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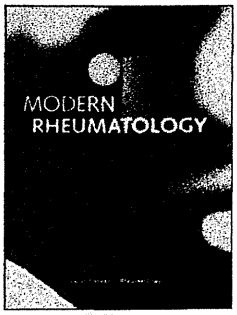

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ORIGINAL ARTICLE

Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis

Masayoshi Harigai[1], Naoki Ishiguro[2], Shigeko Inokuma[3], Tsuneyo Mimori[4], Junnosuke Ryu[5], Syuji Takei[6], Tsutomu Takeuchi[7], Yoshiya Tanaka[8], Yoshinari Takasaki[9], Hisashi Yamanaka[10], Masahiko Watanabe[11], Hiroshi Tamada[11], and Takao Koike[12,13]

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Abstract

Objective: To perform a postmarketing surveillance study evaluating the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis (RA).
Methods: Safety and effectiveness data were collected for all RA patients (at 772 sites) treated with intravenous abatacept between September 2010 and June 2011. Patients were treated by the approved dosing regimen according to the package insert. Treatment effectiveness was evaluated at baseline and at weeks 4, 12, and 24 using Disease Activity Score 28 (DAS28) according to erythrocyte sedimentation rate or serum C-reactive protein concentrations.
Results: Overall, 3882 and 3016 abatacept-naïve RA patients were included in safety and effectiveness analyses, respectively. Adverse drug reactions (ADRs) were reported for 15.66% of patients and serious ADRs were detected for 2.52% of patients. The incidence of serious infections was 1.03% and these were mainly attributed to different types of bacterial pneumonia. Disease activity improved significantly over 6 months. Separate multivariate analysis identified predictors of severe ADR, and severe infections and factors predictive of clinically meaningful DAS28 improvement after 6 months of treatment with abatacept.
Conclusions: Abatacept was efficacious and well tolerated in a clinical setting. No new safety concerns were detected.

Keywords

Abatacept, Japan, PMS, Rheumatoid arthritis, Safety

History

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Introduction

Rheumatoid arthritis (RA) is a persistent and erosive arthritis with systemic inflammation that affects the synovial membrane of the joints, causing erosion of cartilage and bone. Chronic inflammation can lead to joint deformity, disability, and poor quality of life [1,2]. A recently published study based on data from a Japanese claims database reported that the estimated prevalence of RA in Japan is ~0.6–1.0% (about 1.24 million individuals ranging from 16 to 75 years of age) [3].

According to the updated recommendations of the American College of Rheumatology (ACR) [4] and the recommendations of the European League against Rheumatism (EULAR) [5], the treatment goal for RA is to achieve low disease activity or remission using a treat-to-target approach to prevent joint damage and deformity and preserve physical function and quality of life. In the Japanese guidelines [6], biologics are recommended when and if there is lack of response to initial treatment with disease-modifying anti-rheumatic drugs (DMARDs) over 3 months. Among biologic agents for the treatment of RA, tumor necrosis factor (TNF) inhibitors are the most widely used in Japan to reduce inflammation and prevent joint destruction. However, ~30% of patients treated with a TNF inhibitor failed to achieve improvement in ACR20 [7–9], and patients may also develop resistance to anti-TNF agents [10]. Therefore, other biologic agents such as abatacept that function via different mechanisms have been developed as alternatives to anti-TNF therapies.

Joint degradation in RA is caused by an inflammatory cascade triggered by T-cell activation [11]. Abatacept is a genetically engineered fusion protein that selectively inhibits T-cell activation by binding to CD80/86 and modulating its interaction with CD28. The safety and efficacy of abatacept in patients with RA who responded poorly to other biologics or DMARDs, such as TNF antagonists and methotrexate (MTX), have been shown in several randomized, controlled clinical trials (RCTs) [12–14]. Execution of all-cases (a mandatory registry) postmarketing

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surveillance (PMS) was required as a condition of regulatory approval for all patients in Japan undergoing treatment with intravenous (IV) abatacept [15]. This surveillance was undertaken by Bristol-Myers K.K., under the guidance of the Japan College of Rheumatology (JCR), to evaluate the real-world safety and effectiveness of abatacept in Japanese patients with RA.

Materials and methods

Study design and patients

In this all-cases PMS, patients treated with IV abatacept at 772 sites were registered between September 2010 and June 2011. Data on the safety and effectiveness of registered patients were prospectively collected during a 24-week treatment period and a 4-week follow-up period. All patients with RA who received commercial IV abatacept in Japan after the drug was approved were registered for inclusion. With a sample of 3000 patients, the probability of detecting an unknown rare adverse event (occurring at a frequency of 1 per 1000 patients) is 95%. Assuming a dropout rate of 25%, the target number of patients was determined to be 4000.

Abatacept was administered as an IV infusion (following the initial dose, it was given at week 2 and week 4, and then every 4 weeks thereafter). The recommended abatacept dose [15] was based on the patient's body weight and was increased in 250 mg increments as follows: weight <60 kg, 500 mg; 60–100 kg, 750 mg; and >100 kg, 1000 mg in accordance with the indications listed in its package insert and the guidelines of the JCR for the appropriate use of abatacept.

Data collected included age, sex, body weight, disease duration, Steinbrocker stage and class, past medical history, comorbidities, prior use of biologics, concomitant use of MTX and other DMARDs, and concomitant use of glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), or other medications. This PMS was conducted in accordance with Good Postmarketing Surveillance Practices and the ethical principles stated in the Declaration of Helsinki. Data collection was performed using both an electronic data capture system and report forms, depending on the preference of the researchers at each site. The ethics review board of each participating site approved the study.

Endpoints and assessments

Data on all adverse events (AEs, defined as any undesirable experience observed during the use of abatacept in a patient), serious AEs, adverse drug reactions (ADRs, defined as any noxious and unintended responses for which a causal relationship with the use of the drug could not be ruled out), and serious ADRs (defined as any ADR causing death, that was life-threatening, or caused hospitalization or prolongation of hospitalization, disability, or permanent injury) that occurred during the observation period (24-week treatment period and 4-week follow-up period) were prospectively monitored and collected. ADRs were reported in terms of system organ class using MedDRA version 15.0 (Maintenance and Support Services Organization, McLean, VA).

Disease activities were evaluated using Disease Activity Score 28 (DAS28), which takes into account the numbers of tender joints and swollen joints, general health status (patients' visual analog scale [mm], 0–100), and erythrocyte sedimentation rate (ESR, mm/h) or serum C-reactive protein concentration (CRP, mg/dL) [16], before and at weeks 4, 12, and 24 of abatacept treatment. Both DAS28-ESR and -CRP were divided into four categories using the same cut-off values (2.6, 3.2, and 5.1) as follows: remission (DAS28 <2.6), low disease activity (DAS28 ≥ 2.6 and <3.2), moderate disease activity (DAS28 ≥ 3.2 and ≤ 5.1), and high disease activity (DAS28 >5.1). Patients were categorized according to improvement in DAS28 as EULAR good, moderate, and nonresponders. A good response was defined as an improvement in DAS28 from baseline of <-1.2 and a DAS28 of ≤ 3.2 during follow-up. Patients with score improvements of ≥ -0.6, as well as those with improvements <-0.6 and ≥ -1.2 plus a DAS28 of >5.1 during follow-up were defined as nonresponders. Moderate responders were those with DAS28 improvements from baseline of <-1.2 and a DAS28 >3.2 during follow-up and those with score improvements <-0.6 and ≥ -1.2 plus a DAS28 of ≤ 5.1 during follow-up [16].

Statistical analysis

Data from all patients who received at least one dose of abatacept were included in the safety evaluation. The incidence rate of ADRs was determined using descriptive statistics. The cumulative rates of AEs, ADRs, and drug-retention rates of abatacept were determined by the Kaplan–Meier analysis. Variables for multivariate analysis were selected based on the results of univariate analysis and degree of medical significance. Effectiveness was evaluated in all patients for whom DAS28 scores were available before and after abatacept treatment, and the last-observation-carried-forward (LOCF) method was used to impute data for withdrawals. The abatacept retention rate by the Kaplan–Meier analysis and paired *t*-tests were used to compare DAS28 scores change from baseline and week 24. Statistical significance was defined as $p = 0.05$ (two-tailed test). The p values reported in this manuscript are nominal without adjusting for multiplicity. Data and statistical analyses were conducted using SAS V.9.2 (SAS Institute Inc., Cary, NC).

Results

Patient disposition and baseline characteristics

In total, 3985 patients were treated with abatacept, 103 of whom had been administered abatacept in phase II and III clinical trials conducted for the new drug application. These 103 patients (i.e. abatacept non-naïve patients), did not meet the objective of this PMS to evaluate abatacept performance in a real clinical setting and were excluded; therefore, the number of patients in the safety analysis was 3882. For the effectiveness evaluation, a further 866 patients were excluded from the 3882 because their DAS data before abatacept treatment were not available. Table 1 summarizes the baseline characteristics of patients. The majority of patients were women (82.3%) with a mean age (±SD) of 61.4 ± 12.6 years. The median disease duration was 8.2 years (IQR 3.3–15.3), and 69.5% of patients had comorbidities. Additionally, 69.6% of patients had been exposed previously to biologics other than abatacept (mainly anti-TNF agents), and 66.3% and 81.2% were being treated concomitantly with MTX or other DMARDs, respectively.

Overall safety and ADRs of interest

A total of 3882 patients with an observation period of 1886.2 patient-years were included in the safety analysis. Serious ADRs and all ADRs were reported by 2.52% and 15.66% of patients, respectively (Supplementary Table 1). The majority of the serious ADRs (1.03%) were categorized as infections and infestations. Commonly reported categories of all ADRs included infections and infestations (5.87%); skin and subcutaneous tissue disorders (2.19%); respiratory, thoracic, and mediastinal disorders (2.16%); gastrointestinal disorders (1.96%); and hepatobiliary disorders (1.06%).

Table 2 shows the incidence rates of the most commonly reported ADRs in this PMS. Upper respiratory tract inflammation

Table 1. Patient demographic and clinical baseline characteristics.

Variables	Safety analysis set ($n=3882$)	Effectiveness analysis set ($n=3016$)
Sex (females, %)	82.3	82.4
Age [mean ± SD, years (% ≥65 years)]	61.4 ± 12.6 (44.1)	61.1 ± 12.8 (43.4)
Body weight (mean ± SD, kg)	53.5 ± 10.5	53.6 ± 10.4
Disease duration (median and IQR, years)	8.2 (3.3–15.3)	8.3 (3.4–15.5)
Steinbrocker stage I/II/III/IV (%)	10.8/26.0/31.5/31.6	11.2/26.5/31.3/31.0
Steinbrocker class 1/2/3/4 (%)	11.5/63.4/23.5/1.7	11.6/63.7/23.1/1.6
Past medical history (%)	29.1	29.4
Allergy history (%)	19.5	20.2
Smoking history (years)	12.7	12.8
Comorbidities (%)	69.5	69.3
History of surgery for RA (%)	23.6	23.1
Prior use of biologics (%)	69.6	70.2
Concomitant MTX use [% (mean ± SD, mg/week)]	66.3 (7.1 ± 2.7)	66.7 (7.1 ± 2.6)
Concomitant DMARD use (%)	81.2	81.0
Concomitant oral glucocorticoid use [% (mean ± SD, PSL equivalent dose, mg/day)]	63.1 (5.0 ± 3.0)	63.0 (5.0 ± 3.0)
Concomitant NSAID use (%)	69.8	69.3
Other concomitant medication use (%)	85.0	85.8
Baseline DAS28-ESR (mean ± SD)	–	5.07 ± 1.30
Baseline DAS28-CRP (mean ± SD)	–	4.47 ± 1.23

IQR = interquartile range; PSL = prednisolone; SD = standard deviation.

Table 2. Incidence rates of the most commonly reported adverse drug reactions (≥0.5%).

ADRs	PMS ($n=3882$)* ADRs† (%)	Serious ADRs (%)
Upper respiratory tract inflammation	1.21	0.03
Herpes zoster	1.00	0.08
Bronchitis	0.90	0.03
Stomatitis	0.88	0
Nasopharyngitis	0.80	0
Abnormal hepatic function tests	0.75	0.05
Pyrexia	0.62	0
Rash	0.59	0

*1886.20 person-year.
†All ADR events including serious ADRs.

was the most common ADR (1.21%), followed by herpes zoster, bronchitis, stomatitis, nasopharyngitis, abnormal hepatic function tests, pyrexia, and rash, all with incidences ranging from 0.59% to 1.00%. The incidence of serious ADRs was 0.03% for upper respiratory inflammation and bronchitis, 0.05% for abnormal hepatic function tests, and 0.08% for herpes zoster.

A list of ADRs of interest is presented in Table 3. Pneumonia of different types was reported in 28 patients (0.72%), with mean treatment duration of 95.8 days. One and four patients developed tuberculosis (TB; 0.03%) and Pneumocystis pneumonia (0.10%), respectively. Twelve cases of interstitial pneumonia were reported, with an incidence rate of 0.31%. There were six cases of malignancy (0.15%), including two cases of lymphoma and one case each of gastric cancer, malignant lung neoplasm, colorectal cancer, and borderline ovarian cancer. Eight deaths (0.21%) occurred during the PMS, four of which were attributed to interstitial pneumonia and one case each to bronchopulmonary aspergillosis, mycosis/acute disseminated encephalomyelitis, Pneumocystis pneumonia, or pulmonary tuberculosis/tuberculous peritonitis. Kaplan–Meier analysis was used to assess the cumulative occurrence rates of AEs and ADRs (Supplementary Figure 1). Occurrences of both AEs and ADRs increased at a constant rate until Day 197, with a slightly pronounced increase on Days 14 and 29.

Risk factors for ADRs

Multivariate logistic regression analysis revealed risk factors for all ADRs and serious ADRs (Figure 1a and b). Factors that significantly increased the risk for serious ADRs were Steinbrocker class 3 or 4 (odds ratio [OR] 1.63; 95% class interval [CI] 1.04–2.55; $p=0.034$), comorbidity of hepatobiliary disorders (OR 1.99; 95% CI 1.12–3.55; $p=0.020$), renal comorbidity (OR 2.06; 95% CI 1.03–4.10; $p=0.041$), comorbidity or history of respiratory disease (OR 1.79; 95% CI 1.14–2.80; $p=0.011$), peripheral lymphocyte count <1000/mm^3 (OR 1.76; 95% CI 1.11–2.78; $p=0.016$), and concomitant glucocorticoid use (>5 mg/day of prednisolone) (OR 1.63; 95% CI 1.01–2.62; $p=0.046$).

Multivariate logistic regression analysis also revealed significant risk factors for infections as follows: age ≥65 years, comorbidity of hepatobiliary disorders, comorbidity or history of respiratory disease, allergy history, prior use of biologics, and concomitant glucocorticoid use (>5 mg/day of prednisolone) (Figure 1c), and for serious infections: body weight <40 kg, comorbidity or history of respiratory disease, and concomitant glucocorticoid use (>5 mg/day of prednisolone) (Figure 1d).

Effectiveness

Figure 2 shows the change in DAS28 based on ESR (Figure 2a) and CRP (Figure 2c) from baseline to week 24. Mean ± SD DAS28-ESR and -CRP at baseline were 5.07 ± 1.30 and 4.47 ± 1.23, respectively, and 3.93 ± 1.40 and 3.25 ± 1.33 at week 24, respectively. The changes from baseline in DAS28-ESR and -CRP at week 4 were −0.63 ± 1.03 and −0.73 ± 1.03, respectively, and −1.14 ± 1.39 and −1.21 ± 1.34 at week 24, respectively. DAS28-ESR and -CRP at week 24 were significantly lower than at baseline ($p<0.001$, paired t-tests) (Figure 2b and d). The DAS28 decreased progressively and significantly throughout the observation period in both DAS28-ESR and -CRP; however, the trend was more marked with DAS28-CRP.

Table 3. Summary and incidences rates of adverse drug reactions of interest.

Adverse drug reactions	*n*	Incidence rates (%)	Sex (males/females, *n*)	Age (years) Mean	Age (years) Min–Max	Duration of Onset (days) Mean	Duration of Onset (days) Min–Max	Cause of incident
Deaths	8	0.21	3/5	73.5	61–86	97.4	30–176	(1) Interstitial pneumonia ($n=4$) (2) Bronchopulmonary aspergillosis (3) Mycosis/acute disseminated encephalomyelitis (4) Pneumocystis pneumonia (5) Pulmonary tuberculosis/tuberculous peritonitis
Pneumonia	28	0.72	7/21	66.2	25–79	95.8	6–178	(1) Pneumonia ($n=18$) (2) Bacterial pneumonia ($n=5$) (3) Bronchopneumonia ($n=3$) (4) Pneumococcal pneumonia ($n=2$)
Tuberculosis	1	0.03	0/1	86.0	–	176.0	–	Concurrent pulmonary tuberculosis and tuberculous peritonitis
Pneumocystispneumonia	4	0.10	1/3	62.3	60–67	64.5	28–124	
Interstitial pneumonia	12	0.31	4/8	73.3	62–82	101.5	22–183	
Malignancies	6	0.15	1/5	75.2	62–83	98.3	59–127	(1) Lymphoma ($n=2$) (2) Gastric cancer (3) Malignant lung neoplasm (4) Colorectal cancer (5) Borderline ovarian cancer

Supplementary Figure 2a and b illustrates the proportion of patients in each DAS28 category from baseline to week 24. An increasing trend was observed in the proportion of patients with remission (<2.6) and low disease activity (≥2.6 and <3.2) by both DAS28-ESR and DAS28-CRP toward the end of the 24-week treatment period.

Supplementary Figure 2c and d shows the overall EULAR responses at weeks 4, 12, and 24. An increasing trend was observed in the proportion of patients that showed good responses by both DAS28-ESR (from 8.7% at week 4 to 24.3% at week 24) and DAS28-CRP (from 11.1% at week 4 to 27.5% at week 24) or moderate responses by both DAS28-ESR (from 33.9% at week 4 to 38.3% at week 24) and DAS28-CRP (33.3% at week 4 to 36.0% at week 24) toward the end of the 24-week treatment period. The overall Kaplan–Meier-estimated drug retention rate of abatacept decreased slowly and progressively from baseline until the end of the observation period (Day 169), but remained high at 78.9% (data not shown).

Separate multivariate analyses for patients with high or moderate disease activity at baseline were performed to detect factors predictive of a clinically meaningful DAS28 improvement after 6 months of treatment with abatacept. Of 773 patients with high disease activity, DAS28-CRP decreased from <–1.2 at baseline (clinically meaningful difference) in 526 patients. Multivariate analysis revealed that Steinbrocker class 1 and 2 ($p=0.029$), concomitant MTX use ($p=0.003$), and positive serology (ACPA or RF) ($p=0.026$) were significantly associated with a decrease in DAS28-CRP (DAS28-CRP of <-1.2) during abatacept treatment (Figure 3a). Prior use of two or more biologics was associated with not achieving DAS28-CRP <–1.2. Of the 1394 patients with moderate disease activity, 648 achieved a change in DAS28-CRP of <–1.2 from baseline. On logistic regression analysis, Steinbrocker class 1 or 2 ($p<0.001$), biologic-naïve ($p<0.001$), and positive serology (RF or ACPA) ($p=0.002$) were highly significantly associated with DAS28-CRP <-1.2 during abatacept treatment. Concomitant MTX use was not selected as a variable for the final model (Figure 3b).

Discussion

In this PMS, we evaluated the safety and effectiveness of abatacept in a clinical practice setting in Japanese patients with RA. Abatacept was well tolerated, and no new safety concerns were detected. During the observation period, the indexes of disease activity of RA decreased significantly. Risk factors for ADRs and infections, as well as predictors of clinically meaningful improvement in DAS28 (DAS28-CRP change from baseline <–1.2) after 6 months of abatacept treatment, were identified.

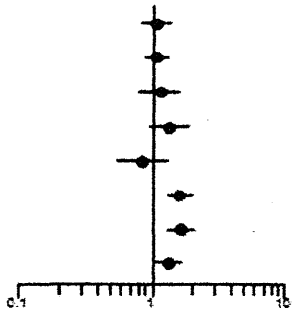
In this PMS, serious ADRs and ADRs were reported by 2.52% and 15.66% of patients, respectively. The incidence rate of serious infections was not high (1.03%), in particular to various types of bacterial pneumonia, which were also the most common serious ADRs reported in PMS of etanercept [17] and adalimumab [18] in Japan. The most common ADR was upper respiratory tract inflammation (1.21%), followed by herpes zoster, bronchitis, stomatitis, nasopharyngitis, abnormal hepatic function tests, pyrexia and rash, all with very low incidences (0.59–1.00%). Furthermore, there were no particular periods of increased overall AE/ADR incidence rates during the treatment course as observed in the Kaplan–Meier analyses. In comparison with the ADRs reported at approval, the ADRs observed at the time of this PMS did not raise any new safety concerns.

Notably, there was only one case of TB reported in this study. This finding is also in line with a previous epidemiological assessment by Simon et al. [19]. Patients to be treated with any of the biologics approved in Japan are required to go through TB screening. Therefore, the low incidence rate of TB found in this PMS suggests that this screening practice was successful for the diagnosis of pre-existing or concurrent pulmonary infections, such as TB, when identifying patients that can benefit from abatacept treatment. However, other PMS studies of biologics in Japan, such as infliximab [20], etanercept [17], and adalimumab [18], found higher incidences of TB. It has been reported that the mechanism of action of TNF inhibitors can activate latent TB infections [21–26]. These findings strongly suggest that TNF is more important for maintaining a latent TB lesion than the interaction with CD28-CD80/86. Additionally, physicians, under the auspices of the JCR, are being educated to screen for TB more thoroughly than before. As a result, patients with higher TB risk were excluded from treatment with abatacept.

Based on logistic regression analysis, we identified several risk factors that were significantly associated with infections and serious infections. Age ≥65 years, comorbidity of hepatobiliary

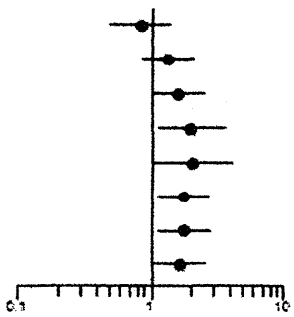
(a) ADRs

			Odds ratio	(95% CI)	p-value
Sex	Females	(vs. Males)	1.09	(0.85, 1.40)	0.499
Age, years	≥ 65	(vs. < 65)	1.08	(0.89, 1.31)	0.420
Disease duration, years	> 2, < 10	(vs. < 2)	1.15	(0.82, 1.60)	0.028
	> 10		1.36	(0.98, 1.88)	
	Unknown		0.86	(0.56, 1.32)	
Comorbidity or history of respiratory disease	Yes	(vs. No)	1.60	(1.31, 1.97)	< 0.001
Allergy history	Yes	(vs. No)	1.64	(1.32, 2.04)	< 0.001
Peripheral lymphocyte counts	> 1,000/mm³	(vs. < 1,000/mm³)	1.33	(1.07, 1.65)	0.011



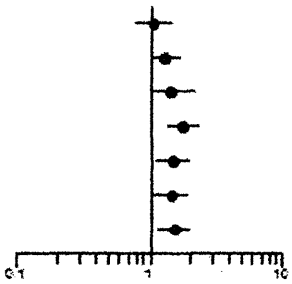
(b) Serious ADRs

			Odds ratio	(95% CI)	p-value
Sex	Females	(vs. Males)	0.83	(0.49, 1.39)	0.475
Age, years	≥ 65	(vs. < 65)	1.34	(0.86, 2.10)	0.194
Steinbrocker class	3 & 4	(vs. 1 & 2)	1.63	(1.04, 2.55)	0.034
Comorbidity of hepatobiliary disorders	Yes	(vs. No)	1.99	(1.12, 3.55)	0.020
Renal comorbidity	Yes	(vs. No)	2.06	(1.03, 4.10)	0.041
Comorbidity or history of respiratory disease	Yes	(vs. No)	1.79	(1.14, 2.80)	0.011
Peripheral lymphocyte counts	< 1,000/mm³	(vs. ≥ 1,000/mm³)	1.76	(1.11, 2.78)	0.016
Concomitant glucocorticoid use	> 5 mg/day	(vs. 0 or ≤ 5 mg)	1.63	(1.01, 2.62)	0.046



(c) Infections

			Odds ratio	(95% CI)	p-value
Sex	Females	(vs. Males)	1.06	(0.77, 1.45)	0.730
Age, years	≥ 65	(vs. < 65)	1.33	(1.03, 1.70)	0.027
Comorbidity of hepatobiliary disorders	Yes	(vs. No)	1.49	(1.02, 2.18)	0.038
Comorbidity or history of respiratory disease	Yes	(vs. No)	1.79	(1.38, 2.32)	< 0.001
Allergy history	Yes	(vs. No)	1.51	(1.14, 2.00)	0.004
Prior use of biologics	Yes	(vs. No)	1.47	(1.10, 1.98)	0.010
Concomitant glucocorticoid use	> 5 mg/day	(vs. 0 or ≤ 5 mg)	1.55	(1.17, 2.05)	0.003



(d) Serious infections

			Odds ratio	(95% CI)	p-value
Sex	Females	(vs. Males)	0.68	(0.33, 1.39)	0.287
Age, years	≥ 65	(vs. < 65)	1.36	(0.73, 2.53)	0.315
Body weight, kg	< 40	(vs. ≥ 40)	3.08	(1.31, 7.26)	0.010
Comorbidity or history of respiratory disease	Yes	(vs. No)	2.44	(1.31, 4.52)	0.004
Concomitant glucocorticoid use	> 5 mg/day	(vs. 0 or ≤ 5 mg)	2.17	(1.15, 4.10)	0.017

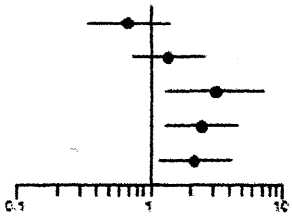


Figure 1. Multivariate logistic regression analysis revealed risk factors for all (a) ADRs, (b) serious ADRs, (c) infections, and (d) serious infections. Candidate variables for multivariate analysis were selected among many others based on their degree of clinical significance and the results of the univariate analysis. Variable selection for the final model of the multivariate logistic regression analysis was performed by stepwise methods.

disorders, comorbidity or history of respiratory disease, allergy history, prior use of biologics, and concomitant glucocorticoid use (>5 mg/day of prednisolone) were associated with a significant increase in the risk for infections. Body weight <40 kg, comorbidity or history of respiratory disease, and concomitant glucocorticoid (>5 mg/day of prednisolone) use were associated with serious infections. Interestingly, in a recent interim analysis of a PMS evaluating the safety of tocilizumab for the treatment of RA, logistic regression analysis indicated that respiratory comorbidities or medical history of respiratory disorders, prednisolone dose >5 mg, and age ≥65 years were significant risk factors for the development of serious infections [27]. Similarly, a recently published PMS report evaluating the safety and effectiveness of adalimumab in Japanese patients with RA identified the concomitant use of glucocorticoids at a prednisolone-equivalent dose >5 mg/day, age, and pulmonary disease

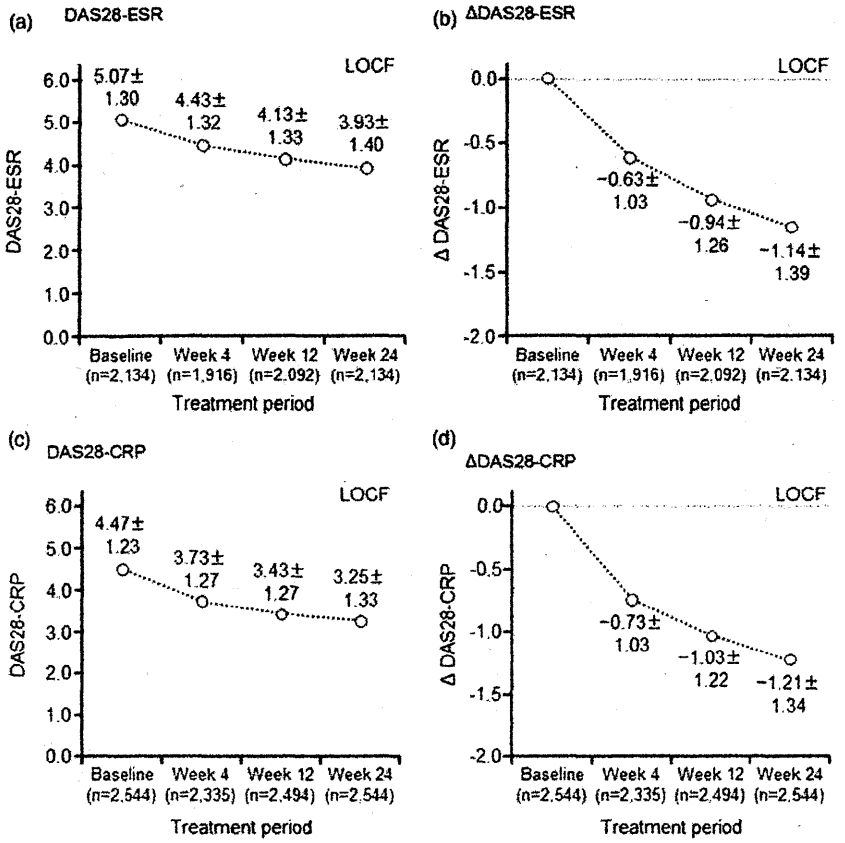


Figure 2. Change in disease activity over time in patients treated with abatacept. The last-observation-carried-forward (LOCF) imputation method was used. (a) DAS28 based on erythrocyte sedimentation rate (DAS28-ESR). (b) DAS28-ESR changes. (c) DAS28 based on C-reactive protein (DAS28-CRP). (d) DAS28-CRP changes.

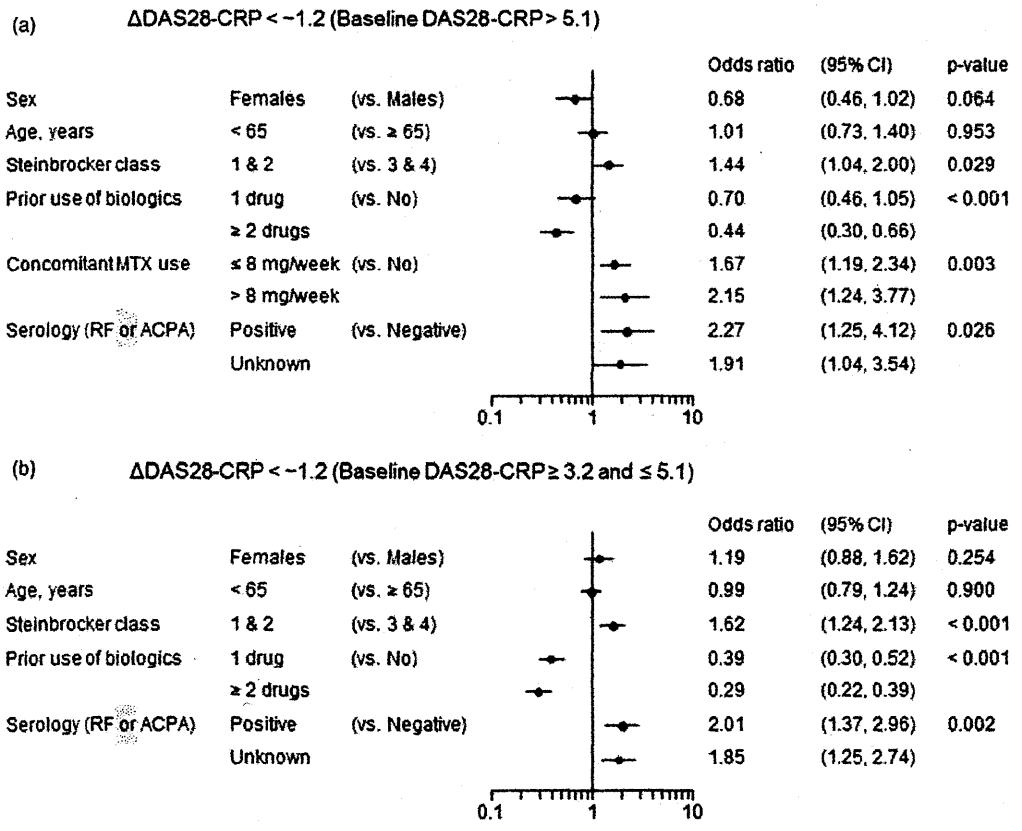


Figure 3. Multivariate logistic regression analysis revealed factors associated with improved DAS (DAS28-CRP < -1.2) in patients with (a) baseline DAS28-CRP > 5.1, and (b) baseline DAS28-CRP ≥ 3.2 and ≤ 5.1. Candidate variables for multivariate analysis were selected among many others based on their degree of clinical significance and the results of the univariate analysis. Variable selection for the final model of the multivariate logistic regression analysis was performed by stepwise methods.

history or comorbidity as risk factors for infections, serious infections, and serious respiratory infections [28]. In the same report, co-existing diabetes mellitus and concomitant MTX at a dose of >8 mg/week were also found to increase the risk of infections and serious infections [28]. Conversely, these factors were not found to increase the risk of infections or serious infections among patients treated with abatacept in this study. These data indicated that respiratory comorbidity and taking prednisolone >5mg/day are common risk factors for serious infection when receiving these biologics, whereas each biologic has its own risk factors. Patients should be evaluated carefully prior to abatacept treatment for the identified risk factors to evaluate benefit–risk balance.

The drug retention rate of abatacept treatment was ~80% in this PMS [29]. As the patients in the study cohort had a mean age of 61 years and long disease duration, RA was generally established and accompanied by comorbidities. Additionally, 70% of patients had a history of use of biologics, and these patients are usually difficult to treat; nonetheless, the majority of patients in this PMS experienced significant improvement in DAS28-ESR and -CRP by the end of the 6 months treatment. The effectiveness data were similar to findings in a recently published retrospective study by Tanaka et al. [30] of Japanese patients with RA treated with abatacept for 24 weeks. They reported that DAS28-ESR significantly decreased from baseline to week 24 (from 5.2 ± 1.4 to 3.9 ± 1.4) [30]. Similar findings were reported by Nüßlein et al. [31,32] in European and Canadian populations.

Multivariate logistic regression analysis indicated that Steinbrocker class 1 or 2, concomitant MTX use and positive serology (RF or ACPA) in patients with high disease activity, and Steinbrocker class 1 and 2 and positive serology (RF or ACPA) in patients with moderate disease activity were the factors significantly associated with an improvement of DAS28-CRP < -1.2. Fewer biological treatment failures reported previously were also predictive of better response to treatment with abatacept. These findings are in line with a recent observational registry on abatacept treatment, which suggested that patients with seropositive RA status may have better responses to abatacept, independent from disease activity [29,33].

This PMS had several limitations, including a short observation period, absence of comparators, and lack of functional and structural endpoints. However, the results of this 6-month PMS demonstrate the only real-world, prospective, powered-for-safety study of abatacept in patients with RA. Abatacept was well tolerated in clinical practice, and no new safety concerns were detected. This study also demonstrated that less exposure to biologics and positive serology were associated with a good clinical outcome. The findings of this PMS should be helpful in considering the appropriate use of abatacept in Japanese patients with RA.

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Conflict of interest

The competing interests of all authors are provided below:

M.H., N.I., S.I., T.M., J.R., S.T., T.T., Y.T., Y.T., H.Y., and T.K. are members of the Postmarketing Surveillance (PMS) Committee of the Japan College of Rheumatology. It is the belief of the authors that this does not constitute a conflict of interest. The doctors participated in review and analysis of the PMS data in their capacity as committee members. The financial relationships of the authors with manufacturers of biological products used in the management of RA are listed. M.H. has received grants/research support from AbbVie, Astellas, Bristol-Myers K.K., Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Santen, Takeda, UCB, and Pfizer; has served as a consultant for AbbVie, Bristol-Myers K.K., Chugai, and Janssen; and has served on speakers bureaus for AbbVie, Astellas, Bristol-Myers K.K., Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Santen, Takeda, UCB, and Pfizer. N.I. has received grants/research support from Astellas and Bristol-Myers K.K.; has served as a consultant for AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, and Takeda; and has served on speakers bureaus for AbbVie, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, and Takeda. S.I. has served on speakers bureaus for Asahi Kasei Pharma, Astellas, AbbVie, Bristol-Myers K.K., Chugai, Eisai, GlaxoSmithKline, Mitsubishi-Tanabe, Pfizer, Takeda, Santen, Teijin, Taisho-Toyama, Taiho, Daiichi-Sankyo, and Kyorin. T.M. has received grants/research support from Asahi Kasei Pharma, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Nippon Kayaku, Santen, and Takeda; and has served on speakers' bureaus for Asahi Kasei Pharma, Astellas, Bristol-Myers K.K., Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Santen, and Taisho Toyama. J.R. has reports no conflicts of interest. S.T. has received grants/research support from Chugai, Eisai, Takeda, and Bristol-Myers K.K.; and has served on speakers bureaus for Chugai, Eisai, Takeda, AbbVie, Astellas, Teijin, Novartis, Pfizer, and Asahi Kasei Pharma. T.T. has received grants/research support from Abbott, AbbVie, Asahi Kasei Pharma, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Sanofi-Aventis, Santen, Taisho-Toyama, Takeda, and Teijin; has served as a consultant for Asahi Kasei Pharma, AbbVie, Daiichi-Sankyo, AstraZeneca, Eli Lilly, Novartis, and Mitsubishi-Tanabe; and has served on speakers bureaus for Abbott, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, and Takeda. Y.Tanaka has received grants/research support from Bristol-Myers K.K., MSD, Chugai, Mitsubishi-Tanabe, Astellas, AbbVie, Eisai, and Janssen; has served as a consultant for Mitsubishi-Tanabe, AbbVie, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, UCB, Quintiles Transnational, Ono, and Novartis; and has served on speakers bureaus for Mitsubishi-Tanabe, AbbVie, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, UCB, and Quintiles Transnational. Y. Takasaki has received grants/research support from Santen Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers K.K., AstraZeneca plc, Astellas Pharma Inc., MSD K.K., Chugai Pharmaceutical Co., Ltd., Asahi Kasei Pharma Corporation, Eisai Co., Ltd., and Janssen Pharmaceutical K.K. H.Y. has received grants/research support from Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers K.K., Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, UCB, and Takeda; has served as a consultant for Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers K.K., Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, UCB, and Takeda; and has served on speakers bureaus for Abbott, AbbVie, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, UCB, and Takeda. M.W. was an employee of Bristol-Myers K.K. during the work. H.T. is an employee of Bristol-Myers K.K. T.K. has served on speakers' bureaus for Chugai, Mitsubishi-Tanabe, Pfizer, Astellas, Bristol-Myers K.K., UCB, Takeda, Taisho-Toyama, Eisai, AbbVie, Teijin, and Santen.

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Supplementary material available online

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Pneumocystis Jirovecii Pneumonia in Japanese Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Pooled Analysis of 3 Agents

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http://www.jrheum.org/content/42/9/1726.3

Pneumocystis Jirovecii Pneumonia in Japanese Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Pooled Analysis of 3 Agents

To the Editor:

Pneumocystis jirovecii pneumonia (PCP) is an infectious fungal disease caused by *P. jirovecii*, which has attracted the attention of physicians treating patients with human immunodeficiency virus infection[1], as well as those with connective tissue diseases, malignancies, and organ transplantation[2].

In patients with rheumatoid arthritis (RA), PCP used to be an uncommon infectious disease, but the number of case reports of PCP in patients with RA has increased since the introduction of low-dose methotrexate as an anchor drug for RA in the 1980s[3]. Moreover, with the introduction of anti-tumor necrosis factor (TNF) therapy, a further increase of incidence of PCP in patients with RA has been noticed, especially in Japan where strict postmarketing surveillance (PMS) programs have been conducted for patients with RA treated with TNF inhibitors[4,5,6]. The numbers of patients with RA with PCP in these PMS programs who were treated with infliximab (IFX), etanercept (ETN), or adalimumab (ADA) were 22 (0.4%) out of 5000[4], 25 (0.18%) out of 13,894[5], and 25 (0.33%) out of 7469 patients[6], respectively. Notably, these incidence rates of PCP in Japan are higher than the corresponding figure (0.01%) reported from the United States. Therefore, we previously analyzed the clinical characteristics and risk factors for PCP in patients with RA in Japan treated with these 3 TNF inhibitors[7,8,9,10]. In most cases, PCP developed rapidly with respiratory failure, and *P. jirovecii* organisms could not be detected microscopically, requiring for diagnosis the PCR test for *P. jirovecii* DNA or the measurement of plasma or serum 1, 3-β-D-glucan levels. Only some of the cases were in an immunocompromised state, showing a remarkable decrease in concentrations of serum immunoglobulins and the number of peripheral blood lymphocytes. Some of the risk factors for PCP were common to IFX and ETN, but others differed among the 3 TNF inhibitors[8,9,10]. It is possible that small sample size, patient background, the launch time of each drug, distinct mechanism of action among TNF inhibitors, or other unmeasured factors resulted in these differences in risk factors for PCP among the drugs. We therefore merged and analyzed the data of our previous studies to identify risk factors for development of PCP common to these 3 TNF inhibitors. Details of the designs and the methods of our previous studies were published elsewhere[8,9,10].

In our previous studies, we accumulated a total of 53 patients with RA who developed PCP under treatment with 1 of the 3 TNF inhibitors: IFX in 21 cases, ETN in 15 cases, and ADA in 17 cases. Of these, 51 patients who developed PCP within 12 months after commencement of a TNF inhibitor (the PCP group) were analyzed. For a control group, 265 patients with RA who did not develop PCP within 12 months after the beginning of a TNF inhibitor (the non-PCP group) were randomly selected from a consecutive series of patients with RA in the hospitals that participated in these studies.

To characterize the PCP group, we compared demographics, comorbidities, laboratory data, and concomitant drugs between the PCP and the non-PCP groups at the time of initiation of treatment with TNF inhibitors (Table 1). Compared with patients of the non-PCP group, patients of the PCP group were significantly older, had a lower percentage of women, had a higher prevalence of comorbid pulmonary disease and diabetes mellitus, and were treated with a higher daily dose of prednisolone. None of the 51 patients were receiving chemoprophylaxis for PCP at the time of PCP diagnosis. All of the patients received therapeutic doses of trimethoprim/sulfamethoxazole, except for 1 who received pentamidine isethionate. One case in an ETN study[9] and 3 cases in an ADA study[10] died after developing PCP.

A multivariate Cox proportional hazard analysis yielded HR and 95% CI for the following risk factors: older age (per 10-yr increment), 1.8 (1.4–2.5); presence of comorbid pulmonary disease, 3.1 (1.8–5.3); comorbid diabetes mellitus, 2.9 (1.5–5.8); and daily dose of prednisolone ≥ 5 mg, 2.7 (1.5–5.0). The cumulative probability for developing PCP was calculated using the Kaplan-Meier method (Figure 1). Patients with 3 or more of these risk factors had a significantly higher risk for PCP than those with 2, 1, or no risk factors ($p < 0.001$ for all comparisons by the log-rank test). Patients with 2 risk factors had a significantly higher risk for PCP than those with 1 or no risk factors ($p = 0.045$ and $p < 0.001$, respectively). Patients with 1 risk factor had a significantly higher risk for PCP than those with no risk factors ($p = 0.008$).

Table 1. Baseline clinical characteristics of patients with RA treated with TNF inhibitors. Values are mean ± SD or % unless otherwise specified.

Variables	PCP Group, n = 51	Non-PCP Group, n = 265	p
Characteristics			
Age, yrs	65.5 ± 9.5	55.2 ± 12.7	< 0.001†
Female	68.6	84.2	0.009‡
Disease duration, yrs	10.8 ± 8.7	9.3 ± 8.3	0.203†
Comorbid pulmonary disease	47.1	14.3	< 0.001‡
Diabetes mellitus	23.5	6.8	0.001‡
Laboratory data			
White blood cells < 4000/μl	2.0	0.8	0.402‡
Lymphocytes < 1000/μl	32.6	23.8	0.222‡
Serum IgG, mg/dl	1370 ± 386	1552 ± 497	0.064†
Concomitant treatment			
MTX	90.2	76.2	0.026‡
MTX dosage, mg/week	8.2 ± 2.9	8.3 ± 2.3	0.447†
MTX dosage > 8 mg/week	23.5	20.4	0.612‡
Oral corticosteroids	86.3	66.0	0.004‡
PSL-equivalent dosage of corticosteroids, mg/day	9.3 ± 9.9	6.0 ± 3.2	0.008†
PSL-equivalent dosage of corticosteroid ≥ 5 mg/day	70.6	47.5	0.003‡

† p values were calculated using the Mann-Whitney U test. ‡ p values were calculated using the chi-square test. Comorbid pulmonary disease = interstitial pneumonia, bronchiectasis, follicular bronchiolitis, chronic obstructive pulmonary diseases, chronic bronchitis, bronchial asthma, middle lobe syndrome, old pulmonary tuberculosis, old pleuritis, pneumoconiosis. RA: rheumatoid arthritis; TNF: tumor necrosis factor; PCP: *Pneumocystis jirovecii* pneumonia; IgG: immunoglobulin G; MTX: methotrexate; PSL: prednisolone.

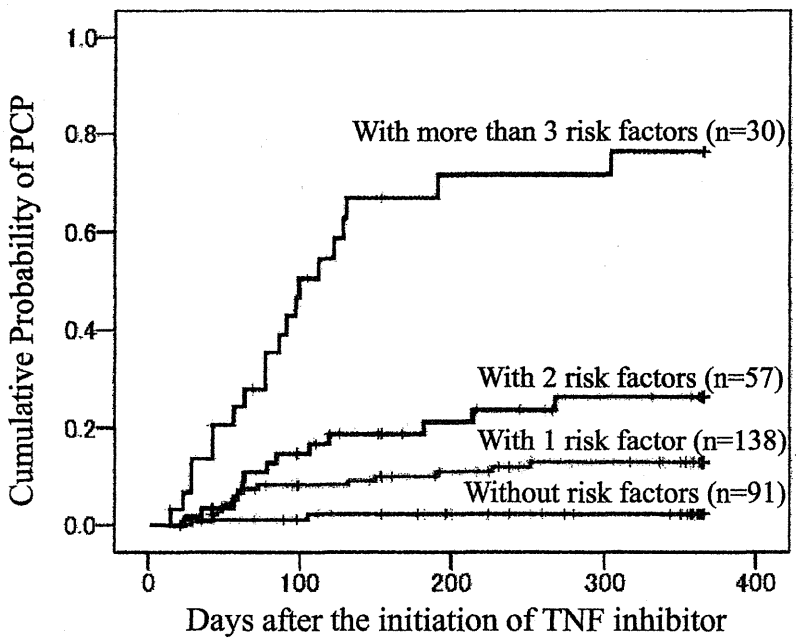

Figure 1. Cumulative probability for developing PCP under treatment with TNF inhibitors by number of risk factors. The cumulative probability was calculated using the Kaplan-Meier method. The differences in cumulative probability among the groups were examined using the log-rank test. Patients with 3 or more risk factors had a significantly higher risk for PCP than those with 2, 1, or no risk factors ($p < 0.001$ for all comparisons by the log-rank test). Patients with 2 risk factors had a significantly higher risk for PCP than those with 1 or no risk factors ($p = 0.045$ and $p < 0.001$, respectively). Patients with 1 risk factor had a significantly higher risk for PCP than those with no risk factors ($p = 0.008$). PCP: *Pneumocystis jirovecii* pneumonia; TNF: tumor necrosis factor.

We were able to identify common and more robust risk factors for the development of PCP by combining the data of PCP developed during treatment with any 1 of the 3 TNF inhibitors. Although prophylaxis success must be demonstrated in randomized controlled trials, we consider that it is important to screen for these risk factors based on this analysis and consider diligent prophylaxis before starting a TNF inhibitor.

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Prevention of joint destruction in patients with high disease activity or high C-reactive protein levels: Post hoc analysis of the GO-FORTH study

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ORIGINAL ARTICLE

Prevention of joint destruction in patients with high disease activity or high C-reactive protein levels: Post hoc analysis of the GO-FORTH study

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Abstract

Objectives: To assess the influence of golimumab dosage and disease activity on joint destruction in patients with active rheumatoid arthritis (RA) in the GO-FORTH study.
Methods: Efficacy was compared among groups given basal methotrexate plus placebo, golimumab (50 mg), or golimumab (100 mg) with stratification by high (HDA) or moderate (MDA) baseline disease activity and by high or low baseline C-reactive protein (CRP).
Results: Among HDA or high CRP patients, the mean change of the total Sharp score was 3.48 and 3.41 in the placebo group, 1.94 and 2.71 in the 50 mg group, and 0.39 and 1.15 in the 100 mg group, respectively. The percentage of progression-free patients with HDA or high CRP was 40.4% and 40.0%, 43.1% and 38.2%, and 69.8% and 61.5%, respectively. Among MDA or low CRP patients, both golimumab doses showed similar prevention of joint destruction. Among HDA or high CRP patients, a shorter disease duration and higher TSS/disease duration ratio were associated with joint destruction.
Conclusion: Both doses of golimumab (50 or 100 mg) prevented joint destruction in MDA or low CRP patients, but 100 mg was better for HDA or high CRP patients with a shorter disease duration or higher TSS/disease duration ratio.

Keywords

Golimumab, High disease activity, Japanese, Rheumatoid arthritis, Total Sharp score

History

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Introduction

Golimumab is a monoclonal human antitumor necrosis factor (TNF)-α antibody that is generated in transgenic mice immunized with human TNF-α [1]. In April 2009, golimumab was approved in the United States for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis. In July 2011, it was approved in Japan for the treatment of RA [2]. Several clinical studies have shown that golimumab effectively controls the signs and symptoms of RA, improves physical function, and suppresses the progression of joint destruction [3–9]. In the GO-FORTH study of Japanese patients with RA who had shown an inadequate response to methotrexate (MTX), golimumab (50 mg or 100 mg/4 weeks) significantly suppressed the progression of joint destruction compared with placebo, with no difference in efficacy between the doses of 50 and 100 mg [8]. Although this study was not primarily designed to compare golimumab dosages, a slight difference of the change in the total Sharp score (ΔTSS) was noted between patients receiving 50 mg or 100 mg of golimumab (ΔTSS was 1.05 vs. 0.33, respectively), as well as a larger difference compared with the ΔTSS of the placebo group (2.51). Therefore, to clarify whether there actually was a difference in the progression of joint destruction between the two dosages of golimumab, we compared outcomes in this study after stratification of patients by two factors that are known to influence joint destruction, that is, disease activity and the C-reactive protein (CRP) level [10–16].

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Methods

Study population and design

The details of the design and patient enrollment criteria for the GO-FORTH study have been published previously [8]. The study population consisted of patients with persistently active RA despite treatment with MTX. They were aged 20–75 years and had RA according to the revised criteria of the American College of Rheumatology (1987) with a disease duration ≥3 months. They had all received oral MTX (≥6 mg/week) for ≥3 months before initiation of study treatment, but still had active disease (≥4/66

swollen joints and ≥4/68 tender joints) and met at least two of the following criteria: (1) CRP>1.5 mg/dL or erythrocyte sedimentation rate (ESR)>28 mm/h, (2) morning stiffness for ≥30 min, (3) radiographic evidence of bone erosion, or (4) positive for anti-CCP antibody or rheumatoid factor. The 261 eligible patients were randomized (1:1:1) to the following three groups: a group treated with placebo + MTX (PBO group), a group receiving golimumab (50 mg/4 weeks) + MTX (GLM-50 group), or a group given golimumab (100 mg/4 weeks) + MTX (GLM-100 group). In the two test drug groups, a subcutaneous injection of golimumab was administered in week 0 and then every 4 weeks until week 24. MTX (6–8 mg/week) was continued without dose modification in all three groups. Patients who showed <20% improvement from baseline of the tender joint count and swollen joint count in week 14 could enter the double-blind early escape phase in week 16. In the early escape phase, golimumab (50 mg/4 weeks) was added for patients in the PBO group, the golimumab dose was increased to 100 mg for those in the GLM-50 group, and golimumab was continued at 100 mg for those in the GLM-100 group.

Efficacy assessment

The methods employed to assess major efficacy outcomes in the GO-FORTH study were reported previously [8]. The following parameters were analyzed: ACR20, ACR50, ACR70, the change from baseline and remission rate of DAS28 (ESR), the change from baseline and remission rate of the Health Assessment Questionnaire Disability Index (HAQ-DI), the change from baseline to week 24 of the modified total Sharp score (ΔTSS), and the percentage of progression-free patients (defined as patients with ΔTSS ≤0). To determine the ΔTSS, hand/foot radiographs were obtained in weeks 0 and 24 before administration of the study drug and the Sharp score (modified according to van der Heijde [17]) was assessed by two readers in a blinded manner. To evaluate the efficacy of golimumab, patients were stratified according to baseline disease activity and CRP as follows. For stratification according to disease activity, patients were classified as having high disease activity (HDA, defined as DAS28 [ESR]>5.1) or moderate disease activity (MDA, defined as DAS28 [ESR]>3.2 to ≤5.1). For stratification according to CRP, patients were classified as having higher than 1.5 mg/dL (CRP ≥1.5 mg/d: high CRP) or under 1.5 mg/dL (CRP <1.5 mg/dL: low CRP). A CRP level ≥1.5 mg/dL and <1.5 mg/dL were one of the enrollment criteria for the subanalysis of GO-FORWARD and GO-BEFORE study [7]. The cutoff value of CRP was set at 1.5 mg/dL because analysis of data from the subanalysis study [7] demonstrated that each group of patients could be appropriately divided into two subgroups using this value. Baseline patient and disease characteristics (age, disease duration, tender joint counts, swollen joint counts, duration of morning stiffness, HAQ-DI, CRP, ESR, rheumatoid factor, anti-CCP antibody, DAS28 [ESR], TSS, and TSS/disease duration ratio) were compared between patients from the GLM-50 and GLM-100 groups who had HDA or high CRP without progression of joint destruction (defined as ΔTSS ≤0) and those with progression of joint destruction (defined as ΔTSS>0).

Statistical analysis

Statistical analysis was performed in a modified intent-to-treat population (full analysis set), which was defined as patients who met the eligibility criteria, started study treatment, and had efficacy data. A probability (p) value of 0.05 (two sided) was used as the indicator of significance unless otherwise specified, and adjustment for multiplicity was not done. Differences of dichotomous variables among the treatment groups were evaluated by the chi-square test or the Fisher's exact test. For continuous variables, differences among groups were assessed with the t-test. For the comparison of changes in the modified Sharp score, analysis of variance (ANOVA) was conducted based on van der Waerden normal scores. Cumulative probability plots were also constructed that depicted changes of the modified Sharp score in ascending order of magnitude, with smaller changes indicating greater inhibition of disease progression. All analyses were performed using SAS software (Version 9.2; SAS Institute Inc., Cary, NC).

Results

Influence of golimumab dose and disease activity on joint destruction

Stratification of the PBO, GLM-50, and GLM-100 groups by disease activity and by CRP is shown in Table 1. Only four patients had low disease activity (DAS28 [ESR] ≤3.2) and they were excluded, leaving nearly all of the patients in the GO-FORTH study for analysis. In the PBO group, the mean ΔTSS values were 3.48 and 3.41 for patients with HDA or high CRP, respectively, which were higher than those for patients with MDA (0.76) and patients with low CRP (1.76) (Table 1). The mean ΔTSS values for patients with HDA or high CRP were 1.94 and 2.71, respectively, in the GLM-50 group versus 0.39 and 1.15 in the GLM-100 group. Among patients with HDA, ΔTSS was significantly lower in the GLM-100 group than in the PBO group ($p<0.0001$), although it was not significantly lower in the GLM-50 group compared with the PBO group ($p=0.2322$). Joint destruction was also significantly suppressed in the GLM-100 group compared with the GLM-50 group (Table 1). Among patients with low CRP values, disease progression was less marked in the GLM-50 group ($p=0.0156$ vs. PBO) and the GLM-100 group ($p=0.0015$ vs. PBO) than in the PBO group, while there was no significant difference between the GLM-50 and GLM-100 groups (Table 1).

To clarify differences of radiographic progression in week 24 (ΔTSS), cumulative probability plots were created for HDA, MDA, low CRP, and high CRP patients (Figure 1). When HDA patients were assessed, the progression-free rate was higher in the GLM-100 group (69.8%) than in the GLM-50 group (43.1%) or the PBO group (40.4%) (Figure 1b, Table 1), whereas MDA patients showed no differences of progression among the three treatment groups. Rapid radiographic progression (RRP) has been defined as a ΔTSS of five in a one-year period [5], corresponding to a ΔTSS of 2.5 after 24 weeks. As shown in Figure 1(b), most of the patients in the GLM-100 group had a ΔTSS <2.5, while almost 35% of the PBO group and 30% of the GLM-50 group had a ΔTSS >2.5. When patients with high CRP levels were assessed, 16 patients (almost 80%) from the GLM-100 group were progression-free and only three patients (about 10%) in this group had a ΔTSS >2.5, while almost 35% of patients in the PBO and GLM-50 groups had a ΔTSS >2.5 (Figure 1d). In contrast, patients with a low CRP level showed no difference of progression between the GLM-50 and GLM-100 groups (Figure 1c). Among HDA or high CRP patients, the percentage with a ΔTSS ≤0 was higher in the GLM-100 group (69.8% or 61.5%) than in the GLM-50 group (43.1% or 38.2%) and the PBO group (40.4% or 40.0%) (Figure 2b and d).

Among MDA or low CRP patients, the DAS remission rate and the percentage with ΔTSS ≤0 were similar in the GLM-50 and GLM-100 groups (Figure 2a–d). Among HDA or high CRP patients, the DAS remission rate was also similar in the GLM-50 and GLM-100 groups. The above findings indicate that 100 mg of golimumab was more effective than 50 mg for preventing joint destruction in patients with HDA or high CRP.

Table 1. Changes of the modified sharp score from baseline.

	PBO group (Placebo + MTX)	GLM-50 group (50 mg + MTX)	GLM-100 group (100 mg + MTX)	Combined (GLM 50 & GLM100)
All subjects				
Total score				
n	88	86	87	173
mean (SD)	2.51 (5.52)	1.05 (3.71)	0.33 (2.66)	0.69 (3.23)
median (min, max)	0.25 [−8.5, 33.5]	0.00 [−6.3, 22.5]	0.00 [−3.5, 19.0]	0.00 [−6.3, 22.5]
p value vs. PBO*	–	0.0363	<0.0001	0.0003
p value vs. GLM-50*	–	–	0.0809	–
ΔTSS ≤ 0				
n (%)	44 (50.0%)	51 (59.3%)	61 (70.1%)	112 (64.7%)
p value vs. PBO**	–	0.2179	0.0066	0.0217
p value vs. GLM-50**	–	–	0.1367	–
DAS 28 (ESR)				
Total score				
n	29	33	34	67
mean (SD)	0.76 (2.174)	−0.2.7 (1.432)	0.23 (1.786)	−0.01 (1.629)
median (min, max)	0.00 [−1.5, 8.0]	0.00 [−3.5, 3.5]	0.00 [−3.5, 6.2]	0.00 [−3.5, 6.2]
p value vs. PBO*	–	0.0823	0.3091	0.1172
>3.2− ≤5.1				
p value vs. GLM-50*	–	–	0.3955	–
ΔTSS ≤ 0				
n (%)	20 (69.0%)	27 (81.8%)	24 (70.6%)	51 (76.1%)
p value vs. PBO**	–	0.2384	0.8888	0.4633
p value vs. GLM-50**	–	–	0.2811	–
Total score				
n	57	51	53	104
mean (SD)	3.48 (6.503)	1.94 (4.475)	0.39 (3.101)	1.15 (3.897)
median (min, max)	1.00 [−8.5, 33.5]	0.50 [−6.3, 22.5]	0.00 [−3.5, 19.0]	0.00 [−6.3, 22.5]
p value vs. PBO*	–	0.2322	<0.0001	0.0018
>5.1				
p value vs. GLM-50*	–	–	0.0051	–
ΔTSS ≤ 0				
n (%)	23 (40.4%)	22 (43.1%)	37(69.8%)	59 (56.7%)
p value vs. PBO**	–	0.7069	0.0019	0.0468
p value vs. GLM-50**	–	—	0.0061	–
CRP (ng/dL)				
Total score				
n	48	52	61	113
mean (SD)	1.76 (4.085)	−0.04 (1.850)	−0.02 (1.670)	−0.03 (1.747)
median (min, max)	0.00 [−1.5, 19.5]	0.00 [−6.3, 5.5]	0.00 [−3.5, 7.0]	0.00 [−6.3, 7.0]
p value vs. PBO*	–	0.0156	0.0015	0.0011
<1.5				
p value vs. GLM-50*	–	–	0.6973	–
ΔTSS ≤0				
n (%)	28 (58.3%)	38 (73.1%)	45 (73.8%)	83 (73.5%)
p value vs. PBO**	–	0.1200	0.0889	0.0579
p value vs. GLM-50**	–	–	0.9337	–
Total score				
n	40	34	26	60
mean (SD)	3.41 (6.811)	2.71 (5.034)	1.15 (4.066)	2.04 (4.668)
median (min, max)	1.00 [−8.5, 33.5]	1.00 [−4.5, 225]	0.00 [−2.0, 19.0]	0.50 [−4.5, 22.5]
p value vs. PBO*	–	0.7642	0.029	0.1777
≥1.5				
p value vs. GLM-50*	–	–	0.0630	–
ΔTSS ≤0				
n (%)	16 (40.0%)	13 (38.2%)	16 (61.5%)	29 (48.3%)
p value vs. PBO**	–	0.8768	0.0871	0.4119
p value vs. GLM-50**	–	–	0.0735	–

*ANCOVA with Van der Waerden scores.
**Chi-square test.
ΔTSS: change from baseline to week 24 of the modified total Sharp score.

Baseline patient and disease characteristics influencing the response to golimumab

Since 50 mg of golimumab seemed to be too low a dose to prevent joint destruction in some HDA or high CRP patients, we investigated the baseline demographic and disease characteristics of the patients with or without progression at this dose of golimumab. Similar trends were identified in HDA patients and high CRP patients. Among HDA patients in the GLM-50 group, the disease duration was significantly shorter for those with progression than for progression-free patients (mean: 6.7 years vs. >12.8 years, $p = 0.0221$). In addition, the mean (median) TSS of patients with progression was 51.1 (27.5), which was significantly lower for than the value of 93.9 (65.8) for progression-free patients ($p = 0.0336$) (Table 2). Furthermore, the TSS/disease duration ratio of high CRP patients from the GLM-50 group was significantly higher for those with progression than for those without progression (mean: 13.9 vs. 7.5; $p = 0.0166$) (Table 3).

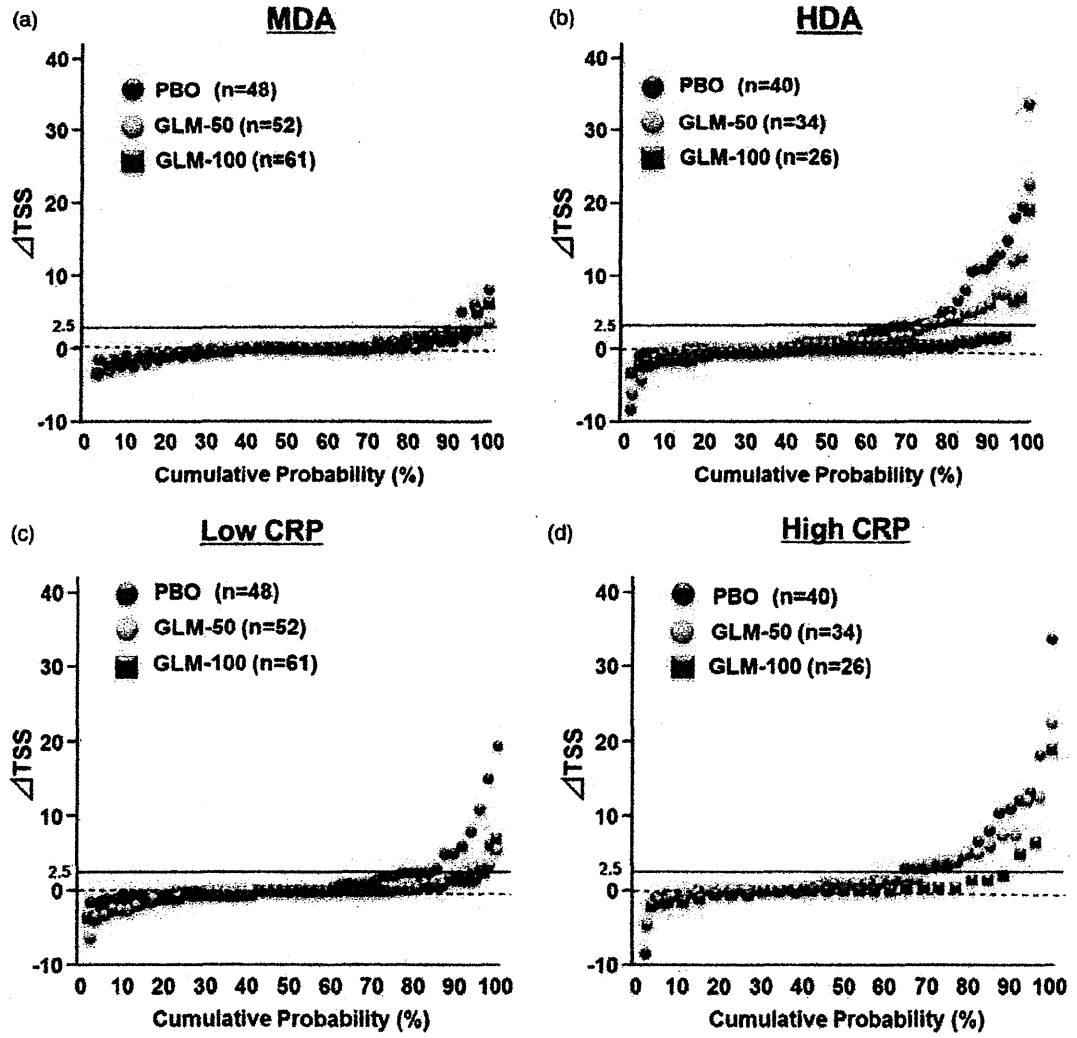

Figure 1. Change of total Sharp score from baseline to week 24 (ΔTSS) in each group. ΔTSS in (a) patients with moderate disease activity (MDA) and (b) patients with high disease activity (HDA) according to baseline DAS28 or ESR. ΔTSS in (c) patients with a low baseline CRP and (d) patients with a high baseline CRP.

Similar analyses were performed in the GLM-100 group, which showed that baseline patient and disease characteristics had no influence on the efficacy of golimumab (data not shown).

Discussion

The GO-FORTH study [8] demonstrated that administration of golimumab combined with MTX to Japanese patients with active RA significantly suppressed disease activity and radiographic progression without any unexpected safety problems. In that study, golimumab doses of 50 mg and 100 mg displayed similar efficacy and safety, but there was a difference between the two dose levels with regard to the percentage of progression-free patients (59.3% at 50 mg vs. 70.1% at 100 mg). Accordingly, the present study was performed to obtain more detailed assessment of the influence of the golimumab dose and the potential for preventing joint destruction by stratified analysis of 24-week data from the GO-FORTH study. This stratified analysis revealed that the ΔTSS of patients with HDA or high CRP from the GLM-50 group was 1.94 and 2.71, respectively (vs. 1.05 for nonstratified analysis), while the patients with HDA or high CRP from the GLM-100 group respectively showed ΔTSS values of 0.39 and 1.15 after stratification (vs. 0.33). In addition, a higher percentage of HDA or high CRP patients achieved ΔTSS $\leq$0 in the GLM-100 group than in the GLM-50 group, while the percentage of MDA or low CRP patients achieving ΔTSS $\leq$0 was similar in both groups. Moreover, the DAS remission rate was comparable between the GLM-100 and GLM-50 groups for high CRP patients, whereas a higher percentage of these patients achieved ΔTSS $\leq$0 in the GLM-100 group than in the GLM-50 group. These results indicate that a golimumab dose of 100 mg is more effective than 50 mg for preventing joint destruction in RA patients with HDA and patients with high CRP levels.

The GO-FORTH study was based on the design of the GO-FORWARD study [4,5], and RA patients with an inadequate response to MTX were enrolled in both studies. However, the week 24 ΔTSS of the PBO + MTX group was much lower in the GO-FORWARD study (0.55) than in the GO-FORTH study (2.51) [8], and no significant preventive effect of golimumab (50 mg or 100 mg) + MTX compared with placebo + MTX was seen in the former study. When ΔTSS data from the GO-FORWARD study were analyzed after stratification according to baseline CRP (cutoff level: 1.5 mg/dL), the week 24 ΔTSS increased 0.85 for high CRP patients in the placebo + MTX group compared with 0.55 according to nonstratified analysis. These results suggest that baseline CRP had an influence on the progression of joint destruction in the GO-FORWARD study [5].

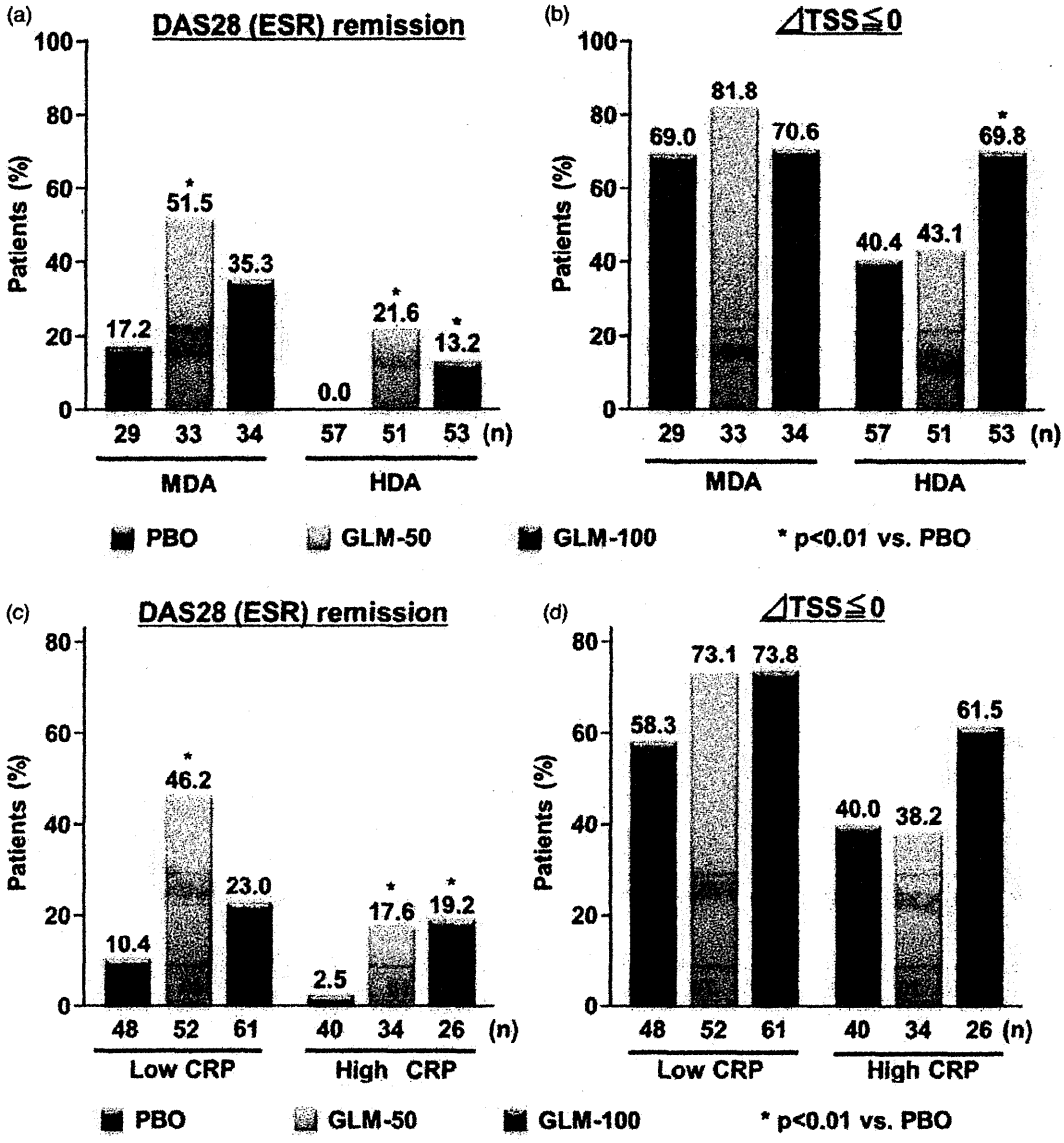

Figure 2. Remission rate in each group. (a) Remission rate (based on DAS28 or ESR) for patients with moderate disease activity (MDA) or high disease activity (HDA). (b) Percentage of patients with MDA or HDA who achieved $\Delta TSS \leq 0$. (c) Remission rate (based on DAS28 or ESR) for patients with low or high CRP levels. (d) Percentage of patients with low or high CRP levels who achieved $\Delta TSS \leq 0$.

We analyzed the baseline characteristics of HDA or high CRP patients who showed progression or remained progression-free in the GO-FORTH study and found several differences.

(1) Among HDA patients in the GLM-50 group, the duration of RA was 6.7 years for those with progression versus 12.8 years for those without progression.
(2) The mean TSS of HDA patients from the GLM-50 group with progression was 51.5, but it was 93.9 for progression-free subjects.
(3) The mean TSS/disease duration ratio of high CRP patients from the GLM-50 group was 13.9 for those with progression versus 7.1 for those without progression.
(4) In the GLM-100 group, disease characteristics did not influence progression, except for a shorter disease duration in high CRP patients (data not shown).

These findings suggest that a relatively short disease duration and high TSS/disease duration ratio may be associated with an increased risk of progression in HDA or high CRP patients treated with 50 mg of golimumab. Our results are consistent with the findings obtained when subanalysis of the DE019 trial was performed by Jamal et al. [18]. They reported that major clinical effects were similar for early disease (≤3 years) and established disease (>3 years), but the progression of joint destruction was different. The Sharp score was 5.32 for patients with early disease and 2.06 for those with established disease (>3 years) in the placebo + MTX group versus 0.39 and 0.05, respectively, in the adalimumab + MTX group. Combining the results of the DE019 and GO-FORTH studies suggests that a short disease duration and a high TSS/disease duration ratio are important background factors to consider when selecting the dose of golimumab. Since 43% of HDA patients and 38% of high CRP patients remained progression-free after treatment in the GLM-50 group, it seems that two background variables are required to identify a high risk of the progression of joint destruction. In the present analysis, the mean DAS28 (ESR) and mean CRP level of HDA or high CRP patients in the GLM-50 group was 6.3 ($n=51$) and 4.1 ($n=34$), respectively. The GO-FORTH study included 20 to 29 patients with a disease duration <3 years in each group. In the DE019