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ORIGINAL ARTICLE

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

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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

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This article was originally published with an error in Figure 1. This version has been corrected. Please see Corrigendum (<http://dx.doi.org/10.3109/14397595.2015.1173986>).

randomized, controlled clinical trials (RCTs) [12–14]. Execution of all-cases (a mandatory registry) postmarketing 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  $\geq$  2.6 and

< 3.2), moderate disease activity (DAS28  $\geq$  3.2 and  $\leq$  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  $\leq$  3.2 during follow-up. Patients with score improvements of  $\geq$  -0.6, as well as those with improvements < -0.6 and  $\geq$  -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  $\geq$  -1.2 plus a DAS28 of  $\leq$  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 ( $\pm$ SD) of 61.4  $\pm$  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 1. Patient demographic and clinical baseline characteristics.

| Variables  | Safety analysis set ( <i>n</i> = 3882) | Effectiveness analysis set ( <i>n</i> = 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 ( <i>n</i> = 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.

Table 2 shows the incidence rates of the most commonly reported ADRs in this PMS. Upper respiratory tract inflammation 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<sup>3</sup> (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) |         | Duration of Onset (days) |         | Cause of incident  |
|------------------------|----|---------------------|------------------------|-------------|---------|--------------------------|---------|--|
|                        |    |                     |                        | Mean        | Min–Max | Mean                     | Min–Max |  |
| Deaths                 | 8  | 0.21                | 3/5                    | 73.5        | 61–86   | 97.4                     | 30–176  | (1) Interstitial pneumonia (n = 4)<br>(2) Bronchopulmonary aspergillosis<br>(3) Mycosis/acute disseminated encephalomyelitis<br>(4) Pneumocystis pneumonia<br>(5) Pulmonary tuberculosis/tuberculous peritonitis |
| Pneumonia              | 28 | 0.72                | 7/21                   | 66.2        | 25–79   | 95.8                     | 6–178   | (1) Pneumonia (n = 18)<br>(2) Bacterial pneumonia (n = 5)<br>(3) Bronchopneumonia (n = 3)<br>(4) Pneumococcal pneumonia (n = 2)<br>Concurrent pulmonary tuberculosis and tuberculous peritonitis                 |
| 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)<br>(2) Gastric cancer<br>(3) Malignant lung neoplasm<br>(4) Colorectal cancer<br>(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 ( $\geq 2.6$  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.

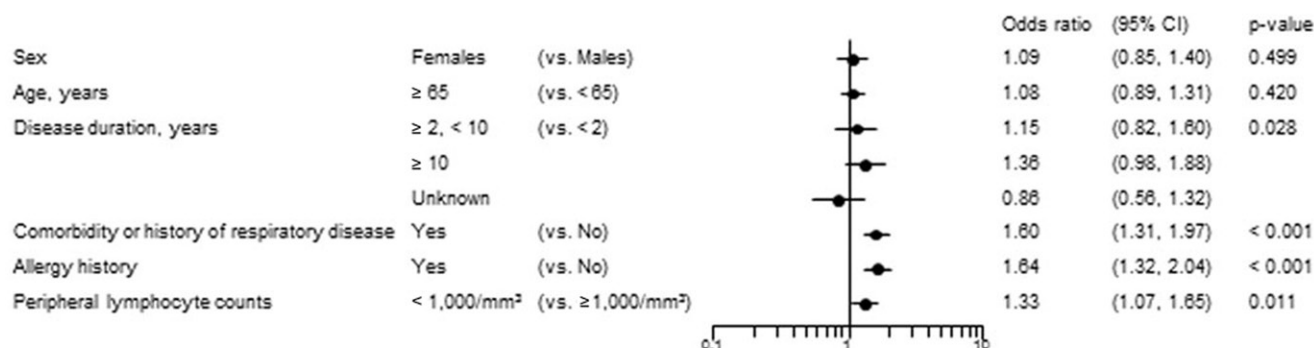
Abatacept was well tolerated, and no new safety concerns were detected. During the observation period, the indexes of disease activity of RA decreased significantly. Risk factors for ADRs and infections, as well as predictors of clinically meaningful improvement in DAS28 (DAS28-CRP change from baseline <−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.

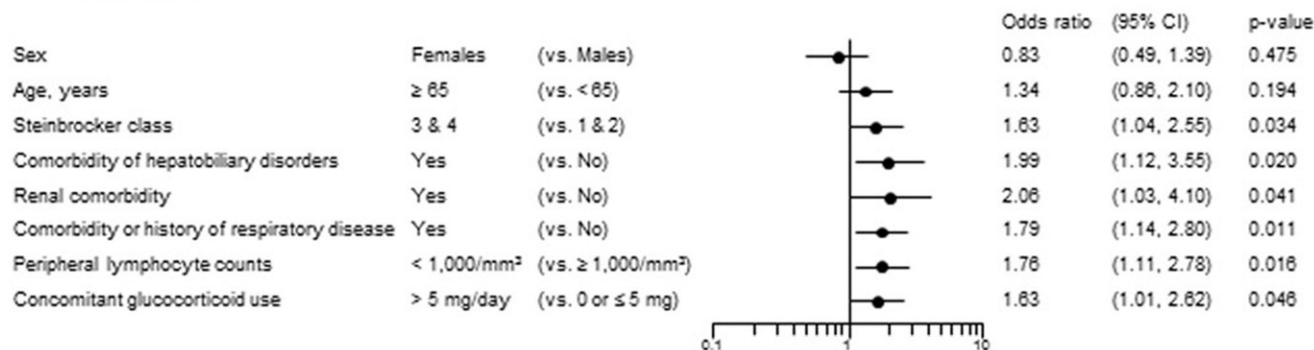
Notably, there was only one case of TB reported in this study. This finding is also in line with a previous epidemiological assessment by Simon et al. [19]. Patients to be treated with any of the biologics approved in Japan are required to go through TB screening. Therefore, the low incidence rate of 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  $\geq 65$  years, comorbidity of hepatobiliary

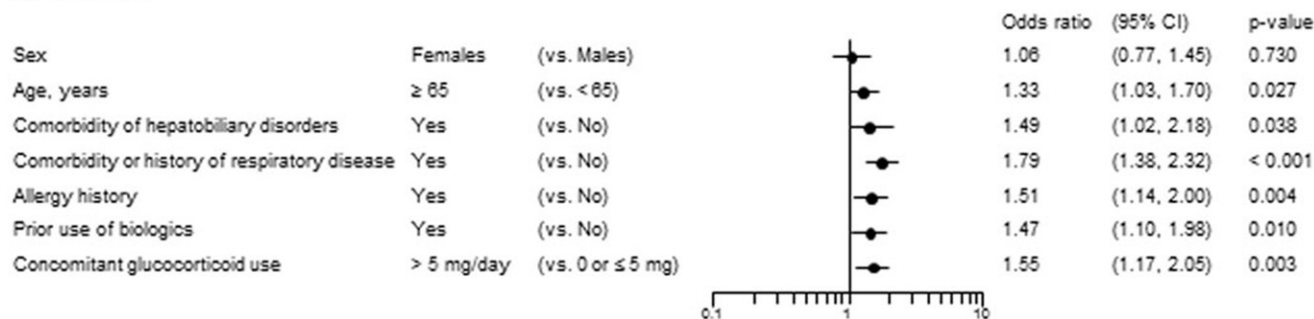
## (a) ADRs



## (b) Serious ADRs



## (c) Infections



## (d) Serious infections

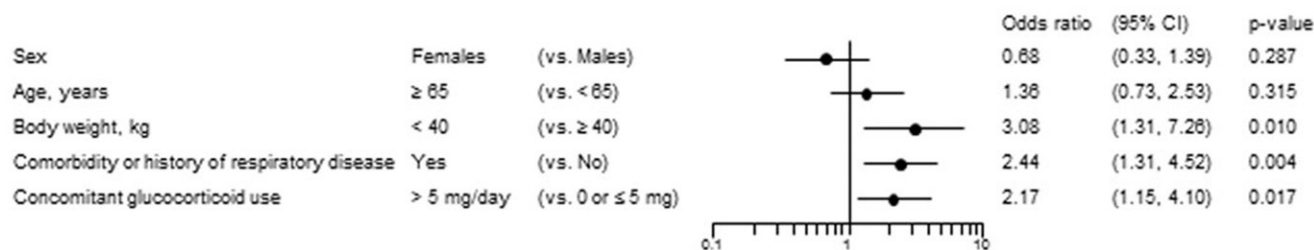


Figure 1. Multivariate logistic regression analysis revealed risk factors for all (a) ADRs, (b) serious ADRs, (c) infections, and (d) serious infections. Candidate variables for multivariate analysis were selected among many others based on their degree of clinical significance and the results of the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

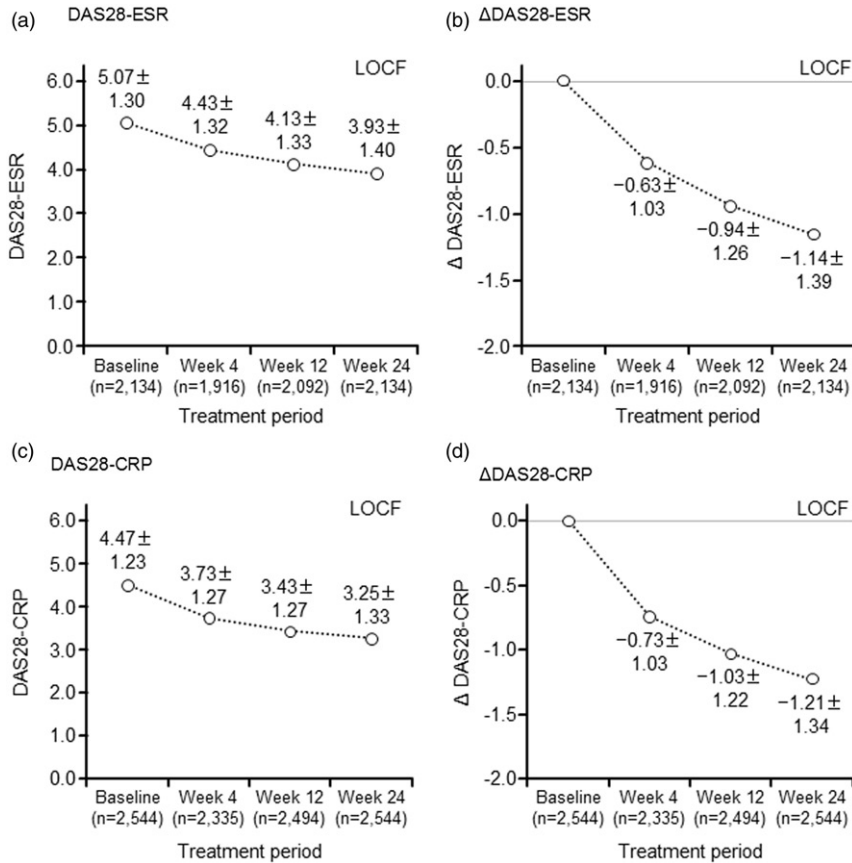
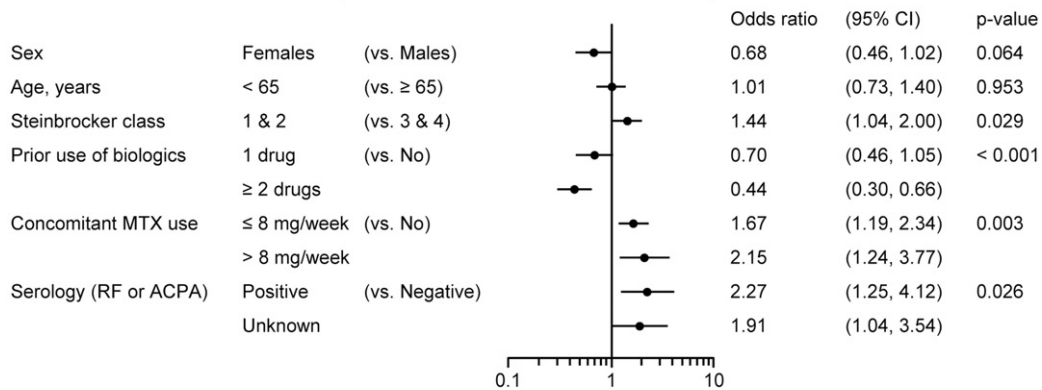


Figure 2. Change in disease activity over time in patients treated with abatacept. The last-observation-carried-forward (LOCF) imputation method was used. (a) DAS28 based on erythrocyte sedimentation rate (DAS28-ESR). (b) DAS28-ESR changes. (c) DAS28 based on C-reactive protein (DAS28-CRP). (d) DAS28-CRP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

(a) ΔDAS28-CRP < -1.2 (Baseline DAS28-CRP > 5.1)



(b) ΔDAS28-CRP < -1.2 (Baseline DAS28-CRP ≥ 3.2 and ≤ 5.1)

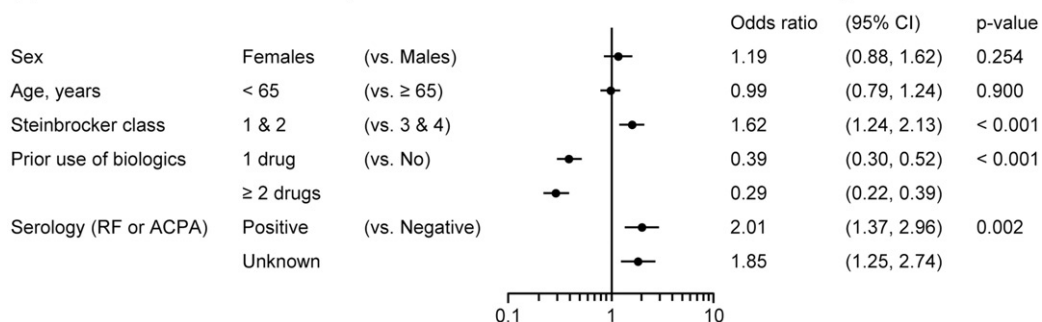


Figure 3. Multivariate logistic regression analysis revealed factors associated with improved DAS (DAS28-CRP51.2) in patients with (a) baseline DAS28-CRP45.1, and (b) baseline DAS28-CRP3.2 and 5.1. Candidate variables for multivariate analysis were selected among many others based on their degree of 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.

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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  $>5$  mg/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  $\sim 80\%$  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  $5.2 \pm 1.4$  to  $3.9 \pm 1.4$ ) [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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## References

- Silman AJ, Hochberg MC. Epidemiology of the rheumatic diseases. 2nd ed. New York: Oxford University Press; 2001.
- Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. *Clin Exp Rheumatol*. 2005;23:S43–52.
- Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). *Mod Rheumatol*. 2014;24:33–40.
- Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2012;64:625–39.
- Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73:492–509.
- Japan College of Rheumatology: Guideline for the use of abatacept in rheumatoid arthritis (revised August 23, 2014). Available from: [http://www.ryumachi-jp.com/info/guideline\\_abatacept.html](http://www.ryumachi-jp.com/info/guideline_abatacept.html) [Japanese] [last accessed 16 February 2015].
- Lipsky PE, Heijde DM van der, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with Concomitant Therapy Study Group. *N Engl J Med*. 2000;343:1594–602.
- Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999;340:253–9.
- Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor  $\alpha$  monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003;48:35–45.
- Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-TNF agents in rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:746–52.
- Schiff M. Abatacept treatment for rheumatoid arthritis. *Rheumatology* 2011;50:437–9.
- Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52:2263–71.
- Schiff M, Keiserman M, Coddling C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis*. 2008;67:1096–103.
- Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2006;144:865–76.
- Takeuchi T, Kameda H. The Japanese experience with biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol*. 2010;6:644–52.
- Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995;38:44–8.
- Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. *J Rheumatol*. 2009;36:898–906.
- Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3000 patients. *Mod Rheumatol*. 2012;22:498–508.
- Simon TA, Askling J, Lacaille D, Franklin J, Wolfe F, Covucci A, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. *Arthritis Res Ther*. 2010;12:R67.
- Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:189–94.
- He D, Bai F, Zhang S, Jiang T, Shen J, Zhu Q, et al. High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy. *Clin Vaccine Immunol*. 2013;20:842–7.
- Askling J, Forell CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum*. 2005;52:1986–92.
- Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum*. 2003;48:2122–7.
- Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J*. 2010;36:1185–206.
- Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis*. 2004;39:1254–5.
- Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum*. 2004;50:372–9.
- Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis*. 2011;70:2148–51.
- Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of 7740 patients. *Mod Rheumatol*. 2014;24:390–8.
- Nüßlein HG, Alten R, Galeazzi M, Lorenz H-M, Nurmohamed MT, Bensen WG, et al. Prognostic factors for abatacept retention in patients who received at least one prior biologic agent: an interim analysis from the observational, prospective ACTION study. *BMC Musculoskelet Disord*. 2015;16:176.
- Tanaka Y, Kubo S, Yamanaka H, Amano K, Hirata S, Tanaka E, et al. Efficacy and safety of abatacept in routine care of patients with rheumatoid arthritis: Orenzia<sup>®</sup> as Biological Intensive Treatment for RA (ORBIT) study. *Mod Rheumatol*. 2014;24:754–72.
- Nüßlein HG, Alten R, Galeazzi M, Lorenz HM, Boumpas D, Nurmohamed MT, et al. Real-world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2-year, observational, prospective ACTION study. *BMC Musculoskelet Disord*. 2014;15:14.
- Finckh A, Neto D, Iannone F, Loza E, Lie E, van Riel P, et al. The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries. *RMD Open* 2015;1:e000040.
- Gottenberg JE, Ravaud P, Cantagrel A, Combe B, Flipo RM, Schaevebeke T, et al. Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the 'Orenzia and Rheumatoid Arthritis' registry. *Ann Rheum Dis*. 2012;71:1815–19.