Incidence and Risk Factors for Serious Infection in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety

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ABSTRACT. ***Objective.*** To compare tumor necrosis factor-α (TNF-α) inhibitors to nonbiological disease-modifying antirheumatic drugs (DMARD) for the risk of serious infection in Japanese patients with rheumatoid arthritis (RA).

Methods. Serious infections occurring within the first year of the observation period were examined using the records for patients recruited to the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety (REAL), a hospital-based prospective cohort of patients with RA. The analysis included 1144 patients, 646 of whom were treated with either infliximab or etanercept [exposed group: 592.4 patient-years (PY)]. The remaining 498 patients received nonbiological DMARD with no biologics (unexposed group: 454.7 PY).

Results. In the unexposed group, the incidence rate for all serious adverse events (SAE) was 9.02/100 PY and for serious infections, 2.64/100 PY. In the exposed group, SAE occurred in 16.04/100 PY and serious infections in 6.42/100 PY. The crude incidence rate ratio comparing serious infections in the exposed group with the unexposed group was 2.43 (95% CI 1.27–4.65), a significant increase. A multivariate analysis revealed that the use of TNF inhibitors is a significant independent risk factor for serious infection (relative risk 2.37, 95% CI 1.11–5.05, p = 0.026).

Conclusion. Our study has provided the first epidemiological data on Japanese patients with RA for the safety of TNF inhibitors compared to nonbiological DMARD for up to 1 year of treatment. Anti-TNF therapy was associated with a significantly increased risk for serious infections, compared to treatment with nonbiological DMARD. (First Release April 15 2011; J Rheumatol 2011; 38:1258–64; doi:10.3899/jrheum.101009)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
TUMOR NECROSIS FACTOR-α
DRUG TOXICITY
ANTIRHEUMATIC AGENTS

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Supported by a grant-in-aid from the Ministry of Health, Labor and Welfare, Japan (no. 2401980 to N. Miyasaka) and by a grant-in-aid for scientific research from the Japan Society for the Promotion of Science (no. 20390158 to M. Harigai and no. 19590530 to R. Koike). Also supported by grants from Abbott Laboratories, Eisai Co. Ltd., Chugai Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corp., Takeda Pharmaceutical Co. Ltd., and Wyeth K.K. (to M. Harigai).

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Accepted for publication February 25, 2011.

The introduction of tumor necrosis factor-α (TNF) inhibitors for treatment of rheumatoid arthritis (RA) is a major therapeutic breakthrough[1]. Because biologics, including TNF inhibitors, have become important and widely used clinical tools for treatment of RA, assessment of their safety is important. There are significant concerns relating to the association between opportunistic infections and TNF inhibitors. One example of this association is the observed reactivation of latent tuberculosis[2]. Serious bacterial, granulomatous, and fungal infections have also been reported to be associated with TNF inhibitor use[3,4].

To develop the safety profiles of biologics, several groups from Europe and the United States have established registries for patients receiving these drugs. Some of these have reported elevated risk for infections in patients with RA treated with biologics, including TNF inhibitors, compared to treatment with nonbiological disease-modifying antirheumatic drugs (DMARD)[5,6,7,8,9,10,11]. To date, there has been no comparable report on the safety of biologics for Asian patients with RA. Because racial and geographic differences occur in morbidities of such infections as *Mycobacterium tuberculosis*, the *Coccidioides* species, and *Pneumocystis jirovecii*, the development of a defined safety profile for treatment with biologics in each geographic area is crucial for clinicians[12,13,14,15].

In Japan, postmarketing surveillance programs of all cases treated with infliximab and etanercept were implemented, revealing several important safety concerns for these TNF inhibitors during the first 6 months of the therapy. These studies identified infection as the most important serious adverse event (SAE) during treatment with the TNF inhibitors[16,17]. These studies, however, had serious deficiencies related to the absence of appropriate comparator groups and the short tracking period. We therefore established the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety (REAL) database in 2005 to compare the safety of midterm to longterm treatment with biological DMARD to treatment with nonbiological DMARD.

The primary purpose of our study was to use the REAL database to compare the incidence of serious infections between TNF inhibitor-treated and nonbiological DMARD-treated patients with RA. A second objective was to identify independent risk factors for serious infections in this population.

MATERIALS AND METHODS

Data source. The REAL database is a hospital-based prospective cohort of patients with RA administered by the Department of Pharmacovigilance of the Tokyo Medical and Dental University. The ethics committee of the Tokyo Medical and Dental University Hospital and those of the participating institutions approved our study. Twenty-three institutions participate in REAL, including 15 university hospitals and 8 referring hospitals. Enrollment to the REAL database began in June 2005.

The criteria for admission to the REAL database include those patients (1) meeting the 1987 American College of Rheumatology criteria for RA; (2) ≥ 20 years old and able and willing to provide written informed consent and comply with the requirements of the protocol, or, for those patients < 20 years, having parents or legal guardians willing and able to provide written informed consent and to comply with the requirements of the protocol; and (3) starting treatment with biologics (the exposed group) or nonbiological DMARD (the nonexposed group) at the time of study entry. In addition, patients receiving treatment with nonbiological DMARD at the time of study entry are also enrolled as the nonexposed group. Exclusion criteria include (1) patient participation in a clinical trial for approval of drugs at the time of enrollment or during the followup in the study, and (2) patients withdrawing consent to join the study. We identified all patients who were registered from the participating hospitals of our study to the postmarketing surveillance programs for each biological DMARD that were implemented by the corresponding pharmaceutical companies. Participating physicians at each hospital enrolled all of these patients to the REAL database. In addition, patients who fulfilled the inclusion criteria were consecutively recruited for both groups by participating physicians at each hospital.

Exposed group. Because infliximab was introduced in Japan in 2003, etanercept in 2005, and adalimumab and tocilizumab in 2008, few data for patients receiving adalimumab or tocilizumab were available in the REAL database at the time we conducted our study. We therefore included only

those patients with RA who had started infliximab or etanercept at enrollment in the REAL database. Nonbiological DMARD were used for these patients at the attending physicians' discretion. Six hundred forty-six patients were enrolled in the exposed group. Patients who switched from infliximab to etanercept or etanercept to infliximab were included in the analysis using the combined time of the treatment. For those patients no longer receiving either infliximab or etanercept, only the time of actual use of these TNF inhibitors was analyzed.

Unexposed group. Four hundred ninety-eight patients were enrolled in the unexposed group. At the time of enrollment in our study, 57.6% of the patients in the unexposed group were being treated with methotrexate (MTX), 20.3% with salazosulfapyridine, 18.7% with tacrolimus, and 13.9% with bucillamine. Nonbiological DMARD used in fewer than 10 patients were leflunomide, actarit, gold salt, auranofin, mizoribine, D-penicillamine, and cyclosporine. Sixty-four patients (12.9%) of the unexposed group were given combination therapy with > 1 nonbiological DMARD agent during the observation period. Some patients who were initially enrolled in the unexposed group received biologics when clinically indicated; the time period following this change was excluded from the analysis.

Data collection. Each patient's recorded baseline data included demography, disease activity, comorbidities, treatments, and laboratory data at the start of the observation period. The same followup forms were used for both groups and included queries about RA disease activity, treatments, laboratory data, and occurrence and details of SAE. The followup forms were submitted every 6 months by the participating physicians to the REAL Data Center at the Department of Pharmacovigilance of Tokyo Medical and Dental University. The participating physicians in each hospital confirmed their submitted data to the REAL Data Center. Data were retrieved from the REAL database on November 30, 2008, for our study.

Baseline characteristics of patients. The observation period for 646 patients in the exposed group was 592.4 patient-years (PY). For 498 patients in the unexposed group, the observation period was 454.7 PY. In the exposed group, 300 patients (272.1 PY) received infliximab but not etanercept and 343 patients (320.3 PY) received etanercept but not infliximab. Three patients were switched from infliximab to etanercept during the observation period. The median length of the observation period was 1 year in both groups, and the percentage of patients followed up for a year was 83.1% in the exposed and 82.1% in the unexposed group. Minimal duration of followup was 2 months in the unexposed group and 3 months in the exposed group. The primary reason for not having at least a full year of followup in about 18% of the patients was that they were enrolled in the REAL database for < 1 year before November 30, 2008, when the data were retrieved from the database. Baseline data at the start of the observation period for the patients are shown in Table 1. Compared to the unexposed group, the exposed group was younger ($p < 0.001$), had more severe disease activity ($p < 0.001$), was treated with higher dosages of MTX ($p < 0.001$) and corticosteroids ($p = 0.001$), and had failed a larger number of DMARD ($p < 0.001$). Percentages of the patients on their first DMARD at baseline were 30.1% for the unexposed group and 24.0% for the exposed group ($p < 0.012$). Significantly more patients having comorbidities, including chronic pulmonary diseases ($p = 0.046$) and diabetes ($p = 0.024$), were seen in the exposed group compared to the unexposed group.

Definition of SAE. Our definition of an SAE was based on events described in the report by the International Conference on Harmonization[18]. In addition, bacterial infections that required intravenous administration of antibiotics, as well as opportunistic infections, including tuberculosis, *P. jirovecii* pneumonia (PCP), systemic fungal infection, cytomegalovirus infection, and herpes zoster were also regarded as SAE. The diagnosis of infections was based on a physician's clinical diagnosis, a comprehensive evaluation based on physical findings, laboratory data, and radiological examinations. The detection of infectious pathogens was not mandatory for making a diagnosis of infection. SAE were classified using the System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA; version 11.1).

Table 1. Comparison of patients with rheumatoid arthritis (RA) treated with (exposed) and without (unexposed) the tumor necrosis factor-α (TNF) inhibitors infliximab or etanercept at the start of the observation period. Values are mean ± SD unless otherwise stated.

Characteristics	Exposed Group, n = 646	Unexposed Group, n = 498	p
Age, yrs	58.3 ± 13.2	61.4 ± 12.8	< 0.001
Women, %	82.0	83.3	0.568
Disease duration, yrs	9.5 ± 8.6	9.2 ± 9.2	0.654
Steinbrocker stage (III or IV), %	55.1	43.8	< 0.001
DAS28 (3/CRP)	3.9 ± 1.0, n = 642	2.8 ± 1.0, n = 495	< 0.001
MTX use, %	69.0	60.2	0.002
MTX dose, mg/wk	7.6 ± 2.2	6.4 ± 2.0	< 0.001
MTX dose > 8 mg/wk, %	11.1	5.0	< 0.001
Use of immunosuppressive drugs, except for MTX, %*	3.7	20.5	< 0.001
Corticosteroid use, %**	71.4	62.0	0.001
Prednisolone dose, mg/day	5.7 ± 3.0	4.6 ± 2.1	< 0.001
> 7.5 mg prednisolone/day, %	13.6	3.1	< 0.001
No of failed DMARD	1.6 ± 1.1	1.3 ± 1.1	< 0.001
Chronic pulmonary disease, %***	21.4	16.7	0.046
Diabetes, %	10.7	6.8	0.024

* Including tacrolimus, leflunomide, mizoribine, and cyclosporine. ** Converted to corresponding prednisolone dosage. *** Including interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, prior pulmonary tuberculosis, and bronchiectasis. DAS28: 28-joint count Disease Activity Score; CRP: C-reactive protein; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug. † Number of DMARD that were tried but did not bring about a response.

Statistical analyses. Serious infections observed within the first year of the observation period were analyzed for each patient. The observation period for the present analysis was defined as follows: for patients who initiated treatment with the TNF inhibitors infliximab or etanercept or nonbiological DMARD at the time of study entry, the start of the observation period was the date these agents were first administered; for patients receiving the treatment with nonbiological DMARD at the time of study entry, the start of the observation period was the date of their enrollment in the REAL database. The observations ended 1 year after the start of the observation period, or on the day a patient died or met the exclusion criteria, or for the exposed group, no longer received either infliximab or etanercept, or for the unexposed group, started biologics, whichever came first. Patients were not removed even after the development of SAE as long as they did not meet the above criteria for censoring a patient. Considering the time it takes for pharmacokinetic/pharmacodynamic effects and data to appear from previous studies of at-risk periods[6], we considered any SAE occurring within 90 days after the last administration of infliximab or etanercept that was within the first year of the observation period to be attributable to the effects of the TNF inhibitors. Because the length of the at-risk period (90 days) after the date of discontinuation of treatment is more than 10 times as long as the half-lives of the 2 TNF inhibitors (i.e., 8.1 days for infliximab and 4.8 days for etanercept), we defined the date of drug discontinuation as the date of last administration, instead of the date of the first missed dose, which was the method used by another study[6]. The same number of SAE was found in the exposed group of our study using either definition for the date of drug discontinuation (data not shown). The date of the last administration of infliximab or etanercept was retrieved from medical records and reported by the participating physicians.

The incidence rates (IR) per 100 PY and incidence rate ratios (IRR) with their 95% CI were calculated. For univariate analysis, the chi-squared

test for categorical variables and the Student t-test or Mann-Whitney U tests for continuous variables were used for comparisons among groups. For multivariate analysis, Poisson regression analyses were used to estimate the risk of serious infection with the TNF inhibitors infliximab and etanercept, and to identify any variable having a significant and independent influence on the development of serious infections. Variables that were included in the multivariate analysis were chosen using the results of univariate analysis. The analyses were conducted using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA) and R statistical language software (version 2.8.1, R Foundation for Statistical Computing, Vienna, Austria). All p values were 2-tailed and $p < 0.05$ was considered statistically significant.

RESULTS

Types and incidence rates of SAE. One hundred thirty-six SAE were reported during the observation period, 41 in the unexposed group and 95 in the group exposed to infliximab or etanercept. Based on the SAE categories classified using the SOC, infections and infestations were the most common, followed by injury, poisoning, and procedural complications, in which fractures accounted for 76% (Table 2). In the exposed group, there were 38 serious infections including 25 bacterial, 11 opportunistic (6 cases of herpes zoster, 3 PCP, 1 pulmonary cryptococcosis, and 1 pulmonary nontuberculous mycobacterial infection), and 2 other infections. In the unexposed group, 12 serious infections occurred, including 8 bacterial, 3 opportunistic (1 each PCP, pulmonary tuberculosis, and pulmonary nontuberculous mycobacterial infection), and 1 viral infection. The respiratory system was the most frequent infection site (23 for the exposed group and 9 for the unexposed group), followed by skin and subcutaneous tissue (9 for the exposed and 1 for the unexposed), urinary tract (1 for each group), and bone and joints (1 for each group). The rates of treatment discontinuation after serious infections were 2.19/100 PY in the exposed group and 0.22/100 PY in the unexposed group. The rate ratio comparing the exposed group with the unexposed group was 9.98 (95% CI 1.31–76.29), a significant elevation. On the other hand, the rates of treatment discontinuation after SAE other than serious infections were not statistically different between the 2 groups [1.86/100 PY in the exposed group and 0.66/100 PY in the unexposed group; the rate ratio was 2.81 (95% CI 0.79–10.09)].

Table 2. Categories of serious adverse events (SAE) using the system organ class (SOC).

System Organ Class Allocation	No. SAE in Study Patients: Exposed Group, n = 646	Unexposed Group, n = 498	Total
Cardiac disorders	2	1	3
Endocrine disorders	1	0	1
Eye disorders	1	1	2
Gastrointestinal disorders	6	4	10
General disorders and administration site conditions	2	1	3
Hepatobiliary disorders	4	4	8
Infections and infestations	38	12	50
Injury, poisoning, and procedural complications	12	5	17
Metabolism and nutrition disorders	0	1	1
Musculoskeletal and connective tissue disorders	1	1	2
Neoplasms benign, malignant, and unspecified	4	5	9
Nervous system disorders	1	1	2
Renal and urinary disorders	3	2	5
Reproductive system and breast disorders	1	0	1
Respiratory, thoracic, and mediastinal disorders	14	2	16
Skin and subcutaneous tissue disorders	2	1	3
Vascular disorders	3	0	
Total	95	41	136

In the exposed group, the IR of SAE was 16.04/100 PY and the IR of serious infection was 6.42/100 PY. The crude IRR comparing the exposed group with the unexposed group for SAE was 1.78 (95% CI 1.23–2.57) and for serious infections was 2.43 (95% CI 1.27–4.65); both of these IRR were significantly elevated (Table 3).

Contribution of TNF inhibitors to the development of serious infections. Because the background data of the patients differed considerably between the exposed and unexposed groups (Table 1), we performed univariate analysis to identify candidate risk factors for the development of serious infections (data not shown) and selected age, chronic pulmonary diseases, Steinbrocker stage[19], disease activity, corticosteroid dosage, and MTX dosage as covariates for multivariate analyses. We used the Poisson regression model to evaluate the risk for development of serious infection from the use of TNF inhibitors. The use of TNF inhibitors was found to constitute a significant risk factor for serious infection. The relative risk (RR) was 2.37 (95% CI 1.11–5.05, $p = 0.026$; Table 4).

Among the confounding factors, we found that these factors were independently associated with development of serious infection (Table 4): increasing age (RR 1.82 per 10-year increment; 95% CI 1.32–2.52; $p = 0.00031$), chronic pulmonary diseases (RR 2.61; 95% CI 1.38–4.94; $p = 0.0031$), advanced disease (Steinbrocker stage III or IV; RR 2.07; 95% CI 1.07–3.97; $p = 0.03$), and dosage of MTX > 8 mg/week (RR 2.61; 95% CI 1.40–4.86; $p = 0.0024$). When the dosages of MTX and prednisolone (PSL) were recategorized as MTX use (yes/no), MTX dosage > 6 mg/week (yes/no), PSL use (yes/no), and PSL dosage > 5 mg/day (yes/no), or were used as continuous variables, the analyses gave essentially the same results (data not shown).

Risk factors for infection during treatment with the TNF inhibitors infliximab or etanercept. To identify the risk factors contributing to the development of serious infections during treatment with infliximab or etanercept, we compared the background data of those patients who did or did not develop serious infections, using univariate analyses (Table 5). The patients who developed serious infections

Table 3. Number and incidence of serious adverse events (SAE) in patients with rheumatoid arthritis who were treated with (exposed) and without (unexposed) the tumor necrosis factor-α inhibitors infliximab or etanercept.

Event	Exposed Group, n = 646 592.35 PY	Unexposed Group, n = 498 454.74 PY	Crude IRR (95% CI)
All SAE, no. events	95	41	0
IR (/100 PY)	16.04 (12.81–19.26)	9.02 (6.26–11.78)	1.78 (1.23–2.57)
Serious infection, no. events	38	12	
IR (/100 PY)	6.42 (4.38–8.46)	2.64 (1.15–4.13)	2.43 (1.27–4.65)
Serious respiratory tract infection, no. events	23	9	
IR (/100 PY)	3.88 (2.30–5.47)	1.98 (0.69–3.28)	1.96 (0.91–4.24)

PY: patient-years; IR: incidence rate; IRR: incidence rate ratio.

Table 4. Multivariate analysis of independent risk factors for serious infections in the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety (REAL) database. The relative risk (RR) of biologics for development of serious infection for up to 1 year of the observation period was calculated using the Poisson regression model after adjusting for the confounding factors of age, chronic pulmonary disease, Steinbrocker stage, disease activity, corticosteroid dosage, and methotrexate dosage.

	RR (95% CI)	p
TNF inhibitor* (yes)	2.37 (1.11–5.05)	0.026
Age, by decade	1.82 (1.32–2.52)	0.00031
Chronic pulmonary disease (yes)	2.61 (1.38–4.94)	0.0031
Stage III or IV (vs Stage I or II)**	2.07 (1.07–3.97)	0.030
MTX dose > 8.0 mg/wk	2.61 (1.40–4.86)	0.0024
DAS28 (3/CRP)	0.87 (0.66–1.14)	0.31
Prednisolone dose > 7.5 mg/day	1.21 (0.58–2.55)	0.61

* Infliximab or etanercept. ** Steinbrocker classification[19] was used to define RA disease stages. TNF: tumor necrosis factor-α; DAS28: 28-joint count Disease Activity Score; CRP: C-reactive protein; MTX: methotrexate.

Table 5. Comparison of background data for patients with rheumatoid arthritis (RA) who were treated with the tumor necrosis factor inhibitors infliximab or etanercept. Values are mean ± SD, unless otherwise stated.

Factors	Infection, n = 612	Without Infection, n = 34	p
Age, yrs	57.9 ± 13.3	67.1 ± 8.1	< 0.001
Women, %	82.0	82.4	0.961
RA disease duration, yrs	9.3 ± 8.5	13.0 ± 10.2	0.008
Steinbrocker stage (III or IV), %*	53.9	76.4	0.010
DAS28 (3/CRP)	3.9 ± 1.0	3.7 ± 1.2	0.356
MTX dose mg/wk	5.2 ± 3.9	5.6 ± 4.2	0.387
Use of immunosuppressive drugs except for MTX, %**	3.8	2.9	0.636
Corticosteroid use, %	62.0	71.4	0.001
Prednisolone dose, mg/day***	4.0 ± 3.6	4.7 ± 3.4	0.214
Chronic pulmonary disease, %†	20.4	38.2	0.014
Diabetes, %	10.3	17.6	0.143

* Steinbrocker classification[19] was used to define RA disease stages. ** Including tacrolimus, leflunomide, mizoribine, and cyclosporine. *** Converted to corresponding prednisolone dosage. † Including interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, prior pulmonary tuberculosis, and bronchiectasis. DAS28: 28-joint count Disease Activity Score; CRP: C-reactive protein; MTX: methotrexate.

were significantly older ($p < 0.001$) and had longer disease duration ($p = 0.008$) as well as more advanced disease (Steinbrocker stage III or IV; $p = 0.01$). The percentages of patients given corticosteroids and having chronic pulmonary diseases were higher for patients who developed serious infections. The contributions of age, disease duration, corticosteroid use, and chronic pulmonary disease to the development of serious infections in the exposed group were analyzed using the Poisson regression model. This multivariate analysis showed increasing age per 10-year increment (RR 1.97; 95% CI 1.34–2.84) and the use of corticosteroids (RR 2.97; 95% CI 1.04–8.50) to be significantly associated ($p = 0.00058$ and $p = 0.042$, respectively) with the development of serious infection during TNF inhibitor therapy.

DISCUSSION

In our prospective study of a Japanese hospital-based cohort of patients with RA, the multivariate analysis demonstrated that treatment with the biologic TNF inhibitors infliximab or etanercept was associated with an increased risk for serious infections. Increasing age, chronic pulmonary diseases, an advanced disease stage of RA, and dosage of MTX were also identified as independent risk factors for serious infections in this population.

The IR of serious infection in the exposed group (6.4/100 PY; 95% CI 4.4–8.5) is comparable to those reported previously [6.2–6.4/100 PY from a German RA registry and 6.1/100 PY (95% CI 5.7–6.5) from a British RA registry][5,6]. Our data were also consistent with the results of the postmarketing surveillance programs in Japan, which found the IR of serious infection during the first 6 months of anti-TNF therapy was 8.1/100 PY in patients treated with infliximab and 7.7/100 PY for those treated with etanercept[16,17,20]. Schneeweiss, *et al*[8] reported a lower IR for serious infection, 4.8/100 PY (95% CI 3.1–6.6), in patients receiving TNF inhibitors. This difference from our results can probably be

explained by variations in such methodologies as inclusion criteria or definition of infectious events. Schneeweiss, *et al*[8] focused on hospitalizations of elderly patients due to serious bacterial infections while being treated with TNF inhibitors. The IR of SAE and serious infections in the unexposed group of our study were similar to those of other clinical trials conducted in Japan[21,22,23], as well as to those reported from 4 European registries (IR 2.3–3.9/100 PY)[5,6,8,9]. Thus, we postulate that our results did not underestimate the risk of serious infections during treatment with nonbiological DMARD. Examining the infection sites in our study, the respiratory system was the most frequent site for both exposed and unexposed groups, followed by skin and subcutaneous tissue, which is consistent with other epidemiological studies of patients with RA[7,24].

Evaluating patients with RA for predisposing factors for infection prior to initiating TNF inhibitor therapy is important. The independent risk factors identified in our study were in overall agreement with previous reports of predictors of infection among patients with RA[25]. First, the association of corticosteroid use with serious infection, as shown by the multivariate analysis of the exposed group, is consistent with several reports describing corticosteroid use as an important risk factor for infection[8,9]. The relatively low number and rate of serious infections in the unexposed group probably resulted in a lack of enough power to detect the risk from corticosteroid in the analysis of the total population of our study. Second, finding an association between Steinbrocker stage and increased risk for serious infection is also supported by the results of the postmarketing surveillance of infliximab in Japanese patients with RA, which found that Steinbrocker stage III or IV was a predictor for bacterial pneumonia by multiple logistic regression analysis[16]. It has been reported that the Health Assessment Questionnaire (HAQ) score is associated with serious infection in patients with RA[7,11]. Because the HAQ comprises disease activity-related and joint damage-related components[26], it is plausible that joint damage can be a risk factor for serious infection. The results of our study and those of postmarketing surveillance of infliximab in Japan[16] support this concept. Third, we found that MTX dosage was associated with increased risk of serious infection; however, this association disappeared when the unexposed and exposed groups were analyzed separately. According to some reports using cohorts much larger than ours, the immunosuppressive DMARD, such as leflunomide, cyclosporine, and azathioprine, were associated with an increased risk of infection, but MTX was not[8,27]. Others have found the use of MTX to be a risk factor for infection in patients with RA[28]. Further studies are needed to assess any association between MTX dosage and serious infection in a larger number of Japanese patients with RA.

Our study provides the first pharmacoepidemiological evidence of the safety of treatment with the TNF inhibitors infliximab or etanercept in Japanese patients with RA, compared to nonbiological DMARD. In our study cohort, treatment with infliximab or etanercept was associated with increased risk for serious infections when compared to treatment with nonbiological DMARD. The results of our study suggest that careful pharmacovigilance procedures are essential to insure safe use of TNF inhibitors in patients with RA.

ACKNOWLEDGMENT

These hospitals are members of the REAL study group as of April 2010, but were not involved in our study: Sasebo Chuo Hospital, Tokyo Metropolitan Geriatric Hospital, Yokohama City Minato Red Cross Hospital, Kagawa University Hospital, and Kurashiki Kohsai Hospital. We sincerely thank all the rheumatologists who are caring for the patients with RA who are registered in REAL.

APPENDIX

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