Laboratory tests included hematology, blood chemistry, and urinalysis. "Abnormal laboratory values" were defined as values that deviated from the normal range defined by the central laboratory. Average changes in laboratory tests were calculated based on the normal ranges in females. Supplementary Tables 1 and 2 available online at: http//informahealthcare.com/doi/abs/10.3109/14397595.2014.899179 show definitions of severity for AEs and criteria for selecting abnormal laboratory values, respectively.

Immunogenicity and pharmacodynamic assessments

Immunogenicity was assessed based on the levels of anti-abatacept (CTLA-4-Ig) antibodies and anti-CTLA-4 antibodies (CTLA-4-T: CTLA-4 without the Ig region) in blood using an enzyme-linked immunosorbent assay (ELISA). Blood samples were collected for immunogenicity assessments prior to abatacept administration at Week 0 and every 24 weeks thereafter. If a patient discontinued the study prematurely, immunogenicity was assessed at discontinuation and at 4, 8, and 12 weeks after the final administration of abatacept. When the serum concentration of abatacept was < 1 μg/mL, seropositive samples with anti-CTLA-4-T reactivity were further characterized using a cell-based neutralization assay to determine whether the sample had neutralizing antibody activity.

Rheumatoid factor (RF) and C-reactive protein (CRP) concentration levels were measured as pharmacodynamic parameters. Samples for the assessment of RF concentration levels were taken at Week 0 and every 12 weeks thereafter. Samples for the assessment of CRP concentration levels were taken at Weeks 0, 2, and 4, and then every 4 weeks for the first year, followed by every 12 weeks for the remainder of the study.

Efficacy assessments

Clinical efficacy was evaluated by ACR20, ACR50, and ACR70 responses [17]. Disease activity was measured by the rates of patients achieving a low disease activity state (LDAS; 28-joint Disease Activity Score [DAS28] [CRP] of ≤ 3.2) and remission (DAS28 [CRP] of < 2.6). Physical function was measured by patient-reported Health Assessment Questionnaire (HAQ) response (improvement from baseline of ≥ 0.3 units) [18]. The above efficacy assessments were made at Week 0 and every 12 weeks thereafter. Health-related quality of life was assessed using the Short Form-36 (SF-36) questionnaire at Week 0, and then every 12 weeks for the first year, followed by every 24 weeks for the remainder of the study.

Statistical analysis

Data are presented for the pooled population and by original cohort. All patients who received at least one infusion of abatacept were included in the safety and efficacy data sets. Patients who discontinued from the study without receiving abatacept were deemed pretreatment dropouts. While there was no hypothesis testing and no power consideration for safety or efficacy, administration of abatacept to 180 patients provided a 95% probability of observing at least one occurrence of any AE that would occur with $\geq 1.7\%$ incidence in the population from which the sample is drawn. All available data from patients who had received abatacept, and for whom baseline and at least one additional measurement had been available, were included in the pharmacodynamic and immunogenicity data sets. Baseline for all patient cohorts was defined as pre-dose of Day 1 for this Phase III study.

Safety data (all AEs) were described and analyzed as frequency distributions. Laboratory test results were summarized using descriptive statistics, and the rate of positive response was calculated for immunogenicity. For pharmacodynamic parameters, concentration levels and changes from baseline were evaluated using descriptive statistics.

All clinical variables, including ACR20/50/70, DAS28 (CRP)-defined LDAS and remission, and HAQ response, were summarized as observed for patients with data available at the visit of interest, using descriptive statistics. In addition to these analyses, a *post hoc* analysis of clinical results (ACR20/50/70, DAS28 [CRP]-defined LDAS and remission, and HAQ response) was carried out using a last observation carried forward (LOCF) analysis. Changes from baseline in each item of the SF-36 were summarized using descriptive statistics.

Results

Patient demographics

Patients completed screening in March 2008; the last day of observation occurred in December 2010. Patient disposition is summarized in Figure 1. A total of 217 patients were treated with abatacept (patients from Phase I, $n = 13$; patients from Phase II, $n = 178$; new patients with MTX intolerance, $n = 26$). Of the 217 patients, 56 (25.8%) discontinued from the study. Reasons for discontinuation included AEs and abnormal laboratory changes (24/217; 11.1%), patient request (13/217; 6.0%), inadequate response (13/217; 6.0%), and other reasons (6/217; 2.8%).

The mean age and weight of patients were 53.8 years and 56.5 kg, respectively, and the majority of patients were female (177/217; 81.6%). Patients had a mean disease duration of 9.1 years at the start of the Phase III study (baseline). The majority (141/217; 65.0%) of patients in each cohort were classified as RA Functional Class II. RA disease activity, as measured by tender joints, swollen joint counts, and CRP levels, was highest in the cohort of new patients with MTX intolerance (Table 1).

While there was at least a 1-year gap between the last day of observation in the Phase I study and the initiation of this Phase III study, there was a median (range) transition period of 12.1 (7.1–25.1) weeks between the final dose of abatacept or placebo in the Phase II study and the first dose of abatacept in the present Phase III study. Following this Phase II to Phase III transition period, patients from Phase II had a median (range) duration of exposure to abatacept of 37.7 (3.6–45.1) months. The median (range) duration of exposure to abatacept in patients from Phase I was 42.4 (31.3–44.0) months, 32.3 (1.0–44.0) months in new patients with MTX intolerance, and 37.7 (1.0–45.1) months in all patients combined. More than half (126/217; 58.1%) of all patients were treated with abatacept for more than 3 years. One abatacept infusion was missed in 34/217 (15.7%) patients during the present treatment period; however, no patients had missed more than two consecutive doses. Seven patients missed three or more doses in total; in all the cases, the reason for missing the dose was an AE.

At the time of enrollment, most patients were receiving concomitant MTX therapy (Table 1). MTX dosage (mean [standard deviation, SD]) was 7.11 (1.45) mg/week in patients from Phase I, and 7.11 (1.07) mg/week in patients from Phase II. Concomitant DMARD therapy was prohibited in new patients with MTX intolerance from the start of the study until the completion of Week 12. Concomitant oral corticosteroid therapy (prednisolone: mean [SD] dose, 5.85 [2.41] mg/day in all cohorts) was used by 182/217 (83.9%) patients in the study.

Safety

Adverse events

The overall safety profile for abatacept in all three patient cohorts is shown in Table 2. The most common AEs were

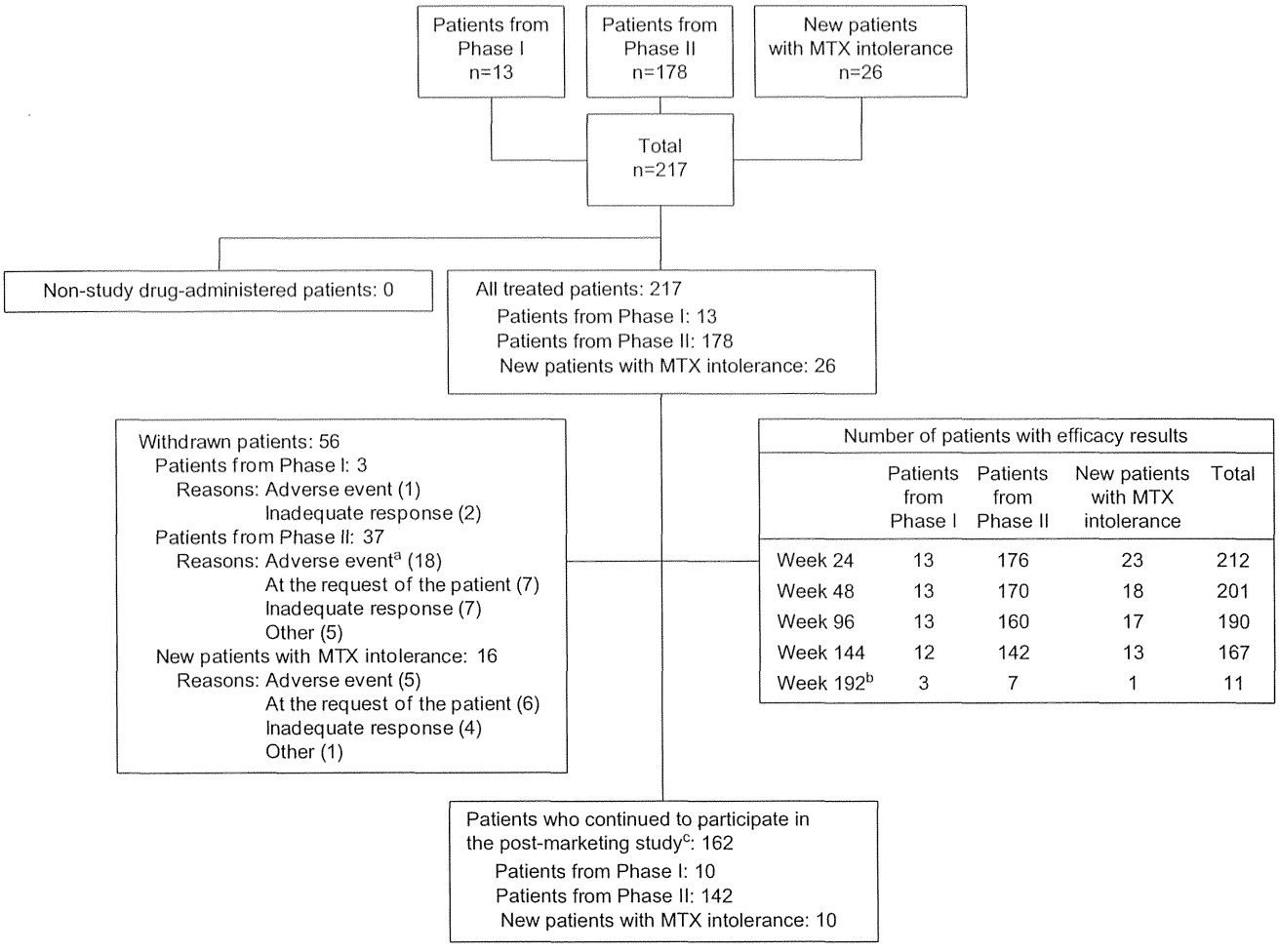

Figure 1. Patient disposition.[a]Discontinuations from adverse events included one discontinuation due to abnormal laboratory changes. [b]Only 11 patients had 192 weeks of treatment at the time of analysis, due to differential enrollment times.[c]The last time point for the study was 27 December 2010, at which point the median (range) cumulative duration of abatacept exposure in all patients combined was 37.7 (1.0–45.1) months. MTX, methotrexate.

Table 1. Patient characteristics.

Variables	Patients from Phase I, $n = 13$	Patients from Phase II, $n = 178$	New patients with MTX intolerance, $n = 26$	Total, $N = 217$
Age (years), mean (SD)	52.8 (11.6)	53.2 (11.5)	57.8 (10.6)	53.8 (11.4)
Weight (kg), mean (SD)	55.2 (9.7)	56.9 (9.4)	53.9 (10.8)	56.5 (9.6)
Number of females, *n* (%)	12 (92.3)	146 (82.0)	19 (73.1)	177 (81.6)
Duration of RA (years), mean (SD)	14.4 (9.0)	8.4 (7.3)	10.9 (10.1)	9.1 (7.9)
Tender joints, mean (SD)	8.4 (5.2)	14.3 (11.2)	22.7 (13.3)	14.9 (11.6)
Swollen joints, mean (SD)	9.1 (4.7)	11.6 (8.7)	17.2 (10.0)	12.1 (8.9)
Pain (VAS 100 mm), mean (SD)	43.1 (23.5)	52.3 (24.9)	80.6 (20.1)	55.1 (26.0)
Physical function (HAQ score), mean (SD)	0.98 (0.57)	1.16 (0.75)	1.80 (0.90)	1.22 (0.79)
Subject Global Assessment (VAS 100 mm), mean (SD)	47.1 (20.7)	50.8 (23.8)	77.3 (20.4)	53.7 (24.8)
Physician Global Assessment (VAS 100 mm), mean (SD)	56.5 (24.7)	47.5 (24.0)	75.5 (16.5)	51.4 (24.9)
CRP (mg/dL), mean (SD)	1.84 (2.84)	2.32 (2.18)	4.67 (3.65)	2.57 (2.55)
Rheumatoid factor (IU/mL)				
Negative (≤ 20), *n* (%)	1 (7.7)	24 (13.5)	4 (15.4)	29 (13.4)
Positive (>20), *n* (%)	12 (92.3)	154 (86.5)	22 (84.6)	188 (86.6)
DAS28 (CRP), *n*	13	176	21	210
Mean (SD)	4.4 (1.0)	4.8 (1.4)	6.3 (1.0)	5.0 (1.4)
Prior MTX use, *n* (%)	9 (69.2)	178 (100.0)	26 (100.0)	213 (98.2)
Prior conventional DMARD use,[a]*n* (%)	3 (23.1)	6 (3.4)	9 (34.6)	18 (8.3)
Prior biologic use, *n* (%)	9 (69.2)	52 (29.2)	14 (53.8)	75 (34.6)
Concomitant MTX use at registration, *n* (%)	9 (69.2)	175 (98.3)	0	184 (84.8)
Dose (mg/week), mean (SD)	7.11 (1.45)	7.11 (1.07)	–	7.11 (1.09)
Concomitant oral corticosteroid use at registration, *n* (%)	13 (100.0)	146 (82.0)	23 (88.5)	182 (83.9)
Dose (mg/day), mean (SD)	6.15 (2.37)	5.67 (2.38)	6.78 (2.48)	5.85 (2.41)

CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; SD, standard deviation; VAS, visual analog scale.
[a]Other than MTX.

Table 2. Adverse events and serious adverse events.

	Number of patients (%)			
	Patients from Phase I, $n = 13$	Patients from Phase II, $n = 178$	New patients with MTX intolerance, $n = 26$	Total, $N = 217$
AEs	13 (100.0)	176 (98.9)	24 (92.3)	213 (98.2)
Drug-related AEs	13 (100.0)	165 (92.7)	24 (92.3)	202 (93.1)
Discontinuation due to AEs	1 (7.7)	17 (9.6)	5 (19.2)	23 (10.6)
Infections and infestations	11 (84.6)	141 (79.2)	16 (61.5)	168 (77.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	22 (12.4)	2 (7.7)	24 (11.1)
Autoimmune disorders	0	7 (3.9)	1 (3.8)	8 (3.7)
Peri-infusional	9 (69.2)	78 (43.8)	16 (61.5)	103 (47.5)
SAEs	4 (30.8)	50 (28.1)	13 (50.0)	67 (30.9)
Drug-related SAEs	2 (15.4)	26 (14.6)	8 (30.8)	36 (16.6)
Discontinuation due to SAEs	0	14 (7.9)	5 (19.2)	19 (8.8)
Infections and infestations	2 (15.4)	11 (6.2)	3 (11.5)	16 (7.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	10 (5.6)	1 (3.8)	11 (5.1)
Abnormal laboratory changes	7 (53.8)	125 (70.2)	19 (73.1)	151 (69.6)
Drug-related abnormal laboratory changes	6 (46.2)	102 (57.3)	13 (50.0)	121 (55.8)
Discontinuation due to abnormal laboratory changes	0	1 (0.6)	0	1 (0.5)
Serious abnormal laboratory changes	0	0	1 (3.8)	1 (0.5)
Drug-related serious abnormal laboratory changes	0	0	1 (3.8)	1 (0.5)
Discontinuation due to serious abnormal laboratory changes[a]	0	0	0	0
Deaths	0	1 (0.6)	0	1 (0.5)

AE, adverse event; SAE, serious adverse event; MTX, methotrexate
[a]There were no serious abnormal laboratory changes that led to discontinuation.

nasopharyngitis (123/217 patients, 56.7%), stomatitis (53/217 patients, 24.4%), increased blood pressure (41/217 patients, 18.9%), upper respiratory tract inflammation (35/217 patients, 16.1%), and eczema (32/217 patients, 14.7%). The majority of AEs were mild or moderate. Severe and very severe AEs occurred in 38/217 (17.5%) and in 3/217 (1.4%) treated patients, respectively; AEs classified as very severe are discussed in further detail below under SAEs. AEs (including SAEs) leading to discontinuation occurred in 23/217 (10.6%) treated patients (Table 2). One (1/217; 0.5%) patient from the Phase II study died due to pancreatic carcinoma (Table 2), which is discussed further below. No deaths were reported in the other two cohorts.

Serious adverse events

For the 67/217 (30.9%) patients who reported SAEs (Table 2), all SAEs resolved with appropriate treatment or follow-up except for pancreatic carcinoma, pinealoma/hydrocephalus, thalamus hemorrhage, cerebral infarction, spinal compression fracture, endometrial cancer, pneumonia, and diffuse large B-cell lymphoma occurring in one patient each. The pancreatic carcinoma, thalamus hemorrhage, and a case of sepsis (one patient; 0.5%) were classified as very severe. Sepsis and pancreatic carcinoma were classified as related to study drug, and thalamus hemorrhage was classified as unrelated to study drug. All three of these events resulted in discontinuation, and the SAE of pancreatic cancer, which developed approximately 20 months following the initiation of abatacept treatment, resulted in the one death during the study period.

Overall, SAEs led to discontinuation in 19/217 (8.8%) treated patients (Table 2). In addition to those events mentioned above, patients discontinued due to one or more of the following: cerebral infarction (2/217 patients; 0.9%), cardiac failure, atrial fibrillation, mitral valve incompetence, inflammatory bowel disease, osteomyelitis, subcutaneous abscess, pharyngeal abscess, B-cell lymphoma, breast cancer, diffuse large B-cell lymphoma, endometrial cancer, gastric cancer, pinealoma, T-cell lymphoma, cervix carcinoma stage 0, cerebral hemorrhage, encephalitis, seventh cranial nerve paralysis, and interstitial lung disease (one patient each; 0.5%). One case of cerebral infarction and the SAEs of sepsis, encephalitis, and pharyngeal abscess all occurred in a single patient, resulting in that patient's discontinuation. Similarly, the SAEs of atrial fibrillation, cardiac failure, and mitral valve incompetence occurred in a single patient, resulting in that patient's discontinuation. Interstitial lung disease and the cranial nerve paralysis were classified as unrelated to study drug, and the other events were classified as related by the study investigators.

Laboratory changes

Of the 217 patients treated with abatacept, AEs of abnormal laboratory changes occurred in 151 (69.6%) patients (Table 2). Decreased lymphocyte count (< 750/μL) was the most common abnormal laboratory change and was reported in 41/217 (18.9%) patients; 34/217 (15.7%) patients exhibited decreased lymphocyte counts classified as related to study drug. Other abnormal laboratory changes (see Supplementary Table 1 available online at: http//informahealthcare.com/doi/abs/10.3109/14397595.2014.899179 for definitions) that occurred in at least 5% of treated patients were as follows: increased white blood cell count (37/217; 17.1%), increased alanine aminotransferase (33/217; 15.2%), increased aspartate aminotransferase (25/217; 11.5%), white blood cells in urine (24/217; 11.1%), increased gamma-glutamyltransferase (16/217; 7.4%), blood present in urine (16/217; 7.4%), red blood cells in urine (16/217; 7.4%), increased eosinophil count (13/217; 6.0%), increased blood glucose (13/217; 6.0%), and glucose present in urine (13/217; 6.0%); none were classified as serious.

Only one patient (1/217; 0.5%) had an abnormal laboratory change (increased CRP) that was classified as serious (Table 2). This patient also had a high white blood cell count, leading study investigators to suspect that these changes occurred due to infection; however, the causative pathogen could not be identified and the patient was discharged when the symptoms resolved. One patient from Phase II, who tested positive for hepatitis B surface antigens, had an abnormal laboratory change that led to discontinuation of study treatment (1/217; 0.5%). This event, which was classified as "possibly" related to study drug, was non-serious. All abnormal laboratory changes were classified as mild or moderate, and no severe or very severe abnormal laboratory changes were observed.

Adverse events of interest

Infections and infestations

Infections and infestations were observed in 168/217 (77.4%) patients (Table 2). The most common infections were nasopharyngitis (123/217; 56.7%), pharyngitis (28/217; 12.9%), and gastroenteritis (22/217; 10.1%). Infections were classified as mild or moderate, with the exception of cellulitis and pneumonia (two patients each; 0.9%), bronchitis, subcutaneous abscess, acute sinusitis, appendicitis, osteomyelitis, bacterial arthritis, and pharyngeal abscess (one patient each, 0.5%), which were classified as severe, and one incidence of sepsis (0.5%), which was classified as very severe.

Serious infections were reported in 16/217 (7.4%) patients (Table 2). All of these serious infections were classified as related to study drug, and treatment was discontinued in two patients with osteomyelitis and sepsis/pharyngeal. However, many of the serious infections either resolved or were relieved with treatment. Opportunistic infections were observed in 33/217 (15.2%) treated patients; they included herpes zoster and oral herpes (ten patients each; 4.6%) and herpes simplex (3/217; 1.4%). Incidences of other opportunistic infections were less than 1.0%. No cases of tuberculosis were reported.

Neoplasms

Neoplasms—benign, malignant, and unspecified (including cysts and polyps)—were reported in 24/217 (11.1%) patients (Table 2). Of these, B-cell lymphoma, breast cancer, diffuse large B-cell lymphoma, endometrial cancer, gastric cancer, pancreatic carcinoma, pinealoma, T-cell lymphoma, lung neoplasm, and cervix carcinoma stage 0 (one patient each, 0.5%) were classified as malignant. Serious neoplasms occurred in 11/217 (5.1%) patients and included the above neoplasms that were classified as malignant (excluding lung neoplasm), an unspecified neoplasm, and uterine leiomyoma. Each of the neoplasms classified as both malignant and serious was classified as related to study drug, and the treatment with abatacept was discontinued.

Autoimmune events

Autoimmune AEs occurred in 8/217 (3.7%) patients (Table 2). Autoimmune events included scleritis, uveitis, atrophic gastritis, Sjögren's syndrome, erythema nodosum, leukocytoclastic vasculitis, Basedow's disease, and inflammatory bowel disease (IBD, one patient each; 0.5%). Only one autoimmune event (IBD) led to discontinuation; this event occurred in a new patient with MTX intolerance, was classified as serious, and was classified as related to study drug by the investigator.

Peri-infusional AEs

Peri-infusional AEs, defined as AEs that occurred after the start of treatment on the day of abatacept administration or the following day, occurred in 103/217 (47.5%) patients (Table 2). All events were classified as mild or moderate with the exception of one T-cell lymphoma and one cervix carcinoma stage 0 that were classified as severe.

Immunogenicity and pharmacodynamics

Immunogenicity

Immunogenicity was evaluated as auto-antibody productive responses in 217 patients using ELISA. Anti-abatacept antibody (23/217; 10.6%) or anti-CTLA-4-T antibody (20/217; 9.2%) were detected from Weeks 0 to 192 in a total of 42/217 (19.4%) patients. Patients with a positive anti-abatacept antibody response (23/217) were found in each of the three cohorts: Phase I, 2/13 (15.4%); Phase II, 19/178 (10.7%); and new patients with MTX intolerance, 2/26 (7.7%). Patients with a positive anti-CTLA-4-T antibody response (20/217; 9.2%) were detected in two of the three cohorts: Phase I, 0; Phase II, 19/178 (10.7%); and newly enrolled patients, 1/26 (3.8%). Among the patients from Phase II with positive immunogenicity responses, 20 were already anti-abatacept antibody (4/178; 2.2%) or anti-CTLA-4-T antibody (17/178; 9.6%) positive at baseline (Week 0) of this Phase III study. Of these patients, 17/178 (9.6%) did not test positive again during the Phase III study (post-baseline). Neutralizing activity was indicated in five patients from Phase II who tested positive for anti-CTLA-4-T antibody at baseline. However, no patients tested positive for neutralizing activity of anti-CTLA-4-T antibody during this Phase III study (post-baseline).

Pharmacodynamics

Pharmacodynamic parameters, including CRP and RF evaluations, improved with abatacept treatment. Mean CRP levels at baseline in Phase I, Phase II, and new patients with MTX intolerance were 1.84, 2.32, and 4.67 mg/dL, respectively (Table 1). In patients from Phase I and Phase II, CRP levels decreased to below the lower limit of the reference range (1 mg/dL) at Week 24, and remained so for over 3 years in the patients from Phase II. Similarly, in new patients with MTX intolerance, mean (SD) CRP level decreased to 0.9 (1.3) mg/dL at Week 48 ($n = 18$, baseline: 4.1 mg/dL) and remained consistently low for over 3 years. RF positivity decreased over time in each cohort. The overall mean RF value decreased from 255.0 IU/mL to 183.5 IU/mL at Week 24 ($n = 210$). The mean (standard error, SE) change from baseline was − 71.6 (13.7) IU/mL at Week 24, − 85.8 (17.4) IU/mL at Week 48, − 89.2 (22.3) IU/mL at Week 96, − 68.2 (23.9) IU/mL at Week 144, and − 176.2 (250.5) IU/mL at Week 192.

Clinical efficacy

ACR responses

Of the 217 patients treated with abatacept, 212 (97.7%) patients completed the efficacy evaluation at 6 months (24 weeks), 201 (92.6%) patients at 1 year (Week 48), 190 (87.6%) patients at 2 years (Week 96), and 167 (77.0%) patients at 3 years (Week 144: Figure 1). Only 11 (5.1%) patients had reached 4 years of treatment (Week 192) at the time of analysis, due to differential enrollment times. Therefore, it was considered possible to accurately evaluate the maintenance of efficacy of long-term administration of abatacept for up to 3 years (rates at 4 years are also given despite the very small sample size). Improvements in signs and symptoms of RA, as measured by ACR responses, were seen in high proportions of patients at Weeks 24 and 48, with ACR response rates maintained for patients who remained on abatacept therapy (as observed from baseline of the present study) for up to 3 years. The as-observed proportion of patients (95% confidence interval [CI]) from all cohorts achieving an ACR20 response at Weeks 24, 48, 96, 144, and 192 was 62.7% (55.8, 69.3), 65.7% (58.7, 72.2), 65.8% (58.6, 72.5), 70.1% (62.5, 76.9), and 81.8% (48.2, 97.7), respectively. For ACR50, as-observed response rates at Weeks 24, 48, 96, 144, and 192 were 28.3% (22.3, 34.9), 40.3% (33.5, 47.4), 38.9% (32.0, 46.3), 47.3% (39.5, 55.2), and 72.7% (39.0, 94.0), respectively. The as-observed proportion of patients with ACR70 response at Weeks 24, 48, 96, 144, and 192 was 11.8% (7.8, 16.9), 16.4% (11.6, 22.3), 18.9% (13.6, 25.3), 20.4% (14.5, 27.3), and 18.2 (2.3, 51.8), respectively. In a *post hoc* analysis, ACR responses were also evaluated using LOCF from baseline of the present study (Table 3) and were similar to the as-observed rates reported above.

ACR response (as-observed) was also analyzed for patients from the Phase II study based on baseline of Week 0 in the original Phase II study. During the Phase II study, ACR20, ACR50, and ACR70 response rates increased over time in the abatacept 10 mg/kg and abatacept 2 mg/kg groups [12]. By Week 24 of the Phase II study, the as-observed proportion of patients (95% CI) with ACR20, ACR50, and ACR70 response were, respectively: 78.3% (65.8, 87.9), 46.7% (33.7, 60.0), and 21.7% (12.1, 34.2) in the abatacept 10 mg/kg group ($n = 60$); 63.6% (50.9, 75.1), 37.9% (26.2, 50.7), and 16.7% (8.6, 27.9) in the abatacept 2 mg/kg group ($n = 66$); and 21.1% (11.4, 33.9), 5.3% (1.1, 14.6), and 0% (0.0, 6.3) in the placebo group ($n = 57$) [12]. The median transition period from the day of the final dose of the study drug in Phase II (Week 20) to the day of the first dose of abatacept in the present Phase III study was approximately 12 weeks for all dose groups. Following this transition and the switch to abatacept approximating 10 mg/kg for all patients, the respective as-observed ACR20, ACR50, and ACR70 response rates (based on Phase II baseline) at Week 24 of Phase III for the original Phase II dose groups were 81.4% (69.1, 90.3), 55.9% (42.4, 68.8), and 33.9% (22.1, 47.4) in the abatacept 10 mg/kg group ($n = 59$); 81.0% (69.1, 89.8), 50.8% (37.9, 63.6), and 25.4% (15.3, 37.9) in the abatacept 2 mg/kg group ($n = 63$); and 77.8% (64.4, 88.0), 50.0% (36.1, 63.9), and 29.6% (18.0, 43.6) in the placebo group ($n = 54$), respectively. At 3 years (Week 144 of Phase III), the respective as-observed ACR20, ACR50, and ACR70 response rates (based on Phase II baseline) for the original Phase II dose groups were 80.9% (66.7, 90.9), 61.7% (46.4, 75.5), and 40.4% (26.4, 55.7) in the abatacept 10 mg/kg group ($n = 47$); 87.2% (74.3, 95.2), 66.0% (50.7, 79.1), and 34.0% (20.9, 49.3) in the abatacept 2 mg/kg group ($n = 47$); and 91.7% (80.0, 97.7), 68.8% (53.7, 81.3), and 45.8% (31.4, 60.8) in the placebo group ($n = 48$), respectively.

Disease activity, physical function, and quality of life

Mean DAS28 (CRP) at baseline in patients from Phase I, Phase II, and in new patients with MTX intolerance was 4.4, 4.8, and 6.3, respectively. High proportions of patients achieved low disease activity (DAS28 [CRP] ≤ 3.2) and remission (DAS28 [CRP] < 2.6) outcomes at Weeks 24 and 48, and maintained these outcomes over time (based on as-observed data): 52.4 and 34.3%, respectively, at Week 24 ($n = 210$); 60.8 and 42.2%, respectively, at Week 48 ($n = 199$); 59.8 and 43.9%, respectively, at Week 96 ($n = 189$); 64.7 and 46.7%, respectively, at Week 144 ($n = 167$); and 54.5 and 45.5%, respectively, at Week 192 ($n = 11$). Additionally, DAS28 (CRP) analyzed using LOCF (Table 4) yielded rates similar to the as-observed analysis reported above; low disease activity and remission rates seen at Weeks 24 and 48 were sustained over the Phase III treatment period (Table 4).

Baseline HAQ scores are shown in Table 1. The as-observed proportion of patients (95% CI) achieving a HAQ response (defined as reduction of HAQ of > 0.3 from baseline) overall was 40.6% (33.9,

Table 3. ACR20, ACR50, and ACR70 responses at Weeks 24, 48, 96, 144, and 192 (LOCF from Phase III baseline).

	ACR responses			
	Patients from Phase I (IM101034), $n = 13$	Patients from Phase II (IM101071), $n = 178$	New patients with MTX intolerance, $n = 26$	Total (all treated patients), $N = 217$
Week 24				
ACR20, *n* (%)	10 (76.9)	106 (59.6)	18 (69.2)	134 (61.8)
95% CI for %	(46.2, 95.0)	(52.0, 66.8)	(48.2, 85.7)	(54.9, 68.2)
ACR50, *n* (%)	4 (30.8)	45 (25.3)	11 (42.3)	60 (27.6)
95% CI for %	(9.1, 61.4)	(19.1, 32.3)	(23.4, 63.1)	(21.8, 34.1)
ACR70, *n* (%)	1 (7.7)	19 (10.7)	5 (19.2)	25 (11.5)
95% CI for %	(0.2, 36.0)	(6.6, 16.2)	(6.6, 39.4)	(7.6, 16.5)
Week 48				
ACR20, *n* (%)	8 (61.5)	111 (62.4)	17 (65.4)	136 (62.7)
95% CI for %	(31.6, 86.1)	(54.8, 69.5)	(44.3, 82.8)	(55.9, 69.1)
ACR50, *n* (%)	2 (15.4)	66 (37.1)	14 (53.8)	82 (37.8)
95% CI for %	(1.9, 45.4)	(30.0, 44.6)	(33.4, 73.4)	(31.3, 44.6)
ACR70, *n* (%)	2 (15.4)	26 (14.6)	5 (19.2)	33 (15.2)
95% CI for %	(1.9, 45.4)	(9.8, 20.7)	(6.6, 39.4)	(10.7, 20.7)
Week 96				
ACR20, *n* (%)	9 (69.2)	108 (60.7)	16 (61.5)	133 (61.3)
95% CI for %	(38.6, 90.9)	(53.1, 67.9)	(40.6, 79.8)	(54.5, 67.8)
ACR50, *n* (%)	3 (23.1)	61 (34.3)	12 (46.2)	76 (35.0)
95% CI for %	(5.0, 53.8)	(27.3, 41.7)	(26.6, 66.6)	(28.7, 41.8)
ACR70, *n* (%)	1 (7.7)	31 (17.4)	4 (15.4)	36 (16.6)
95% CI for %	(0.2, 36.0)	(12.2, 23.8)	(4.4, 34.9)	(11.9, 22.2)
Week 144				
ACR20, *n* (%)	8 (61.5)	114 (64.0)	16 (61.5)	138 (63.6)
95% CI for %	(31.6, 86.1)	(56.5, 71.1)	(40.6, 79.8)	(56.8, 70.0)
ACR50, *n* (%)	4 (30.8)	74 (41.6)	12 (46.2)	90 (41.5)
95% CI for %	(9.1, 61.4)	(34.2, 49.2)	(26.6, 66.6)	(34.8, 48.3)
ACR70, *n* (%)	0 (0.0)	35 (19.7)	4 (15.4)	39 (18.0)
95% CI for %	(0.0, 24.7)	(14.1, 26.3)	(4.4, 34.9)	(13.1, 23.7)
Week 192				
ACR20, *n* (%)	9 (69.2)	111 (62.4)	17 (65.4)	137 (63.1)
95% CI for %	(38.6, 90.9)	(54.8, 69.5)	(44.3, 82.8)	(56.3, 69.6)
ACR50, *n* (%)	5 (38.5)	78 (43.8)	13 (50.0)	96 (44.2)
95% CI for %	(13.9, 68.4)	(36.4, 51.4)	(29.9, 70.1)	(37.5, 51.1)
ACR70, *n* (%)	0 (0.0)	40 (22.5)	6 (23.1)	46 (21.2)
95% CI for %	(0.0, 24.7)	(16.6, 29.3)	(9.0, 43.6)	(16.0, 27.2)

ACR, American College of Rheumatology; CI, confidence interval; LOCF, last observation carried forward; MTX, methotrexate

Table 4. DAS28 (CRP) LDAS and remission at Weeks 24, 48, 96, 144, and 192 (LOCF from Phase III baseline).

	LDAS and remission[a]			
	Patients from Phase I (IM101034), $n = 13$	Patients from Phase II (IM101071), $n = 178$	New patients with MTX intolerance, $n = 26$	Total (all treated patients), $N = 217$
Week 24				
LDAS, *n* (%)	9 (69.2)	95 (53.4)	6 (23.1)	110 (50.7)
Remission, *n* (%)	6 (46.2)	60 (33.7)	6 (23.1)	72 (33.2)
Week 48				
LDAS, *n* (%)	9 (69.2)	108 (60.7)	8 (30.8)	125 (57.6)
Remission, *n* (%)	4 (30.8)	78 (43.8)	5 (19.2)	87 (40.1)
Week 96[b]				
LDAS, *n* (%)	6 (46.2)	106 (59.9)	7 (26.9)	119 (55.1)
Remission, *n* (%)	3 (23.1)	79 (44.6)	5 (19.2)	87 (40.3)
Week 144				
LDAS, *n* (%)	6 (46.2)	113 (63.5)	9 (34.6)	128 (59.0)
Remission, *n* (%)	4 (30.8)	83 (46.6)	4 (15.4)	91 (41.9)
Week 192				
LDAS, *n* (%)	7 (53.8)	111 (62.4)	10 (38.5)	128 (59.0)
Remission, *n* (%)	4 (30.8)	86 (48.3)	7 (26.9)	97 (44.7)

DAS28 (CRP), 28-joint Disease Activity Score (C-reactive protein); LDAS, low disease activity state; LOCF, last observation carried forward; MTX, methotrexate.
[a]LDAS was defined as a DAS28 (CRP) of ≤ 3.2, and remission was defined as DAS28 (CRP) of < 2.6.
[b]At Week 96, 177 patients from Phase II were evaluated (Total = 216).

47.5) at Week 24 ($n = 212$), 43.8% (36.8, 50.9) at Week 48 ($n = 201$), 50.0% (42.7, 57.3) at Week 96 ($n = 190$), 50.3% (42.5, 58.1) at Week 144 ($n = 167$), and 90.9% (58.7, 99.8) at Week 192 ($n = 11$). As with the as-observed data reported above, initial improvement and subsequent maintenance of response over time also occurred when HAQ response was evaluated using LOCF (Table 5).

All cohorts showed an improvement from baseline in physical component summary and mental component summary scores of the SF-36 over 3 years. The mean (SE) change from baseline in physical component summary score for all cohorts combined was 8.4 (0.8) at Week 24, 10.2 (0.9) at Week 48, 10.7 (0.9) at Week 96, 8.6 (1.0) at Week 144, and 13.8 (6.3) at Week 192. The mean (SE) change from baseline in mental component summary score for all cohorts was 3.2 (0.6) at Week 24, 3.6 (0.6) at Week 48, 3.0 (0.7) at Week 96, 3.2 (0.7) at Week 144, and 11.5 (5.2) at Week 192. Improvement from baseline was also achieved in the eight SF-36 subscales (not shown).

Discussion

Although the majority of patients with RA begin long-term treatment with MTX, some patients do not respond adequately to MTX alone or are not candidates for MTX, and therefore require additional therapeutic options. Previous studies have demonstrated the long-term efficacy and favorable safety of IV abatacept in patients with an inadequate response to MTX [9,10]. In this long-term study in Japanese patients with RA and an inadequate response to MTX or other conventional or biologic DMARDs, IV abatacept monotherapy and IV abatacept with background MTX demonstrated acceptable safety and sustained efficacy over 3 years of treatment.

This Phase III, open-label, long-term study of IV abatacept included patients with RA from the Japanese Phase I clinical trial [13], patients with active RA and an inadequate response to MTX from the Japanese Phase II clinical trial [12], and newly enrolled patients with RA and MTX intolerance. Although all patients had

Table 5. Patients who presented HAQ response at Weeks 24, 48, 96, 144, and 192 (LOCF from Phase III baseline).

	HAQ response[a]			
	Patients from Phase I (IM101034), $n = 13$	Patients from Phase II (IM101071), $n = 178$	New patients with MTX Intolerance, $n = 26$	Total (all treated patients), $N = 217$
Week 24				
n (%)	5 (38.5)	70 (39.3)	12 (46.2)	87 (40.1)
95% CI for %	(13.9, 68.4)	(32.1, 46.9)	(26.6, 66.6)	(33.5, 46.9)
Week 48				
n (%)	4 (30.8)	73 (41.0)	15 (57.7)	92 (42.5)
95% CI for %	(9.1, 61.4)	(33.7, 48.6)	(36.9, 76.6)	(35.7, 49.3)
Week 96				
n (%)	6 (46.2)	81 (45.5)	15 (57.7)	102 (47.0)
95% CI for %	(19.2, 74.9)	(38.0, 53.1)	(36.9, 76.6)	(40.2, 53.9)
Week 144				
n (%)	7 (53.8)	82 (46.1)	13 (50.0)	102 (47.0)
95% CI for %	(25.1, 80.8)	(38.6, 53.7)	(29.9, 70.1)	(40.2, 53.9)
Week 192				
n (%)	8 (61.5)	80 (44.9)	14 (53.8)	102 (47.0)
95% CI for %	(31.6, 86.1)	(37.5, 52.6)	(33.4, 73.4)	(40.2, 53.9)

CI, confidence interval; HAQ, Health Assessment Questionnaire; LOCF, last observation carried forward; MTX, methotrexate
[a]HAQ response was defined as at least a 0.3-point decrease in HAQ score.

been treated previously with MTX, approximately one-third of patients also had prior biologic DMARD use. At enrollment, the majority of patients from the Phase I and Phase II studies were receiving concomitant MTX, and the newly enrolled patients received abatacept monotherapy. All patients were treated with IV abatacept for a mean of 3 years, and 58.1% patients were maintained on IV abatacept for more than 3 years.

The variety, frequency, and severity of the AEs in patients treated with abatacept as monotherapy or concomitantly with DMARDs were not significantly different from those reported in long-term international clinical trials of abatacept (NCT00162266 [19]; NCT00048568 [9]; and NCT00048581 [20]) and the Japanese Phase II clinical trial (NCT00345748 [12]). Most of the AEs observed, including abnormal laboratory changes, were mild or moderate, and most SAEs resolved or were relieved by treatment. Among the three patient cohorts, newly enrolled patients had the highest rates of SAEs and discontinuation due to SAEs. As expected, these patients also had higher baseline disease activity.

In addition to assessment of AEs, the immunogenicity results from the present study fall within the range of results seen in the previous Japanese trials [12,13]. During the Phase I study, 7/21 (33%) patients were positive for anti-CTLA-4-T antibodies [13], while positive immunogenicity responses were not detected in any patient during the Phase II study [12]. In the present study, the majority of patients with a positive immunogenicity response were from the Phase II study. Of these Phase II patients, approximately half had positive responses that were transient and occurred only at baseline.

Improvements from baseline in CRF and RF levels were demonstrated in all cohorts. Reductions in CRP have been shown to be correlated with clinical response in previous studies of abatacept [21,22]. The CRP reduction in the present study is also consistent with the Phase I Japanese trial that demonstrated mean decreases in CRP levels [13]. In a Phase II study of IV abatacept (~10 mg/kg) in patients with very early RA (NCT00124449), reductions in RF levels from baseline were seen at 6 months and 1 year, and, similar to CRP, changes in RF levels were correlated with clinical response to abatacept [23].

As this study was an uncontrolled, open-label study, and the evaluation of efficacy was a secondary objective, no tests based on a formal statistical hypothesis were conducted, and the efficacy was based on as-observed analyses for up to 3 years following baseline (Week 0) of this Phase III study. The majority of the 217 evaluated patients had previously received abatacept either as part of the Phase I study (2, 8, and 16 mg/kg abatacept) or as part of the Phase II trial (2 or 10 mg/kg abatacept or placebo plus MTX), and as such had lower mean clinical disease severity at baseline than the newly enrolled patients. Improvements in clinical efficacy were seen in patients from Phase I and Phase II following initiation of abatacept at Week 0, likely due to the transition period between studies, and the fact that not all patients had been receiving abatacept at therapeutic doses. Patients who were newly enrolled on abatacept as monotherapy experienced improvements in signs and symptoms of RA, as evaluated by ACR response, following initiation of therapy. Following the initial clinical response, ACR response rates were maintained over 3 years in all three patient cohorts.

For patients from Phase II, ACR response rates declined in both abatacept-treated groups (2 and 10 mg/kg) during the period between the last efficacy analysis of the Phase II study and the start of Phase III (data not shown). However, the ACR response rates increased in all treatment groups after the start of abatacept administration in Phase III. Based on baseline of Week 0 in the original Phase II study, ACR responses at Week 24 of this Phase III study for each of the original Phase II dose groups were similar to those observed for the abatacept 10 mg/kg group at Week 24 of the Phase II study [12]. Furthermore, based on a baseline of Week 0 in the original Phase II study, these response rates were sustained for up to 3 years in the present study for patients who remained on treatment.

DAS28 (CRP) and HAQ outcomes (based on as-observed data) were also maintained over the 3-year period in all patient cohorts, which included patients receiving IV abatacept as monotherapy and when administered with concomitant DMARDs, demonstrating sustained benefits in disease activity and physical function for patients who remained on treatment. Since as-observed analyses are vulnerable to the discontinuation of patients, a *post hoc* analysis using the more stringent LOCF method was performed for the above clinical efficacy measures. Using LOCF, rates of ACR response, DAS28 (CRP)-defined LDAS and remission, and HAQ response were sustained over 3 years, confirming the results from the as-observed analyses. Finally, SF-36 physical component summary and mental component summary scores (as-observed) also showed improvement from baseline in all cohorts, and generally continued at the same improved levels over the same time frame.

Interpretation of results should take into consideration the limitations of the study. This study, being an open-label extension, creates a number of challenges for data analysis and interpretation. These challenges, which include bias in patient inclusion and outcomes, have been previously outlined by Buch et al. [24]. Furthermore, the three cohorts utilized in this study had different baseline disease states with varying prior and current concomitant medication usage, and the results from the pooled patient population should be interpreted with caution. In addition, the sample size of this study was small; for this reason, the findings of this study alone should be extrapolated to the broader community with appropriate caution.

In conclusion, no new safety signals were identified in this long-term study of IV abatacept in Japanese patients with RA compared with previous international trials, based on the assessment of AEs and immunogenicity. IV abatacept as monotherapy and in combination with MTX was confirmed to be well tolerated, and improvements in clinical and functional efficacy were maintained for up to 3 years with continued treatment.

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Conflict of interest

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Supplementary material available online

Supplementary Tables 1 and 2.

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ORIGINAL ARTICLE

Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3,267 Japanese patients with rheumatoid arthritis

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Abstract
Objectives A post-marketing surveillance (PMS) program was implemented to assess the safety and effectiveness of tacrolimus (TAC) in Japanese rheumatoid arthritis (RA) patients and to identify risk factors related to adverse drug reactions (ADRs).
Methods Patients were registered centrally and monitored for all adverse events (AEs) for 24 weeks. Effectiveness was evaluated using the Disease Activity Score 28-CRP (DAS28-CRP).
Results Data from 3,172 patients (mean age 62.2 years) were evaluated in the safety analysis. Of the safety population, 78.5 %were female and 25.9 % were in Steinbrocker's functional class 3 or 4. TAC was prescribed as monotherapy in 52.5 % and the most common concomitant disease modifying antirheumatic drug (DMARD) was methotrexate, used in 28.9 % of the patients. The incidence of AEs, serious AEs (SAEs), ADRs and serious ADRs were 41.2, 6.4, 36.0, and 4.9 %, respectively. The most frequent serious ADR category was infections and infestations. Age ≥65 years, concurrent renal dysfunction, and concurrent diabetes mellitus were identified as significant risk factors for ADR. Based on EULAR response criteria, 65.4 % of the patients showed moderate or good response.
Conclusions The results demonstrate that TAC is well tolerated by Japanese patients with active RA, including those receiving concomitant methotrexate, in the real world.

Keywords Effectiveness · Post-marketing surveillance · Rheumatoid arthritis · Safety · Tacrolimus

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Introduction

Rheumatoid arthritis (RA) is characterized by persistent synovitis and structural damage of joints in part through the abnormal activation of immunocompetent cells, including T cells. It has been reported that pathogenesis of RA remains elusive in terms of active T cell- or macrophage-induced cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, and molecules that cause interaction between antigen presenting cells and T cells [1–4].

Tacrolimus (TAC), a macrolide lactone discovered in 1984, mainly exerts its immunosuppressive effects through

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inhibition of T cell activation and production of inflammatory cytokines, such as TNF, IL-1β, and IL-6, all involved in the pathogenesis of RA [5–7]. TAC has been used for the prevention of rejection in organ transplantation and graft-versus-host disease after bone marrow transplantation, as well as for the treatment of myasthenia gravis, lupus nephritis, and ulcerative colitis. In addition, it was approved for RA patients with inappropriate response to conventional treatments in Japan in April 2005, and subsequently approved for RA in Canada, Korea, and Hong Kong.

The efficacy of TAC against RA has been demonstrated in several clinical trials [8–12]. Although the information obtained from the clinical trial settings is straightforward and robust, it has several limitations. For example, in post-marketing settings, TAC is used in patients with various comorbidities or in patients concomitantly taking a variety of drugs, including corticosteroids, DMARDs, and even biological agents. In this regards, the safety and effectiveness of TAC in clinical practice settings remains to be investigated. To address these issues, we implemented a nationwide post-marketing surveillance (PMS) program on safety and effectiveness of TAC in RA patients with central registration and a six-month tracking period in each patient.

Materials and methods

This study was conducted in accordance with a protocol approved by the Ministry of Health, Labor and Welfare (MHLW). A Prograf post-marketing surveillance committee consisting of rheumatologists was convened, which evaluated the obtained interim results in collaboration with Astellas Pharma Inc.

During the study period from April 2005 to March 2009, cases were collected from 406 institutions in Japan. Patients were registered centrally at an independent patient registration center over a 2-year period. The planned study sample size of 3,000 patients was calculated to provide a 95 % confidence level of detecting any adverse event (AE) that occurs at in least 1 of 1,000 exposed individuals.

A written agreement was obtained from participating institutions. The study was also in accordance with the standards for Good Post-Marketing Study Practice (GPSP) provided by the MHLW in Japan.

The MHLW instructed the investigators to perform the PMS study according to GPSP, which is the authorized standard for PMS studies of approved drugs in clinical practice; therefore, no formal ethics committee approval was necessary. The PMS study in Japan is allowed to be conducted without informed consents.

This study was conducted in clinical practice settings in Japan. RA patients who had shown inappropriate response to conventional treatments for RA and who started treatment with TAC for the first time during the registration period (April 2005 to March 2007) were enrolled. Each enrolled patient was followed up for up to 24 weeks. Information regarding background of the patients, status of the TAC treatment, and use of concomitant drugs were collected.

In accordance with the approved dosage and method of administration, adult patients received 3 mg of TAC once daily after dinner. For elderly patients, TAC was started at 1.5 mg once daily after dinner and could be increased to 3 mg if signs and symptoms were not well controlled.

For 24 weeks after the start of treatment with TAC, all AEs and laboratory values were prospectively monitored. Terminology of the Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) version 11.1 was used for summarizing and reporting AEs. AEs were recorded with the physician's assessment of causality, and seriousness according to the International Conference on Harmonization standards.

Of 3,347 patients enrolled, case report forms from 3,267 patients were collected who had at least one follow-up visit after the first dose of TAC. Categorized by clinical department, 1,396 subjects (42.7 %) were from rheumatology departments, 871 (26.7 %) were from internal medicine departments, and 778 (23.8 %) were from orthopedic surgery departments. In accordance with the warnings section of the tacrolimus package insert, which states that "tacrolimus should be administered only by physicians familiar with the treatment of rheumatoid arthritis", the survey was conducted by clinical departments staffed by physicians familiar with the treatment of rheumatoid arthritis. Ninety-five patients were excluded because of unknown status of AEs ($n = 33$), no follow-up visit after the first dose of TAC ($n = 26$), outside enrollment period ($n = 8$), no administration of TAC ($n = 7$), overlapping patients among institute ($n = 7$), no enrollment ($n = 3$), use of TAC before the survey ($n = 2$), and others ($n = 9$). As a result, 3,172 patients were included in the safety population.

Seventeen patients were excluded because of off-label use of, or unknown response to TAC out of 3,172 patients in the safety population. As a result, 3,155 were included in the effectiveness population.

Of 3,155 patients in the effectiveness population, disease activity scores (DAS28) were reported in only 680 patients due to the observational study. Thus, it should be noted that the results of effectiveness [European League Against Rheumatism (EULAR) response rate, DAS28 scores] obtained in this study are difficult to generalize. Nevertheless, the information may be useful for understanding TAC in the real world, and therefore the results of effectiveness in 680 patients were included.

The effectiveness was evaluated by EULAR response criteria, physician's assessment (with three categorical treatment responses of good, moderate, and no response), and DAS28-CRP, which is based on the 28 joint counts, a general health assessment of a patient, and C-reactive protein (CRP). DAS28-CRP was divided into 4 categories: remission ($\leq$2.6), low disease activity (>2.6 and $\leq$3.2), moderate disease activity (>3.2 and $\leq$5.1), and high disease activity (>5.1). The analysis for EULAR response criteria at week 24 was conducted using the last observation carried forward (LOCF) method in RA patients whose DAS28 scores were obtained both at the baseline and at least one follow-up visit after the first dose of TAC. Of 3,155 patients in the effectiveness population, 680 patients were evaluated by EULAR response criteria.

All statistical analyses were performed using SAS statistical software (BASE/SAS SAS/STAT Ver. 8.2; SAS Institute Inc., Cary, NC, USA).

In the statistical analysis, proportions were compared using Chi squared test or Fisher's exact test, as appropriate. Testing was 2-sided, and a significance level of 0.05 was used for each comparison. To determine risk factors for ADRs, candidate factors were identified using univariate analyses, followed by multivariate analyses with Cox proportional hazards models. The analyses were performed using a stepwise variable selection method (backward elimination), at a significance level of 0.05.

Results

The main patient characteristics of the safety population (n = 3,172) are shown in Table 1. Most patients were female (78.5 % of the overall patient population). Mean (±SD) age was 62.2 ± 12.0 years and 47.5 % of the patients were 65 years or older. Of all the patients, 64.0 % were in Steinbrocker's stage III or IV and 25.9 % in functional class 3 or 4. Mean disease duration was 11.1 years and 44.4 % of the patients had RA for 10 years or longer. Comorbidities were reported in 2,590 patients; the most common comorbidity was osteoporosis in 1,229 patients, followed by hypertension, dyslipidaemia, interstitial pneumonia, and diabetes mellitus. Just before the initiation of TAC treatment, 79.2 % of the patients used DMARDs, including mainly methotrexate (MTX), salazosulfapyridine, and bucillamine. Just before the initiation of TAC treatment, biological DMARDs, etanercept or infliximab, were used in 9.7 % of the patients. Mean CRP level was 3.3 mg/dl and 3.9 % of the patients had a CRP of 10 mg/dl or higher. Baseline mean DAS28-CRP was 5.1 and 48.7 % of the patients had a DAS28-CRP of 5.1 or higher. As for other characteristics, there were more outpatients than inpatients, with the former accounting for 89.6 % of the population. Corticosteroid was administered in 81.5 % of the safety population and the mean daily dose in these concomitant users was 6.8 mg (prednisolone [PSL] equivalent dose). The dose of corticosteroid was 10 mg/day or higher in 16.3 %. TAC was used as a monotherapy (i.e., without other non-biological DMARDs) in 52.5 % and the rest of the patients received non-biological DMARDs other than TAC; MTX was used in 28.9 %, salazosulfapyridine in 14.3 %, and bucillamine in 7.4 %. Biological DMARDs were administered in 7.1 %; etanercept was used in 4.4 % and infliximab in 3.0 %.

Among the patients included in the safety population, 69.8 % continued the treatment until week 24, 27.8 % discontinued the treatment before week 24, and 2.3 % were lost to follow-up. Mean (±SD) daily doses of TAC at week 0 were 1.6 ± 0.8 mg/day in nonelderly patients (<65 years) and 1.4 ± 0.6 mg/day in elderly patients (≥65 years). Mean (±SD) daily doses of TAC during the observation period were 1.9 ± 0.8 mg/day in nonelderly patients (<65 years) and 1.6 ± 0.6 mg/day in elderly patients (≥65 years).

Reasons for discontinuation were AEs in 14.3 %, lack of effectiveness in 7.2 %, patient's preference in 5.7 %, and improvement of signs and symptoms in 0.1 % (Table 2).

Of the 3,172 patients included in the safety population, 1,308 patients developed 2,292 AEs and 1,142 patients developed 1,855 ADRs; the incidences of AEs and ADRs were 41.2 and 36.0 %, respectively. The common system organ classification (SOC) categories for ADRs were abnormal laboratory values in 12.5 %, gastrointestinal disorders in 6.4 %, infections and infestations in 5.8 %, metabolism and nutrition disorders in 4.3 %, and renal and urinary disorders in 2.7 % (Table 3). The most frequently reported ADRs were pneumonia (1.0 %), diabetes mellitus (1.5 %), nausea (1.5 %), diarrhea (1.3 %), abnormal hepatic function (1.1 %), pruritus (1.0 %), renal impairment (1.2 %), elevation of white blood cell count (2.5 %), elevation of β-*N*-acetyl-D-glucosaminidase (2.1 %), elevation of blood urea (1.6 %), elevation of glycosylated hemoglobin (1.2 %), depletion of lymphocyte (1.2 %), elevation of blood creatinine (1.1 %), and elevation of urine β2 microglobulin (1.0 %). The overall incidence of ADRs was significantly higher in elderly patients compared to non-elderly patients (40.5 vs. 31.9 %, $p < 0.001$). The incidences of the following ADRs were higher in elderly than in nonelderly patients: abnormal laboratory values (14.5 vs. 10.7 %, $p = 0.001$), gastrointestinal disorders (7.4 vs. 5.5 %, $p = 0.035$), infections and infestations (6.9 vs. 4.9 %, $p = 0.015$), metabolism and nutrition disorders (5.8 vs. 2.9 %, $p < 0.001$), and renal and urinary disorders (3.8 vs. 1.6 %, $p < 0.001$) (Table 3).

Of the patients included in the safety population, 203 patients (6.4 %) developed 263 serious AEs and 157

Table 1 Patient characteristics of the safety population

Items All patients	Patients (%) 3,172
Sex	
Male	682 (21.5)
Female	2,490 (78.5)
Age (years)	
<20	9 (0.3)
20–29	40 (1.3)
30–39	103 (3.2)
40–49	258 (8.1)
50–64	1,256 (39.6)
65–74	1,088 (34.3)
≥75	418 (13.2)
Mean ± SD	62.2 ± 12.0
Inpatient/outpatient status	
Outpatient	2,843 (89.6)
Inpatient	329 (10.4)
Steinbrocker's stage classification (n = 3,134)	
I	256 (8.2)
II	873 (27.9)
III	1,010 (32.2)
IV	995 (31.7)
Steinbrocker's functional classification (n = 3,139)	
1	281 (9.0)
2	2,043 (65.1)
3	745 (23.7)
4	70 (2.2)
Disease duration (years) (n = 2,845)	
<3	576 (20.2)
≥3 to <5	339 (11.9)
≥5 to <10	666 (23.4)
≥10	1,264 (44.4)
Mean ± SD	11.06 ± 9.7
Comorbidity (n = 3163)	
No	573 (18.1)
Yes	2,590 (81.7)
Use of nonbiological DMARDs just before study entry*	
No	660 (20.8)
Yes	2,512 (79.2)
Use of nonbiological DMARDs just before study entry**	
Methotrexate	1,353 (42.7)
Salazosulfapyridine	809 (25.5)
Bucillamine	477 (15.0)
Use of biological DMARDs just before study entry*	
No	2,864 (90.3)
Yes	308 (9.7)
Use of biological DMARDs just before study entry**	
Etanercept	174 (5.5)
Infliximab	129 (4.1)
CRP (mg/dl) (n = 2,374)	
<1.0	545 (23.0)
≥1.0 to <3.0	775 (32.6)
≥3.0 to <5.0	519 (21.9)
≥5.0 to <10.0	443 (18.7)
≥10.0	92 (3.9)
Mean ± SD	3.3 ± 3.0
DAS28-CRP (n = 680)	
≤3.2	13 (1.9)
>3.2 to ≤5.1	336 (49.4)
>5.1	331 (48.7)
Mean ± SD	5.1 ± 1.0
Concomitant corticosteroid***	
No	588 (18.5)
Yes	2,584 (81.5)
Dose of concomitant corticosteroid*** (prednisolone equivalent, mg/day) (n = 3,169)	
0 (non use)	588 (18.6)
0< to <5	621 (19.6)
≥5 to <7.5	1,077 (34.0)
≥7.5 to <10	365 (11.5)
≥10	518 (16.3)
Mean ± SD	6.8 ± 4.7
Concomitant nonbiological DMARD***	
No	1,665 (52.5)
Yes	1,507 (47.5)
Concomitant nonbiological DMARD**	
Methotrexate	916 (28.9)
Salazosulfapyridine	454 (14.3)
Bucillamine	236 (7.4)
Concomitant biological DMARD***	
No	2,947 (92.9)
Yes	225 (7.1)
Concomitant biological DMARD**	
Etanercept	140 (4.4)
Infliximab	94 (3.0)
Concomitant NSAID*** (n = 3,162)	
No	950 (30.0)
Yes	2,212 (70.0)

CRP C-reactive protein, *DAS28-CRP* disease activity score 28-CRP, *DMARD* disease modifying antirheumatic drug, *NSAID* non-steroidal anti-inflammatory drug

* Within 4 weeks of the start of treatment with TAC (For IFX, within 8 weeks); ** multiple response; *** drugs used before the date of onset of the first adverse drug reaction were included. In patients who did not develop adverse drug reactions, drugs which were used during the observation period were included

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

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

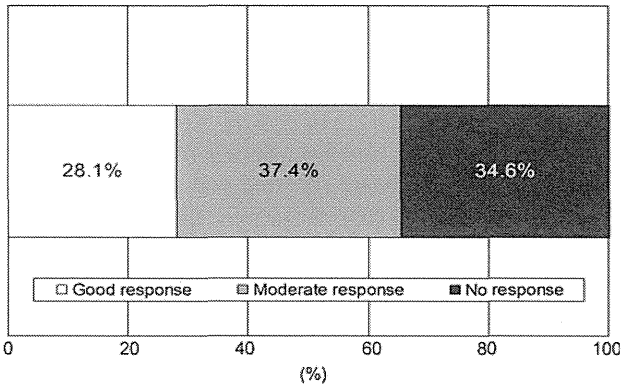

Fig. 1 Response to treatment according to the EULAR criteria ($n = 680$). The response response rate was defined as the proportion of patients with good or moderate response

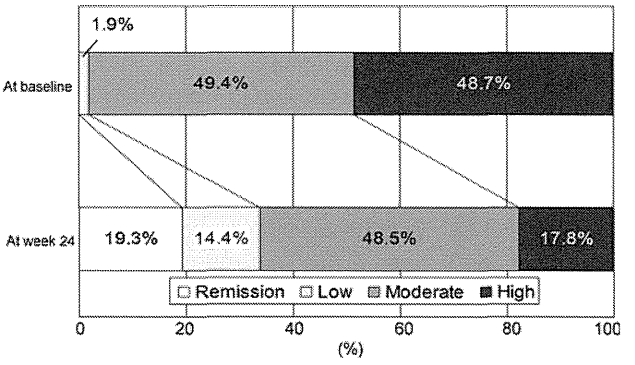

Fig. 2 Disease activity of rheumatoid arthritis at baseline and at the end of observation using the last observation carried forward (LOCF) method. Disease activity was defined using DAS28-CRP scores as follows: remission, DAS28-CRP < 2.6; low disease activity, 2.6 ≤ DAS28-CRP ≤ 3.2; moderate disease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

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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OPEN ACCESS

EXTENDED REPORT

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

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ABSTRACT

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

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

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

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

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INTRODUCTION

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

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

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

PATIENTS AND METHODS

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

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

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

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

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

Statistics

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

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

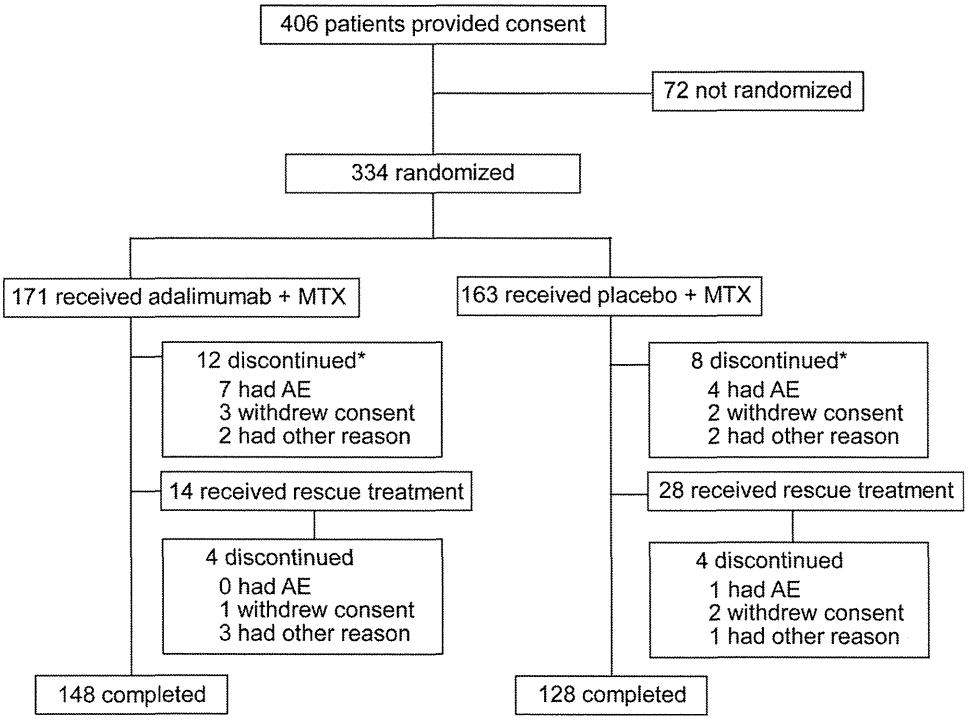

Figure 1 Patient disposition through week 26. *Three adalimumab+MTX patients and one MTX alone patient discontinued from the study by week 26; however, they were included in the efficacy analyses at week 26. AE, adverse event; MTX, methotrexate.

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

RESULTS

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

Radiographic progression

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

Clinical response

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

Table 1 Demographics and baseline characteristics

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

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

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

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

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