired glucose tolerance			
Concurrent diabetes mellitus (presence vs. absence)	5.63	<0.001	3.85–8.21
Dose of concomitant corticosteroids (≥10 vs. 0 mg)	2.36	0.012	1.20–4.62

Infectious events (84 serious and 159 non-serious) for this analysis mainly included pneumonia (23 serious and 10 non-serious), upper respiratory tract infection (21 non-serious), nasopharyngitis (19 non-serious)

Renal impairment events (7 serious and 264 non-serious) for this analysis mainly included elevation of β-*N*-acetyl-D-glucosaminidase (68 non-serious), elevation of blood urea (2 serious and 50 non-serious), renal impairment (1 serious and 36 non-serious)

Impaired glucose tolerance events (9 serious and 174 non-serious) for this analysis mainly included diabetes mellitus (7 serious and 40 non-serious), elevation of glycosylated hemoglobin (39 non-serious), glucose tolerance impaired (1 serious and 29 non-serious), elevation of blood glucose (30 non-serious)

Concurrent renal dysfunction included membranous nephropathy (6 patients), interstitial nephritis (4 patients), IgA nephropathy (3 patients), lupus nephritis (2 patients), renal amyloidosis (2 patients) and other renal dysfunction (392 patients)

NSAID non-steroidal anti-inflammatory drug

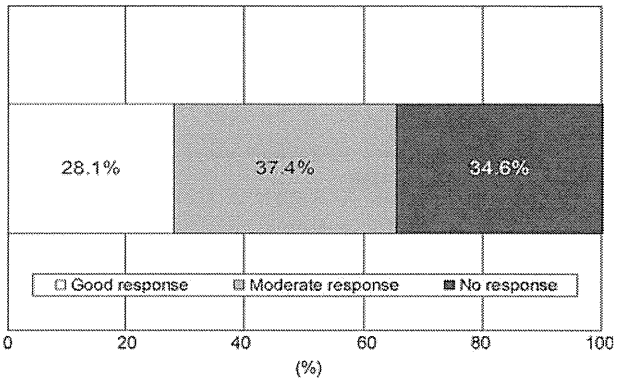

Fig. 1 Response to treatment according to the EULAR criteria ($n = 680$). The response rate was defined as the proportion of patients with good or moderate response

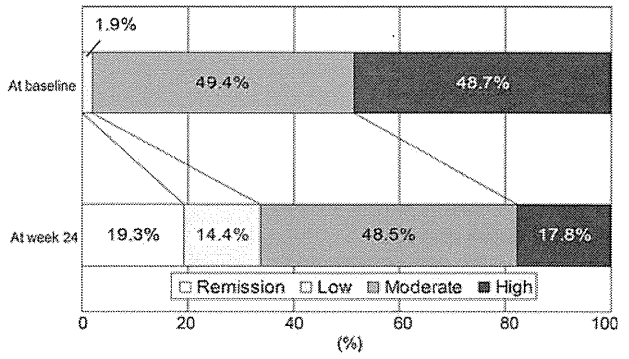

Fig. 2 Disease activity of rheumatoid arthritis at baseline and at the end of observation using the last observation carried forward (LOCF) method. Disease activity was defined using DAS28-CRP scores as follows: remission, DAS28-CRP < 2.6; low disease activity, 2.6 ≤ DAS28-CRP ≤ 3.2; moderate disease activity, 3.2 < DAS28-CRP ≤ 5.1; high disease activity, 5.1 < DAS28-CRP

abnormal glucose tolerance; these results are similar to those obtained in the present study.

Infection was the most frequently reported serious ADR in this study. Of 75 serious infectious events, 39 were pulmonary infections, including 23 pneumonia. It has been reported that pulmonary infection, especially pneumonia, is the major site-specific infection in RA [13–16, 20–26]; this is compatible with the results of this study. In this study, we identified advanced functional class and dosage of concomitant corticosteroid as risk factors for infections using multivariate analysis. Usage or dosage of corticosteroid are reported as risk factors for infections in various cohort studies for RA and in Japanese PMS studies for biological DMARDs as well [14–16, 21, 22, 27–31].

Risk factors for impaired glucose tolerance were concurrent diabetes mellitus and concomitant use of corticosteroids at doses of ≥10 mg (PSL equivalent). In the present study, 17.7 % of patients had diabetes mellitus at baseline and a higher percentage of these patients (17.6 %) reported impaired glucose tolerance as AE compared to those who did not have diabetes mellitus, suggesting that diabetes mellitus should be checked before starting TAC. In light of the influence on infection and diabetes mellitus, dose reduction of corticosteroids should be considered in patients with improved signs and symptoms of RA. The mean dose of corticosteroids used in this study was 6.8 mg/day at baseline and 6.1 mg/day at week 24. Furthermore, at week 24, 4.0 % ($n = 69$) of patients withdrew from corticosteroid therapy. The mean dose of corticosteroids in the

present study was comparable with the one reported in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) database for the RA patients treated with TAC, which is 7.0 mg/day [32].

In this study, 21 serious respiratory, thoracic and mediastinal disorders were reported and 15 of these were interstitial pneumonia (IP). Regarding the outcome of 15 patients (16 cases); 4 cases died, 4 cases improved, 3 cases resolved, 3 cases are unknown, 2 cases did not improve. Corticosteroid was administered in 13 patients and the daily dose of corticosteroid in 3 patients when IP occurred was higher than the mean daily dose (6.8 mg/day at baseline, 6.1 mg/day at week 24). The case report forms of 13 patients said "worsening of IP" and of these, comorbidity of IP was reported in 12 patients. It has been reported that TAC-associated IP depicts various imaging patterns on thoracic computed tomography [33]. TAC-associated IP is sometimes life-threatening and should be included in differential diagnoses in RA patients who develop respiratory symptoms during treatment with TAC.

Toxicity or tolerability issues for MTX such as liver dysfunction, cytopenia, or interstitial pneumonia have been reported [34–37]. It may be useful to evaluate the effectiveness of TAC in patients who cannot tolerate further increase of MTX dose. It has been recently demonstrated that the addition of TAC to MTX for the treatment of active Japanese RA patients who failed with MTX monotherapy was effective [38, 39].

Limitations of this study include that DAS28 scores were reported in only 680 patients, and that not all RA patients who were treated with TAC were registered during the registry period.

In conclusion, this study provides evidence that TAC is well tolerated in Japanese patients with active RA. In addition, given that several risk factors were identified, screening of these risk factors prior to the treatment with TAC and careful monitoring for ADRs are necessary to obtain better benefit-risk balance of treatment with TAC.

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American College of Rheumatology/European League Against Rheumatism Remission Criteria for Rheumatoid Arthritis Maintain Reliable Performance When Evaluated in 44 Joints

Yuko Kaneko, Harumi Kondo and Tsutomu Takeuchi

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American College of Rheumatology/European League Against Rheumatism Remission Criteria for Rheumatoid Arthritis Maintain Reliable Performance When Evaluated in 44 Joints

Yuko Kaneko, Harumi Kondo, and Tsutomu Takeuchi

ABSTRACT. ***Objective.*** To investigate the performance of the new remission criteria for rheumatoid arthritis (RA) in daily clinical practice and the effect of possible misclassification of remission when 44 joints are assessed.

Methods. Disease activity and remission rate were calculated according to the Disease Activity Score (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and a Boolean-based definition for 1402 patients with RA in Keio University Hospital. Characteristics of patients in remission were investigated, and the number of misclassified patients was determined — those classified as being in remission based on 28-joint count but as nonremission based on a 44-joint count for each definition criterion.

Results. Of all patients analyzed, 46.6%, 45.9%, 41.0%, and 31.5% were classified as in remission in the DAS28, SDAI, CDAI, and Boolean definitions, respectively. Patients classified into remission based only on the DAS28 showed relatively low erythrocyte sedimentation rates but greater swollen joint counts than those classified into remission based on the other definitions. In patients classified into remission based only on the Boolean criteria, the mean physician global assessment was greater than the mean patient global assessment. Although 119 patients had ≤ 1 involved joint in the 28-joint count but > 1 in the 44-joint count, only 34 of these 119 (2.4% of all subjects) were found to have been misclassified into remission.

Conclusion. In practice, about half of patients with RA can achieve clinical remission within the DAS28, SDAI, and CDAI; and one-third according to the Boolean-based definition. Patients classified in remission based on a 28-joint count may have pain and swelling in the feet, but misclassification of remission was relatively rare and was seen in only 2.4% of patients under a Boolean definition. The 28-joint count can be sufficient for assessing clinical remission based on the new remission criteria. (First Release June 15 2013; J Rheumatol 2013;40:1254–8; doi:10.3899/jrheum.130166)

Key Indexing Terms:
RHEUMATOID ARTHRITIS REMISSION CRITERIA 44 JOINTS VERIFICATION

Therapeutic developments over the past several decades in the treatment of rheumatoid arthritis (RA) have made remission an achievable goal. While different remission criteria had been used, new criteria have recently been presented by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)[1]: the index-based criteria defined as a Simplified Disease Activity Index (SDAI) of ≤ 3.3 and a Boolean-based definition requiring 4 criteria to be ≤ 1 [patient global assessment (PGA; in cm), swollen and tender joint counts (SJC, TJC), and C-reactive protein (CRP; in mg/dl)]. Definitions for clinical practice were also proposed: a Clinical Disease Activity Index (CDAI) level of ≤ 2.8 and a Boolean-based definition requiring 3 criteria to be ≤ 1, eliminating the CRP. In the past, the most widely used criteria were the Disease Activity Score (DAS) and DAS28, with 44 and 28 joints assessed, respectively. While the 44-joint count is more comprehensive, the 28-joint count correlates well with the full joint count[2,3,4] and is easier to assess and more convenient in daily practice; the newly suggested criteria are also based on a 28-joint count. However, the 28-joint count excludes evaluation of ankle and foot joints, potentially leading to misclassification of patients to remission status, particularly if the patient has disease activity only in the ankles and feet.

While van Tuyl, *et al*[5] did report that residual disease activity in the forefeet had a limited effect on outcome using a 38-joint count, it remains unclear whether using only a

From the Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

Y. Kaneko, Instructor; H. Kondo, Research Nurse; T. Takeuchi, Professor, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine.

Address correspondence to Dr. Y. Kaneko, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan. E-mail: ykaneko@z6.keio.jp

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28-joint count is sufficiently accurate in evaluating remission, because the van Tuyl team did not assess activity in the ankles. We assessed the performance of the new remission criteria in daily clinical practice and evaluated the effects of possible misclassification of remission on their performance when 44 joints are assessed instead of 28.

MATERIALS AND METHODS

All patients with RA in Keio University Hospital were evaluated cross-sectionally in the period December 2011 to February 2012. Joint counts were assessed by 6 rheumatologists, all of whom had at least 10 years' experience. The 44-joint count includes ankle (n = 2), metatarsophalangeal (n = 10), sternoclavicular (n = 2), and acromioclavicular (n = 2) joints, as well as the usual 28-joint count.

Findings for laboratory data included CRP, erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3). Patient pain, patient global assessment (PGA), and physician global assessment (PhGA) were measured on a visual analog scale ranging from 0 to 100 mm. A Health Assessment Questionnaire (HAQ) was filled out by each patient.

We first classified patient disease activity into states of remission and low, moderate, and high activity, based on DAS28, SDAI, and CDAI values, and then examined the number of criteria that were satisfied under a Boolean-based definition. We also assessed the characteristics of patients in remission according to each definition and then evaluated the number of misclassified patients — those classified into remission based on a 28-joint count but as nonremission based on a 44-joint count for each definition criterion. In addition, for patients with an involved joint count ≤ 1 in the 28-joint count but > 1 in the 44-joint count (meaning they could have been misclassified into remission under the Boolean definition) who were not classified into remission, variables that prevented them from being misclassified were also investigated.

Comparisons of mean values were performed using Student's t test with IBM SPSS version 20.0 (IBM Corp.).

RESULTS

Characteristics of all study patients and those in remission for each definition. Of the 1449 patients with RA in our hospital, 47 were excluded because of insufficient data, resulting in a total of 1402 patients (83% female) included in study analysis. Mean patient age was 60.1 years, mean disease duration 10.9 years, and mean DAS28 was 2.8. About half the patients were treated with a biologic agent (Table 1).

Characteristics of patients in remission according to DAS28, SDAI, and CDAI values as well as Boolean-based criteria are shown in Table 1. The remission rates were 46.6% in DAS28, 45.9% in SDAI, 41.0% in CDAI, and 31.5% under a Boolean definition. The mean value of HAQ score was significantly better in patients in remission under the Boolean definition than in those deemed to be in remission based on the other definitions.

Comparison of characteristics of patients in various remission states by definition. We compared the characteristics of patients whose remission status varied among the 4 sets of remission criteria (Table 2). Patients classified into remission based only on the DAS28 showed relatively low ESR but higher PGA values and SJC than those classified into remission based on the other definitions, while those classified into nonremission using only DAS28 showed relatively high ESR. Although few patients were classified into remission only by the Boolean definition, their mean PhGA was greater than their mean PGA score.

Possible misclassification with assessment of 44 joints instead of 28 joints. We then investigated the effect of possible misclassification into remission on the performance of each remission definition when 44 joints were assessed instead of the 28-joint count. The numbers of patients classified into remission using the 28-joint count but as nonremission with the 44-joint count were 38, 40, 36, and 34 under the DAS28, SDAI, CDAI, and Boolean definitions, respectively, which means the possible remission rate would be 43.9%, 43.1%, 38.4%, and 29.0% according to the 44-joint count. Although the effect of possible misclassifications on performance was smallest using the Boolean definition, the difference was modest (Figure 1A).

A total of 119 patients (8.5% of all subjects) had ≤ 1 involved joint in the 28-joint count but > 1 in the 44-joint count, indicating the potential for misclassification into remission using the Boolean definition. However, only 34 of these 119 patients (2.4% of all subjects) were actually misclassified into remission, which was averted largely due to the presence of high PGA (45%), high SJC (1%), high TJC (1%), high CRP (1%), or a combination of several findings (24%) (Figure 1B). Given these findings, the remission rate could have potentially decreased from 31.5% to 29.0% using a Boolean definition when 44 joints were assessed.

DISCUSSION

Our study investigated effects of possible misclassification of remission on the performance of new ACR/EULAR remission criteria when 44 joints are assessed instead of 28, and we found that misclassification was relatively rare and was seen only in 2.4% of patients under a Boolean definition.

Although assessment of all joints is clearly required in a patient assessment, a 28-joint count has frequently been used because it has been recognized to provide as much information as a full joint count with considerably greater feasibility. However, there should be a compromise between comprehensiveness and feasibility[6], and several groups have studied the residual disease activity in feet and ankles of patients in remission using a reduced joint count. Landewé, *et al* showed that remission defined by DAS28, which excludes ankles and feet, is inferior to the original DAS definition because of residual swelling and tenderness in the ankles and feet[7]. Kapral, *et al* compared the extended joint count with the limited joint count in DAS28 and SDAI, noting a negligible difference in findings, because other components of remission criteria would be higher in patients with foot joint involvement, helping to avoid misclassification[8]. In our study, we noted only a modest effect of

Table 1. Characteristics of all patients studied and patients in remission according to SDAI, CDAI, and Boolean-based definition. Data are expressed as mean (SD), unless otherwise indicated.

Characteristic	All Patients	Remission			
		DAS28	SDAI	CDAI	Boolean
No. cases (%)	1402 (100)	654 (46.6)	644 (45.9)	575 (41.0)	441 (31.5)
Age, yrs	60.1 (14.5)	56.8 (14.9)	58.1 (14.6)	58.2 (14.8)	57.3 (14.9)
Disease duration, yrs	10.9 (9.9)	8.9 (8.3)	9.3 (8.8)	9.2 (8.8)	8.4 (8.1)
TJC28 (n, %)					
0	931 (66.4)*	608 (93.0)	606 (94.1)	548 (95.3)	400 (90.7)
1	204 (14.6)*	34 (5.2)	34 (5.3)	24 (4.2)	41 (9.3)
≥ 2	267 (19.0)*	12 (1.8)	4 (0.6)	3 (0.5)	0
SJC28, n (%)					
0	762 (54.4)*	522 (79.8)	567 (88.0)	521 (90.6)	364 (82.5)
1	228 (16.2)*	74 (11.3)	68 (10.6)	52 (9.0)	77 (17.5)
≥ 2	412 (29.4)*	58 (8.9)	9 (1.4)	2 (0.4)	0
TJC44, n (%)					
0	884 (63.1)*	579 (88.5)	581 (90.2)	526 (91.5)	381 (86.4)
1	194 (13.8)*	44 (6.7)	48 (7.5)	36 (6.3)	50 (11.3)
≥ 2	324 (23.1)*	31 (4.7)	15 (2.3)	13 (2.3)	10 (2.3)
SJC44, n (%)					
0	692 (49.4)*	478 (73.1)	523 (81.2)	480 (83.5)	333 (75.5)
1	218 (15.5)*	84 (12.8)	87 (13.5)	69 (12.0)	79 (17.9)
≥ 2	492 (35.1)*	92 (14.1)	34 (5.3)	26 (4.5)	29 (6.6)
CRP, mg/dl	0.4 (1.0)*	0.1 (0.2)	0.1 (0.3)	0.2 (0.4)	0.1 (0.2)
ESR, mm/h	28.2 (27.3)*	13.3 (8.2)	21.5 (23.7)	22.1 (25.0)	20.1 (25.3)
MMP-3, mg/dl	106 (184)*	83 (54)*	77 (47)	78 (55)	73 (38)
PGA, mm	22.5 (22.7)*	12.7 (15.5)*	8.2 (8.0)*	7.3 (7.1)*	3.6 (3.0)
Pain VAS, mm	21.9 (22.8)*	12.4 (15.9)*	8.2 (8.0)*	7.5 (8.6)*	4.4 (6.0)
PhGA, mm	9.9 (14.2)*	3.3 (7.1)	1.7 (3.0)	1.5 (2.9)*	2.3 (6.2)
HAQ	0.63 (0.75)*	0.34 (0.55)*	0.29 (0.50)*	0.29 (0.50)*	0.18 (0.66)
DAS28	2.8 (1.1)*	1.9 (0.5)	2.1 (0.6)	2.1 (0.6)	2.0 (0.7)
SDAI	6.0 (7.2)*	2.2 (2.3)*	1.3 (1.0)*	1.2 (0.9)*	1.0 (1.1)
CDAI	5.6 (6.7)*	2.1 (2.3)*	1.2 (1.0)*	1.0 (0.8)*	0.9 (1.0)
Biologic agent use, %	48.0	52.6	50.5	49.5	50.2
Methotrexate use, %	72.4	74.3	74.4	73.8	74.3
Corticosteroid use, %	26.5*	20.7*	17.6	17.8	14.6
Comorbidity†, %	18.5	14.4	14.3	13.9	13.9

* $p < 0.05$ compared with Boolean definition. † Comorbidity included chronic infection, interstitial lung disease, current or previous malignancy, viral hepatitis, and chronic renal failure. DAS28: 28-joint count Disease Activity Score; SDAI: Simplified Disease Activity score; CDAI: Clinical Disease Activity score; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloprotease-3; PGA: patient global assessment; VAS: visual analog scale; PhGA: physician global assessment; HAQ: Health Assessment Questionnaire.

possible misclassification into a remission category on the performance of the provisional ACR/EULAR remission criteria. While 8.5% of patients had ≤ 1 involved joint in a 28-joint count, but > 1 in a 44-joint count, only 2.4% were misclassified into remission under the Boolean-based definitions, mainly due to PGA values. Reinforcing the findings of the ACR/EULAR remission task force in their development of these new criteria that the effect of missing residual disease activity in the ankles and feet appeared to be limited because patients with activity in those joints showed increased levels in other measures in the definition, we demonstrated here that the 28-joint count can be sufficiently accurate in assessing remission status based on Boolean definition criteria. However, whereas the disease duration of our study patients varied considerably, Wechalekar, *et al* examined 123 patients with RA who had synovitis symptoms for less than 24 months and reported that remission criteria using 28-joint count did not adequately identify the resolution of foot synovitis[9]. This should be confirmed in a large population in a future study.

We also observed that 46.6%, 45.9%, and 41.0% of patients with RA could be deemed to be in remission using DAS28, SDAI, and CDAI values, respectively, with 31.5% remaining valid even using a Boolean-based definition. The remission rates with SDAI and CDAI were quite similar to that under DAS28 and were higher than values in other reports[5,10,11]. We believe this discrepancy exists because about half of our patients were treated with biologic agents,

Table 2. Comparison of characteristics of patients in various remission states stratified by definition.

DAS28 remission	Yes	Yes	No	Yes	No	No
SDAI remission	Yes	Yes	Yes	No	No	No
CDAI remission	Yes	Yes	Yes	No	No	No
Boolean remission	Yes	No	Yes	No	Yes	No
Number	351	125	60	136	16	594
Age, yrs	54.2 (15.2)	57.9 (14.2)	60.1 (13.9)	56.2 (15.4)	65.5 (11.7)	62.8 (13.8)
Disease duration, yrs	7.9 (7.6)	9.3 (8.2)	10.6 (10.1)	10.9 (9.5)	6.8 (7.1)	12.6 (10.8)
TJC28, n (%)						
0	342 (97.4)	122 (97.6)	48 (80)	106 (77.9)	4 (25)	206 (34.7)
1	9 (2.6)	2 (1.6)	12 (20)	19 (14.0)	12 (75)	136 (22.9)
≥ 2	0	1 (0.8)	0	11 (8.1)	0	252 (42.4)
SJC28, n (%)						
0	316 (90.0)	124 (99.2)	44 (73.3)	58 (42.6)	2 (12.5)	128 (21.5)
1	35 (10.0)	0	16 (26.7)	27 (19.9)	14 (87.5)	115 (19.4)
≥ 2	0	1 (0.8)	0	51 (37.5)	0	351 (59.1)
TJC44, n (%)						
0	342 (97.4)	118 (94.4)	48 (80)	99 (72.8)	4 (25)	192 (32.3)
1	8 (2.3)	3 (2.4)	12 (20)	19 (14.0)	12 (75)	114 (19.2)
≥ 2	1 (0.3)	4 (3.2)	0	18 (13.2)	0	288 (48.5)
SJC44, n (%)						
0	316 (90.0)	116 (92.8)	48 (73.3)	52 (38.3)	2 (12.5)	110 (18.5)
1	27 (7.7)	6 (4.8)	11 (18.3)	24 (17.6)	10 (62.5)	96 (16.2)
≥ 2	8 (2.3)	3 (2.4)	1 (1.7)	60 (44.1)	4 (25.0)	388 (65.3)
CRP, mg/dl	0.1 (0.1)	0.1 (0.2)	0.2 (0.3)	0.1 (0.4)	0.2 (0.3)	0.8 (1.4)
ESR, mm/h	14.9 (9.0)	14.5 (7.3)	53.4 (54.0)	8.9 (5.1)	31.1 (12.2)	39.7 (29.1)
MMP-3, mg/dl	75 (39)	86 (68)	66 (35)	102 (67)	72 (38)	138 (273)
PGA, mm	3.4 (3.0)	16.9 (4.5)	3.8 (3.1)	31.4 (21.9)	5.3 (3.3)	36.7 (24.1)
Pain VAS, mm	4.1 (6.1)	15.2 (8.8)	5.0 (5.4)	29.9 (22.5)	6.9 (5.3)	35.7 (24.5)
PhGA, mm	1.5 (3.1)	0.8 (1.8)	2.9 (3.4)	9.6 (12.3)	17.3 (22.3)	18.6 (16.3)
HAQ	0.16 (3.4)	0.45 (0.57)	0.30 (0.43)	0.69 (0.72)	0.17 (0.26)	0.99 (0.82)
DAS28	1.8 (0.5)	2.0 (0.5)	2.9 (0.4)	2.2 (0.4)	3.1 (0.2)	3.8 (0.92)

DAS28: 28-joint count Disease Activity Score; SDAI: Simplified Disease Activity score; CDAI: Clinical Disease Activity score; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloprotease-3; PGA: patient global assessment; PhGA: physician global assessment.

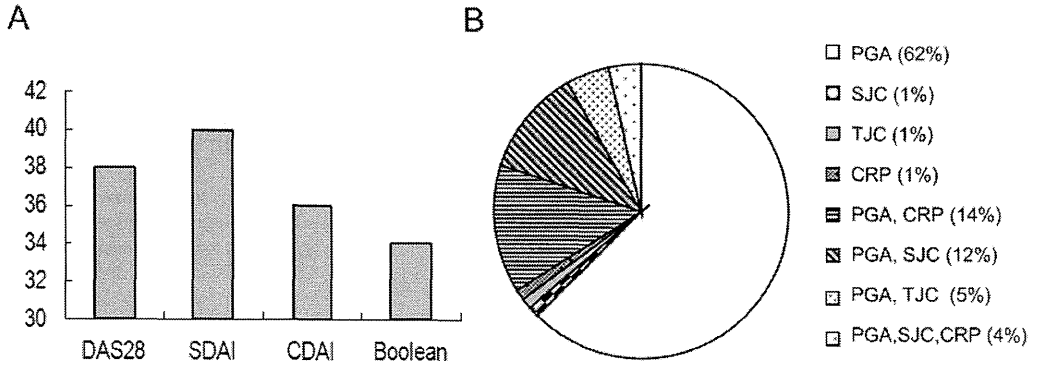

Figure 1. A. Number of patients classified as "in remission" in the 28-joint count but as "nonremission" when 44 joints were assessed. This number was smallest under a Boolean definition, but the difference was modest. B. Variables preventing patients with ≤ 1 involved joint in the 28-joint count but > 1 in the 44-joint count from being misclassified as "in remission." Almost all reasons (97%) included patient global assessment (PGA). DAS28: 28-joint Disease Activity Score; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; SJC: swollen joint counts; TJC: tender joint counts; CRP: C-reactive protein.

which can lead patients not only into remission but into a deep remission. While the prevalence of clinical remission in patients with RA after 6 months of treatment with anti-tumor necrosis factor (TNF) agents was previously reported to be 27% in DAS28 and 6% under Boolean definitions[12], we noted that patients received various biologic agents in our study, i.e., 65% were receiving anti-TNF, 26% tocilizumab, and 9% abatacept.

Some patients were classified into the remission category based on only DAS28 or Boolean criteria. Reflecting the marked difference in the formulas between the DAS28 and SDAI, CDAI, and Boolean definitions, patients who were classified into remission based only on DAS28 showed relatively low ESR but higher values for PGA and SJC than those classified into remission based on the other definitions, while those classified as being in nonremission based only on DAS28 showed relatively high ESR. Moreover, while Studenic, *et al* reported that pain is the most important determinant in the PGA whereas it is mostly joint swelling in the PhGA[13], in our study the mean PhGA of patients classified into remission based only on Boolean definitions was found to be greater than the mean PGA, and interestingly, this phenomenon was noted only in that particular group. The relatively low number of patients in this group, however, hampered our investigation, and future studies should therefore assess this matter in greater detail.

Several limitations to our study warrant mention. First, we assessed remission status cross-sectionally at 1 timepoint. It is known that there are patients with predominant foot involvement who could be underestimated in the 28-joint count, as reported by Bakker, *et al*[14], and because the aim of sustained remission is to achieve little or no radiographic and functional deterioration, we need to also examine structural and functional outcomes under 44-joint counts longitudinally. Second, all data used in this study were obtained from a single hospital in Japan. While we are confident that our patients are representative of those in other clinics nationally, because our hospital is one of the biggest rheumatology centers in Japan, the high rate of use of biologic agents might hinder generalizations about the results.

In daily clinical practice, roughly half of patients with RA can be deemed to be in a state of clinical remission based on DAS28, SDAI, and CDAI values, while one-third can be so classified under a Boolean-based definition. Patients deemed to be in remission based on a 28-joint count may show pain and swelling in the feet, but misclassification was relatively rare in our study and was observed in only 2.4% of patients under a Boolean definition. The 28-joint count seems to be sufficient for assessing remission using the ACR/EULAR remission criteria.

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Safety and Effectiveness of 6 Months' Etanercept Monotherapy and Combination Therapy in Japanese Patients with Rheumatoid Arthritis: Effect of Concomitant Disease-modifying Antirheumatic Drugs

Takao Koike, Masayoshi Harigai, Shigeko Inokuma, Naoki Ishiguro, Junnosuke Ryu, Tsutomu Takeuchi, Yoshiya Tanaka, Hisashi Yamanaka, Tomohiro Hirose, Takunari Yoshinaga and Michio Suzukawa

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Safety and Effectiveness of 6 Months' Etanercept Monotherapy and Combination Therapy in Japanese Patients with Rheumatoid Arthritis: Effect of Concomitant Disease-modifying Antirheumatic Drugs

Takao Koike, Masayoshi Harigai, Shigeko Inokuma, Naoki Ishiguro, Junnosuke Ryu, Tsutomu Takeuchi, Yoshiya Tanaka, Hisashi Yamanaka, Tomohiro Hirose, Takunari Yoshinaga, and Michio Suzukawa

ABSTRACT. ***Objective.*** To assess real-world safety, tolerability, and effectiveness of etanercept monotherapy, etanercept plus methotrexate (MTX), or etanercept plus other disease-modifying antirheumatic drugs (DMARD) in Japanese patients with active rheumatoid arthritis (RA) despite previous treatment with DMARD.

Methods. In this 24-week, all-cases postmarketing surveillance study, adverse events (AE) were coded using the *Medical Dictionary for Regulatory Activities*. Effectiveness was assessed every 4 weeks using the 28-joint Disease Activity Score and the European League Against Rheumatism response criteria.

Results. Of 13,861 patients (81% women) in the analysis, 3616, 2506, and 7739, respectively, were classified into etanercept monotherapy (ETN-mono), etanercept plus DMARD other than MTX (ETN + DMARD), and etanercept plus MTX (ETN + MTX) groups. Rates of AE and serious AE (SAE) in the ETN + MTX group were lower than in other groups. Risk of SAE or serious infections was not significantly increased with higher versus lower MTX doses at baseline or with concomitant use of salazosulfapyridine or bucillamine in ETN + DMARD versus ETN-mono groups. A greater likelihood of achieving clinical remission was seen with ETN + MTX versus ETN-mono (OR 1.36; 95% CI, 1.16–1.60; $p < 0.001$). Higher MTX dose at baseline was associated with a higher remission rate (> 8 mg vs 0 to ≤ 4 mg, OR 1.47, 95% CI 1.07–2.00, $p = 0.016$; 6 to ≤ 8 mg vs 0 to ≤ 4 mg, OR 1.27, 95% CI 1.01–1.60, $p = 0.038$).

Conclusion. Combination therapies with etanercept plus MTX or other DMARD were reasonably well tolerated, and ETN + MTX at higher doses was more effective than ETN-mono in Japanese patients with RA. (First Release Aug 1 2013; J Rheumatol 2013;40:1658–68; doi:10.3899/jrheum.120490)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ETANERCEPT METHOTREXATE
PRODUCT SURVEILLANCE POSTMARKETING

From the NTT Sapporo Medical Center, Sapporo; Tokyo Medical Dental University Graduate School, Tokyo; Japanese Red Cross Medical Center, Tokyo; Nagoya University Graduate School of Medicine, Nagoya; Nihon University School of Medicine, Tokyo; Keio University, Tokyo; University of Occupational and Environmental Health, Kitakyushu; Tokyo Women's Medical University, Tokyo; Pfizer Japan Inc., Medical Affairs, and Postmarketing Surveillance, Tokyo, Japan.

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T. Koike, MD, PhD, NTT Sapporo Medical Center; M. Harigai, MD, PhD, Tokyo Medical Dental University Graduate School; S. Inokuma, MD, Japanese Red Cross Medical Center; N. Ishiguro, MD, PhD, Nagoya University Graduate School of Medicine; J. Ryu, MD, PhD, Nihon University School of Medicine; T. Takeuchi, MD, PhD, Keio University; Y. Tanaka, MD, PhD, University of Occupational and Environmental Health; H. Yamanaka, MD, PhD, Tokyo Women's Medical University; T. Hirose, MS, Pfizer Japan Inc., Medical Affairs; T. Yoshinaga, MD, PhD, Pfizer Japan Inc., Postmarketing Surveillance; M. Suzukawa, MD, PhD, Pfizer Japan Inc., Medical Affairs.

Address correspondence to Dr. T. Yoshinaga, MD, PhD, Pfizer Japan Inc., 3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589, Japan.
E-mail: takunari.yoshinaga@pfizer.com

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Rheumatoid arthritis (RA), a chronic inflammatory disease affecting joints and extraarticular tissues, is associated with pain, disability, and decreased life expectancy[1,2]. Among the newer treatments for RA, agents that inhibit tumor necrosis factor (TNF) have proven to be effective in controlling disease activity and reducing radiographic progression of the condition.

Etanercept is a recombinant, human, soluble, dimeric fusion protein that competitively binds to TNF and lymphotoxin-α and prevents its binding to endogenous receptors on the cell surface[3]. Randomized clinical trials have demonstrated the efficacy and safety of etanercept as monotherapy or combined with methotrexate (MTX), a disease-modifying antirheumatic drug (DMARD) that is now a standard treatment for RA[4,5,6,7]. Etanercept has shown efficacy superior to MTX in patients with RA[7], and combining etanercept with MTX was superior to either agent alone[6]. In addition, the combination did not increase the risk for adverse events (AE) compared with monotherapy with either agent[6].

A postmarketing surveillance (PMS) study in Japanese patients with RA was conducted by Wyeth (now integrated into Pfizer as of October 2009) under the request of the Japanese Pharmaceutical and Medical Device Agency (PMDA). This was a unique study in that all patients who were administered etanercept after its approval in Japan were enrolled in this PMS study for a 2-year survey period. Eventually, 13,894 patients were registered from 1334 medical sites. This study demonstrated the safety and effectiveness of etanercept in a real-world setting[8].

We reported that the average dose of MTX in the PMS study was lower than that typically used in Western countries, and bucillamine (BUC), which has not been approved in Western countries, is one of the major DMARD in the PMS study[8,9]. Although our previous report of this PMS study showed that concomitant MTX seemed to result in better effectiveness and fewer safety problems[8,10], the safety and effectiveness of concomitant use of DMARD other than MTX, such as BUC and sulfasalazine (SSZ), still have not been clarified. Further, the difference in safety and effectiveness between etanercept monotherapy and combination therapy has not yet been elucidated. In this analysis, we took advantage of the unique all-patients PMS study and the distinguishing characteristics of concomitant DMARD use in Japanese patients with RA to evaluate the safety and effectiveness of etanercept alone or in combination with MTX or with DMARD other than MTX in a large Japanese patient population.

MATERIALS AND METHODS

Patients. In the 2-year period from March 2005 to April 2007, 13,894 Japanese patients with RA participated in a 6-month PMS study of etanercept (ClinicalTrials.gov, NCT00503503). Candidates were deemed suitable for treatment with etanercept based on guidelines from the Japan College of Rheumatology[11]. Criteria for inclusion were active RA with at least 6 tender joints and at least 6 swollen joints and erythrocyte sedimentation rate ≥ 28 mm/h or C-reactive protein levels ≥ 2.0 mg/dl despite more than 3 months of previous treatment with DMARD[8]. In addition, participants were required to have leukocyte count ≥ 4000/μl, including peripheral blood lymphocyte count ≥ 1000/μl, and had to be negative for serum β-D-glucan (an indicator of immune activity). The dosage of etanercept in our study was determined by the discretion of the attending rheumatologists.

Assessments at study entry included chest radiographs, tuberculin tests, and medical history, including comorbid diseases. Characterization of RA was based on Steinbrocker radiographic stage and functional class[12], duration of RA, and previous or current use of glucocorticoids or DMARD.

Patients were retrospectively classified into 3 treatment groups by concomitant use of DMARD at baseline: etanercept monotherapy (ETN-mono), etanercept plus DMARD other than MTX (ETN + DMARD), and etanercept plus MTX with or without DMARD other than MTX (ETN + MTX). Etanercept 10 or 25 mg was administered subcutaneously twice weekly (dosage determined by the physician). Patients were allowed to self-inject after training.

The protocol was reviewed and approved by the Japanese Ministry of Health, Labor, and Welfare. Data were collected electronically or on hard-copy case report forms, and representatives from Wyeth and Takeda visited study sites to collect additional data as required.

Assessments. Safety assessments were performed every 2 weeks and included recording of all AE occurring from the first etanercept dose to 30 days after the last dose. Safety data were coded with the matching terms from the Medical Dictionary for Regulatory Activities[13]. All AE, serious AE (SAE), serious infections (SI), and adverse drug reactions were defined

based on International Conference on Harmonization guidelines[14]. Safety information was independently evaluated by the Japan College of Rheumatology PMS committee.

Treatment effectiveness was measured every 4 weeks using the 28-joint Disease Activity Score (DAS28)[15] and the European League Against Rheumatism (EULAR) response criteria[16]. Missing data were processed using the last observation carried forward method, except for baseline values, which were not carried forward. The DAS28 scores were divided into 4 categories: remission (< 2.6), low disease activity (≥ 2.6 to ≤ 3.2), moderate disease activity (> 3.2 to ≤ 5.1), and high disease activity (> 5.1). EULAR responses were based on DAS28 results. A good response was defined as an improvement (i.e., a reduction in DAS28 score) of > 1.2 from baseline and DAS28 ≤ 3.2 at evaluation. A moderate response was defined as an improvement of 0.6 to 1.2 and DAS28 ≤ 5.1 at evaluation. Nonresponse was defined as an improvement of ≤ 0.6 or an improvement of 0.6 to 1.2 and DAS28 > 5.1 at evaluation. Treatment was deemed effective in patients with EULAR ratings of moderate or good response.

Patients < 17 years old were excluded from the study. For the effectiveness analyses, we also excluded patients who were treated for a nonapproved indication, whose treatment period was shorter than 2 weeks, whose DAS28 data either at baseline or 24 weeks were missing, or who had a DAS28 < 2.6 at baseline.

Statistical analysis. Baseline differences among the 3 treatment groups were assessed by 1-way ANOVA or chi-square tests. For each group, the change in DAS28 from baseline to each posttreatment assessment (every 4 weeks up to 24 weeks) was analyzed using the Jonckheere Terpstra test, and the change in response rates was assessed by Cochran-Armitage tests. Differences between groups on DAS28 at baseline and each posttreatment assessment point (every 4 weeks) were analyzed by 1-way ANOVA and Dunnett multiple comparison tests, and differences in EULAR responses rate at each posttreatment assessment point were analyzed by chi-square tests. Differences between groups on DAS28 improvement from baseline to Week 24 were analyzed by 1-way analysis of covariance, with combination treatment as factors and the baseline value as a covariate. The incidence of most common AE and SAE among the 3 subgroups were assessed by chi-square test or Fisher's exact test (when n < 5) and used the Bonferroni correction to adjust the result of multiple testing.

Cox proportional hazard models were used to estimate the influence of combination with DMARD (concomitant use of MTX or DMARD other than MTX) on the occurrence of SAE and SI, after adjusting for the following major confounders: age, sex, history of infectious disease, history of tuberculosis, previous use of infliximab, Steinbrocker class, and presence of combined risk factors. In patients who had 2 or more SAE, only the first SAE was counted for Cox proportional hazard models.

The combined risk factors included 3 risk factors that are indicated by our previous report[17]: comorbidities, concomitant glucocorticoid use, and disease duration > 15 years. Association of the combined effect and numbers of risk factors were further explored by the Wald test.

We also used multiple logistic regression models to estimate the effect of concomitant DMARD use (concomitant use of MTX or DMARD other than MTX) on the likelihood of achieving remission and good response after adjusting for the following major confounders: age, sex, baseline disease activities, previous use of infliximab, presence of any comorbidities, Steinbrocker functional class, and duration of RA. Treatment effectiveness was assessed in treated patients with DAS28 evaluated at baseline and at 24 weeks. Patients were excluded from these models based on missing DAS28 data either at baseline or at 24 weeks, DAS28 < 2.6 at baseline, or missing data for adjustment factors (e.g., age, sex, disease duration).

Further, we estimated the effect of MTX dosage on safety and effectiveness. The HR or OR and the 95% CI for each factor after adjustment for major confounders were estimated. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc.). Statistical significance was defined by 2-sided p values < 0.05.

RESULTS

Patients. A total of 13,894 patients were treated with etanercept alone or in combination with DMARD. Overall, 13,861 patients who were older than 17 years of age at baseline in the treated population were evaluated for safety and tolerability in the 3 treatment groups: ETN-mono (n = 3616, 26.1%), ETN + DMARD (n = 2506, 18.1%), and ETN + MTX (n = 7739, 55.8%). The numbers of patients with concomitant use of 1, 2, 3, and 4 or more DMARD including MTX were 7801 (56.3% of total patients), 2165 (15.6%), 247 (1.8%), and 32 (0.2%), respectively. The percentage of patients who received SSZ or BUC in the ETN + MTX groups (18.8%) was significantly lower than in the ETN + DMARD groups (61.7%). Patient numbers with SSZ and/or BUC are described in detail in Figure 1. Of the 13,861 patients, 7325 patients with available data were evaluated for effectiveness (Figure 1).

Among the 3 groups, most of the demographic and baseline disease characteristics were significantly different, such as age, disease activity, disease duration, comorbidities, and concomitant corticosteroid, etc. The mean age, disease activity (DAS28), and the percentage of patients with comorbidities and history of selected diseases were significantly lower in the ETN + MTX group than in the other groups. The previous use of infliximab was significantly higher in the ETN + MTX group than those in the other groups. Most of the demographic and baseline disease characteristics were similar between the ETN + DMARD and the ETN-mono groups (Table 1).

Safety. Compared with the ETN-mono and the ETN + DMARD groups, the ETN + MTX group showed significantly lower incidence rates for total AE, total SAE, the 2 most frequently observed AE, and the 4 most frequently observed SAE (Table 2). Further, both of the incidences of AE and SAE were significantly lower with MTX than with no MTX (both p < 0.001). Within the ETN + MTX group, for AE and SAE, there was no evidence of significant correlation between incidence and increasing MTX dosage (both trend p > 0.05; Table 3).

We initially implemented Cox proportional hazard regression model using all patients for safety analysis. Compared with the ETN-mono group, the risks of SAE and SI were significantly lower in the ETN + MTX group (HR, 0.59 and 0.61; 95% CI, 0.50–0.70 and 0.47–0.79, respectively; all p < 0.001) but not in the ETN + DMARD group (data not shown). These findings are compatible with our previous report[10]. Considering significant difference in the demographic and baseline disease characteristics among the 3 groups, we postulated that analyzing all patients in 1 statistical model for safety was not satisfactory and conducted Cox proportional model analysis for safety for each group.

Risk factors for the development of SAE and SI within the ETN + MTX group are shown in the model for baseline

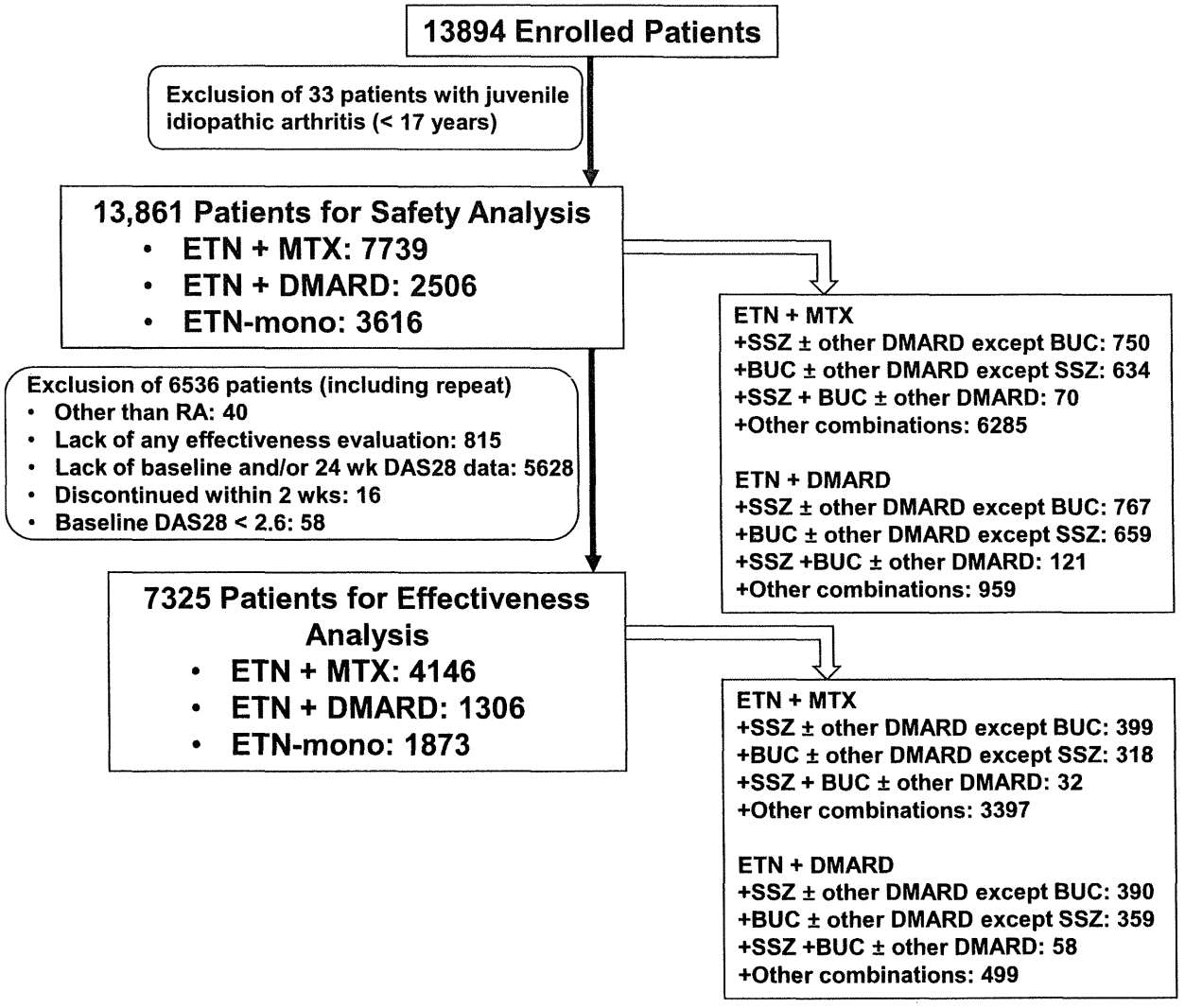

Figure 1. Flow chart of the evaluated patients.

characteristics in Table 4. These results were similar to those previously reported[10]. The results in the model for MTX dosage in Table 4 showed that higher MTX dose at baseline did not significantly increase the risk of SAE and SI.

Risk factors for the development of SAE and SI within the ETN + DMARD group are shown in Table 5. The results were somewhat different from those of the ETN + MTX group.

Within the ETN + DMARD group and the ETN-mono group, proportional hazards models indicated that both concomitant use of SSZ with or without other DMARD (ETN + SSZ) and concomitant use of BUC with or without other DMARD except SSZ (ETN + BUC) was not significantly associated with the risk for SAE and SI when comparing with the ETN-mono group (data not shown).

Effectiveness. Similar to the results previously reported for all subjects[10], for all treatment groups, the mean DAS28 scores, the DAS remission rate, and the EULAR good response rate showed a trend of significant improvement throughout the observation period. The EULAR good response rate at 24 weeks of the ETN + MTX group was significantly greater than those of the ETN-mono group or the ETN + DMARD group (29.8%, p = 0.003 at Week 24); further, there were no significant differences in improvement between the ETN-mono and the ETN + DMARD groups at 24 weeks (data not shown).

The DAS28 remission rate (< 2.6) was increased with higher dosages of MTX (Figure 2A). The remission rate for patients who received MTX > 10 mg weekly was 29.6%, about twice as high as that of patients who received no MTX. The EULAR good response rate increased with higher dosages of MTX (Figure 2B), from 27.2% at 0 mg weekly to 46.8% at > 10 mg weekly.

Table 1. Demographic and baseline disease characteristics of patients included in the safety analysis.*

Characteristics	ETN-mono, n = 3616	ETN + DMARD (excluding MTX), n = 2506	ETN + MTX, n = 7739	p
Women, n (%)	2960 (81.9)	1953 (77.9)	6372 (82.3)	< 0.001†
Age, yrs, mean ± SD	60.4 ± 12.5	61.9 ± 12.3	55.9 ± 12.9	< 0.001‡
Age distribution, yrs, n (%)				< 0.001†
17–20	7 (0.2)	3 (0.1)	33 (0.4)	
20–29	83 (2.3)	43 (1.7)	268 (3.5)	
30–39	208 (5.8)	109 (4.3)	650 (8.4)	
40–49	282 (7.8)	188 (7.5)	1110 (14.3)	
50–59	902 (24.9)	599 (23.9)	2433 (31.4)	
60–69	1255 (34.7)	818 (32.6)	2122 (27.4)	
≥ 70	879 (24.3)	746 (29.8)	1123 (14.5)	
Weight, kg (mean ± SD)	52.6 ± 9.9	52.4 ± 10.4	53.8 ± 10.0	< 0.001‡
Disease activity				
DAS28, mean ± SD	5.95 (1.20)	5.97 (1.17)	5.82 (1.18)	< 0.001‡
Disease duration, yrs, n (%)				< 0.001†
< 2	329 (9.1)	238 (0.5)	1023 (14.5)	
2 to < 5	535 (14.8)	401 (17.8)	1485 (21.1)	
5 to < 10	738 (20.4)	505 (22.4)	1727 (24.6)	
10 to < 15	619 (17.1)	433 (19.2)	1199 (17.1)	
15 to < 20	403 (11.1)	267 (11.8)	690 (9.8)	
≥ 20	681 (18.8)	415 (18.4)	907 (12.9)	
Steinbrocker stage, n (%)				< 0.001†
I	202 (5.6)	131 (5.2)	520 (6.7)	
II	756 (20.9)	521 (20.8)	1967 (25.4)	
III	1244 (34.4)	921 (36.8)	2757 (35.6)	
IV	1408 (38.9)	930 (37.2)	2492 (32.2)	
Steinbrocker class, n (%)				< 0.001†
1	279 (7.7)	174 (7.0)	758 (9.8)	
2	1925 (53.2)	1373 (54.9)	4750 (61.4)	
3	1256 (34.7)	855 (34.2)	2061 (26.6)	
4	150 (4.2)	101 (4.0)	167 (2.2)	
History of selected diseases, n (%)	1340 (37.1)	1010 (40.3)	1714 (22.1)	< 0.001†
Tuberculosis	235 (6.5)	204 (8.1)	438 (5.7)	< 0.001†
Interstitial pneumonitis	431 (11.9)	421 (16.8)	182 (2.4)	< 0.001†
Follicular bronchitis	6 (0.2)	8 (0.3)	23 (0.3)	NS†
COPD	31 (0.9)	22 (0.9)	31 (0.4)	0.002†
Comorbidities, n (%)	2314 (64.0)	1669 (66.6)	3938 (50.9)	< 0.001†
Hepatic	205 (5.7)	128 (5.1)	296 (3.8)	< 0.001†
Renal	292 (8.1)	128 (5.1)	127 (1.6)	< 0.001†
Hematologic	243 (6.7)	162 (6.5)	391 (5.1)	< 0.001†
Cardiac	253 (7.0)	206 (8.2)	327 (4.2)	< 0.001†
Infections (nonserious)	72 (2.0)	54 (2.2)	98 (1.3)	< 0.001†
Diabetes mellitus	336 (9.3)	278 (11.1)	483 (6.2)	< 0.001†
Interstitial pneumonitis	334 (9.2)	352 (14.0)	162 (2.1)	< 0.001†
Previous corticosteroids, n (%)	3034 (83.9)	2149 (85.8)	6379 (82.4)	< 0.001†
Previous infliximab, n (%)	213 (5.9)	103 (4.1)	1553 (20.1)	< 0.001†
Baseline dose of etanercept, mg/weekly (mean ± SD)	46.1 (9.6)	45.5 (10.0)	45.9 (9.5)	NS†
Concomitant corticosteroid at baseline, n (%)	2690 (74.4)	1907 (76.1)	7739 (72.5)	< 0.001†

* Among the 13,894 total patients, 33 patients who were < 17 years old were excluded from the analysis. † The p value was calculated by the chi-square test for 3 groups. ‡ The p value was calculated by 1-way ANOVA. DMARD: disease-modifying antirheumatic drug; ETN: etanercept; MTX: methotrexate; NS: not significant; DAS28: 28-joint Disease Activity Score; COPD: chronic obstructive pulmonary disease.

Next, we focused on the effects of concomitant DMARD and clinical response to treatment with ETN. Concomitant use of MTX was associated with a greater likelihood of achieving significant clinical remission, whereas concomitant use of DMARD other than MTX, including SSZ and BUC, did not show statistically signif-

Table 2. Incidence of most common AE and SAE among the 3 subgroups.

	ETN-mono, n = 3616		ETN + DMARD, Excluding MTX, n = 2506		ETN + MTX, n = 7739	
	n	%*	n	%*	n	%
AE[§]	1339	37.03[†]	885	35.32[†]	2104	27.19
Injection site reaction	221	6.11[†]	122	4.87[†]	266	3.44
Rash	110	3.04[†]	83	3.31[†]	146	1.89
Abnormal hepatic function	74	2.05	52	2.08	202	2.61
Nasopharyngitis	76	2.10	46	1.84	165	2.13
Pyrexia	88	2.43[††]	52	2.08	120	1.55
SAE[§]	313	8.66[†]	236	9.42[†]	308	3.98
Pneumonia[‖]	42	1.16[†]	31	1.24[†]	38	0.49
Interstitial lung disease	30	0.83[†]	26	1.04[†]	21	0.27
Pyrexia	15	0.41[¶]	10	0.40	15	0.19
Sepsis	10	0.28[¶]	9	0.36[††]	8	0.10
Pneumocystis jiroveci pneumonia	6	0.17	4	0.16	14	0.18

* Compared with the ETN + MTX group, chi-square test or Fisher's exact test (when n < 5). According to the Bonferroni correction, statistical significance was defined as 2-sided p values < 0.017. [†] p < 0.001. [††] p < 0.01. [§] Patients who have at least 1 AE or SAE, respectively. The 5 most frequent AE and SAE are listed according to MedDRA preferred term level. [‖] Total pneumonia = pneumonia + bacterial pneumonia + bronchopneumonia + chlamydia pneumonia + staphylococcal pneumonia + *Candida* pneumonia + fungal pneumonia. [¶] The significant difference will disappear when using the Bonferroni correction. AE: adverse event; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; MTX: methotrexate; SAE: serious adverse event.

Table 3. Incidence of AE and SAE among the MTX dose subgroups.

MTX Weekly Dose at Baseline, mg/wk[a]	Total Patients	Patients with AE*			Patients with SAE*		
	n	n	%	p	n	%	p
MTX (without)	6122	2224	36.3		549	9.0	
MTX (+)	7738	2103	27.2	< 0.001[†]	307	4.0	< 0.001[†]
≤ 4	1713	494	28.8		59	3.4	
> 4 to ≤ 6	2593	677	26.1		109	4.2	
> 6 to ≤ 8	2687	753	28.0		109	4.1	
> 8 to ≤ 10	438	110	25.1		19	4.3	
> 10	307	69	22.5	NS[‡]	11	3.6	NS[‡]

* Patients who had at least 1 AE or SAE, respectively. [a] One patient who lacked the dose data was excluded in the analysis. [†] Compared with 0 mg/wk by chi-square test. [‡] The trend on MTX dose and incident rate (Cochran-Armitage test). AE: adverse event; MTX: methotrexate; SAE: serious adverse event; NS: not significant.

icant differences (Table 6). With regard to other variables, our results were similar to those previously reported[10]. Further, results of the multiple logistic regression model within the ETN + MTX group showed that higher MTX dose at baseline was associated with a higher remission rate than lower MTX doses at baseline as well as higher rate of good response.

DISCUSSION

This PMS study was one of the largest surveillance studies of biologic use in rheumatology, with nearly 14,000 patient registrations. Mandatory registration for all patients with RA receiving etanercept regimens in Japan covered almost all patients treated with etanercept during the 2-year study duration. Almost three-quarters of the 13,861 patients were treated with etanercept plus at least 1 DMARD and over half of patients were treated with etanercept plus MTX. Therefore, this PMS study provided a unique and valuable opportunity to evaluate the real-world safety and effectiveness data for etanercept with and without DMARD in a large number of patients in Japan. DMARD, such as MTX, BUC, and SSZ, are often used as treatment for patients in Japan with RA. When patients are not achieving adequate response or cannot continue these DMARD because of

Table 4. Risk factors for SAE and serious infections in the ETN + MTX group.

Baseline Variables	Comparison	Results of SAE HR	95% CI	p	Results of Serious Infections HR	95% CI	p
Model for baseline characteristics*							
Sex	women vs men	0.66	0.50–0.86	0.002	0.64	0.43–0.97	0.034
Age, yrs	≥ 65 vs < 65	1.84	1.45–2.34	< 0.001	2.01	1.39–2.91	< 0.001
Disease characteristics							
Concomitant of nonserious infection	yes vs no	2.00	0.99–4.04	0.055	3.18	1.30–7.81	0.012
History of tuberculosis	yes vs no	1.19	0.77–1.84	0.445	1.11	0.56–2.21	0.760
Previous use of infliximab	yes vs no	0.75	0.54–1.04	0.079	1.12	0.72–1.75	0.616
Steinbrocker functional class	4 vs 1 + 2 + 3	2.67	1.67–4.27	< 0.001	3.03	1.53–6.01	0.002
Selected risk factors†	1 vs 0	2.11	1.14–3.89	0.017	1.94	0.75–5.02	0.174
	2 vs 0	4.16	2.31–7.49	< 0.001	4.44	1.79–11.00	0.001
	3 vs 0	4.35	2.30–8.22	< 0.001	2.93	1.05–8.17	0.040
Model for MTX dosage‡							
Concomitant MTX dose (mg/week)	> 4 to ≤ 6 vs > 0 to ≤ 4	1.31	0.95–1.82	0.105	1.47	0.89–2.43	0.134
	> 6 to ≤ 8 vs > 0 to ≤ 4	1.28	0.92–1.78	0.145	1.12	0.66–1.90	0.679
	> 8 vs > 0 to ≤ 4	1.42	0.89–2.25	0.138	1.51	0.75–3.04	0.247

* Multivariate analysis was performed on 7027 cases within the ETN + MTX group. † Risk factors include concomitant disease, concomitant glucocorticoids use, and disease duration > 15 years. ‡ Cox proportional hazards models were used to estimate the influence of MTX dosage, after adjusting for age, sex, concurrent nonserious infection, history of tuberculosis, previous use of infliximab, Steinbrocker functional class, and selected risk factors. MTX: methotrexate; ETN: etanercept; SAE: serious adverse event.

Table 5. Risk factors for SAE and serious infections in the ETN + DMARD group. Multivariate analysis was performed on 2257 cases.

Baseline Variables	Comparison	Results of SAE HR	95% CI	p	Results of Serious Infections HR	95% CI	p
Sex	women vs men	0.62	0.46–0.82	0.001	0.73	0.46–1.15	0.173
Age, yrs	≥ 65 vs < 65	1.44	1.10–1.89	0.008	1.44	0.95–2.18	0.088
Disease characteristics							
Concurrent nonserious infection	yes vs no	1.25	0.59–2.67	0.558	2.79	1.20–6.44	0.017
History of tuberculosis	yes vs no	1.15	0.74–1.79	0.538	1.58	0.86–2.98	0.144
Previous use of infliximab	yes vs no	1.23	0.63–2.40	0.544	1.27	0.47–3.48	0.637
Steinbrocker functional class	4 vs 1 + 2 + 3	1.57	0.91–2.70	0.108	1.79	0.82–3.90	0.141
Selected risk factors*	1 vs 0	1.17	0.54–2.54	0.685	0.67	0.209–2.128	0.493
	2 vs 0	2.66	1.30–5.45	0.007	2.07	0.747–5.732	0.162
	3 vs 0	2.64	1.24–5.62	0.012	2.70	0.936–7.807	0.066

* Risk factors include concomitant disease, concomitant glucocorticoids use, and disease duration > 15 years. DMARD: disease-modifying antirheumatic drug; ETN: etanercept; SAE: serious adverse event.

toxicity, TNF inhibitors are usually prescribed for further treatment, as add-ons or substitutes. Therefore, it is important to evaluate the safety and effectiveness of etanercept with or without these DMARD.

As described, among the patients in this PMS study, occurrence rates of AE, SAE, and SI were comparable to those seen in clinical trials and registries[17]. In this PMS study of Japanese patients with active RA despite previous treatment with DMARD, treatment with etanercept in combination with MTX was at least as safe and well tolerated as etanercept monotherapy or etanercept plus DMARD other than MTX, as assessed by the incidences of overall and 5 most common AE and SAE. We should carefully compare these incidence rates because of the significant difference in demographic and baseline disease characteristics of patients such as age, disease activity, disease duration, comorbidities, and concomitant corticosteroid use among the 3 groups. Results of the Cox proportional hazard model indicated that treatment with etanercept plus different doses of MTX did not alter risk for SAE and SI in the ETN + MTX group. Risk factors for SAE and SI found in the ETN + MTX group (male sex, older age, Steinbrocker class 4, concomitant disease, concomitant glucocorticoid use, and long disease duration for both SAE

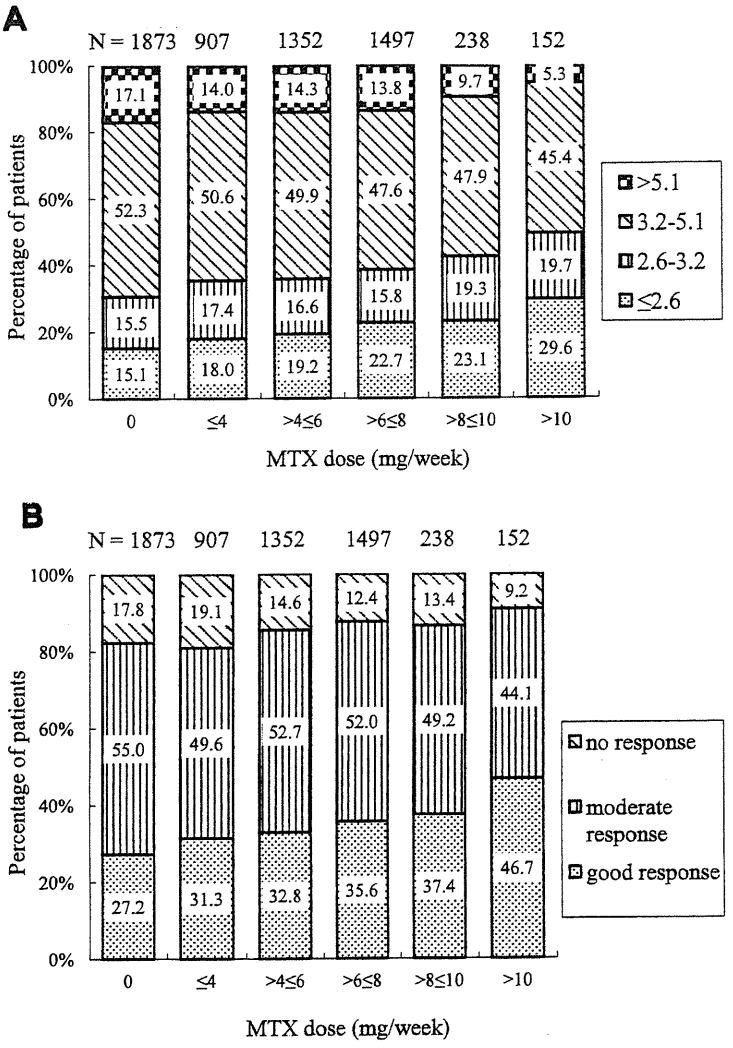

Figure 2. Effectiveness for the first 24 weeks in patients receiving etanercept monotherapy or etanercept plus MTX by categories of MTX dosage at baseline as indicated by (A) disease activity status and (B) EULAR response criteria. The trend on remission rate and response rate was significant ($p < 0.001$, Cochran-Armitage test). EULAR: European League Against Rheumatism; MTX: methotrexate.

and SI; concomitant nonserious infections for SI only) were also reported as risk factors for etanercept use in the RADIUS registry[17].

Results of the Cox proportional hazard model also indicated that there were differences in the risk factors for SAE and SI between the ETN + MTX groups and the ETN + DMARD group. The results show no significant difference in the ETN + DMARD group for SAE and SI in a higher Steinbrocker class and for SI in the group with > 1 selected-risk factor, but statistically significant results in the ETN + MTX group for this specific aspect. Although there are several possible reasons, such as the differences in baseline characteristics between the ETN + DMARD group and the ETN + MTX group, the sample size is not large enough to show significant difference. These results suggested that it is better to carefully observe the SAE and/or SI when ETN + MTX was used to treat patients with higher Steinbrocker class and/or with > 1 selected-risk factor.

Etanercept alone or in combination with other DMARD was also effective for improving RA symptoms, as assessed by DAS28 measurement of disease severity and EULAR response categories from Week 4, and this improvement had not yet plateaued at Week 24 (data not shown). The EULAR good response rate was significantly higher in the ETN + MTX group compared with the ETN-mono group or the