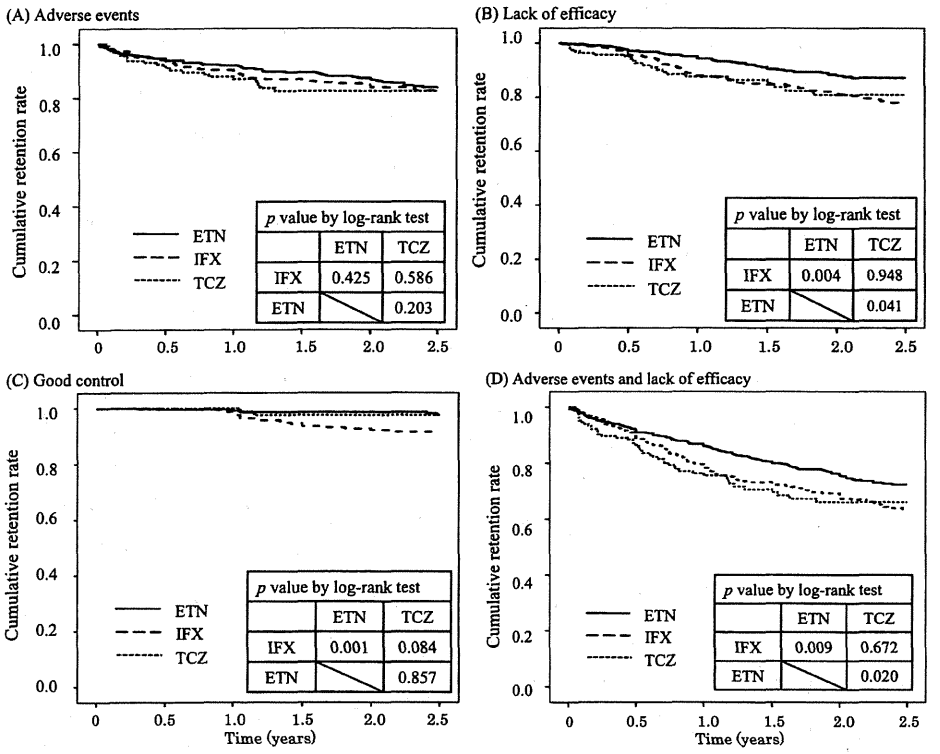

Figure 1 Kaplan-Meier curves for time to discontinuation for each biological agent (etanercept (ETN); infliximab (IFX); tocilizumab (TCZ)). Withdrawal for adverse events (A), lack of efficacy (B), good control (C), and adverse events and lack of efficacy (D) are presented separately. Drug retention rates are compared using the long-rank test among groups. The y axis shows the cumulative retention rates.

reason for discontinuation was LOE in the infliximab group, development of AE in the etanercept group and both in the tocilizumab group (table 2).

The retention rates of biological agents

Because the distribution of reasons for drug discontinuation was significantly different among these biological agents (table 2), we investigated drug retention rates per reason for discontinuation. Kaplan–Meier curves for time to discontinuation for each agent due to AE and LOE are shown in figure 1A,B, respectively. No significant differences existed among the three drugs for treatment discontinuation due to AE. The discontinuation rate due to LOE was significantly lower for etanercept compared with that of infliximab (p=0.004, log-rank test) and tocilizumab (p=0.041) (figure 1B), and the discontinuation rate for infliximab due to good control was significantly higher than that for etanercept (p=0.001, log-rank test) (figure 1C). We combined withdrawals due to AE and LOE to assess treatment failure; etanercept had a significantly lower discontinuation rate due to treatment failure compared with the other two agents (p=0.009 vs infliximab, p=0.020 vs tocilizumab, log-rank test) (figure 1D). To evaluate the possible effects of previous treatment with biological agents on drug discontinuation due to AE and LOE, we compared the retention rates per reason except for good control in the etanercept and tocilizumab groups between biological-naive and non-naive patients (see supplementary figures, available online only). In both groups, there was no significant difference in drug retention rates between biological-naive and non-naive patients. However, we found a numerically higher discontinuation rate of biological agent non-naive patients due to LOE in the tocilizumab group (see supplementary figure S3, available online only).

Multivariate analysis of the risk for discontinuation of biological agents due to AE

We compared patients who discontinued treatment with biological agents due to AE and remaining patients using a univariate analysis (see supplementary table S1, available online only) and used the same variables for the multivariate analysis of table 3. Although we found no significant difference in the use of infliximab and tocilizumab in the univariate analysis (table S1, available online only), the Cox regression hazard model revealed that the adjusted risk for discontinuation due to AE was significantly higher in patients using infliximab (HR 1.69; 95% CI 1.14 to 2.51) and tocilizumab (HR 1.98; 95% CI 1.04 to 3.76) compared with etanercept (table 3). Among the other variables, the risk of discontinuation due to AE was also significantly higher in patients with increasing age by decade (HR 1.64; 95% CI 1.38 to 1.97) and with the previous use of three or more non-biological DMARD (HR 1.86; 95% CI 1.30 to 2.67).

DISCUSSION

To our knowledge, this is the first report comparing drug retention rates among TNF inhibitors and tocilizumab and identifying risk factors causing drug discontinuation due to AE. The major findings of this study are: (1) the reasons for discontinuation were significantly different among the three biological agents studied; (2) the risk of discontinuation due to AE was significantly higher in patients using infliximab and tocilizumab compared with etanercept; and (3) other significant risk factors for the discontinuation due to AE were increasing age and the previous use of three or more non-biological DMARD.

There are some reports describing drug retention rates and reasons for drug discontinuations in patients treated with TNF

Table 3 Multivariate analysis for drug discontinuation due to adverse events in RA patients treated with infliximab, etanercept or tocilizumab*

	HR (95% CI)	p Value
Infliximab (vs etanercept)	1.69 (1.14 to 2.51)	0.009
Tocilizumab (vs etanercept)	1.98 (1.04 to 3.76)	0.037
Age by decade	1.64 (1.38 to 1.97)	<0.001
Class 3 or 4 (vs class 1 or 2)	1.07 (0.74 to 1.54)	0.727
DAS28 (3/CRP) at baseline (per 1.0 increment)	1.03 (0.92 to 1.17)	0.585
Chronic pulmonary disease	1.19 (0.83 to 1.70)	0.336
Diabetes mellitus	0.95 (0.58 to 1.56)	0.841
Concomitant use of oral corticosteroids at baseline	1.15 (0.78 to 1.70)	0.489
Concomitant use of immunosuppressive drugs except for methotrexate at baseline	0.56 (0.20 to 1.55)	0.262
Previous use of three or more non-biological DMARD	1.86 (1.30 to 2.67)	0.001
Previous use of biological agents	1.05 (0.64 to 1.72)	0.842

*Cox regression hazard model analysis, adjusted for the variables included in the table, gender and calendar year.
Class, Steinbrocker's class; CRP, C-reactive protein;
DAS28, disease activity score including 28-joint count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.

inhibitors.[14 16–18 20 22 24 26 27 33–35] Among patients stopping treatment with TNF inhibitors due to any reason, approximately half of those discontinued due to AE, and the proportions of patients who discontinued the agents due to AE or LOE were similar in each group in the Swiss[14] and the French[16] registries. In this study, AE and LOE were the two major reported reasons for discontinuation, with similar percentages also for all three groups, but the discontinuation rate due to good control in the infliximab group was significantly higher than those in the other two groups. Several studies have shown successful discontinuation of treatment with infliximab[10 36–40] and tocilizumab[41] without flare of RA, but the reported percentage of patients who could discontinue infliximab was higher compared with tocilizumab. In contrast, there is no evidence of the successful discontinuation of treatment for etanercept to date. Therefore, our results might be influenced by physicians' expectations for successful discontinuation of biological agents based on previous reports.

We observed a significantly lower discontinuation rate due to LOE in the etanercept group compared with infliximab and tocilizumab (figure.1B), which can be explained by the following reasons. First, treatment with infliximab induces the formation of human antichimeric antibody in some patients, which may lead to LOE or adverse drug reactions.[42 43] The prevalence of antidrug antibodies in RA patients who were treated with infliximab is much higher compared with etanercept[44 45] and tocilizumab.[15 46] Second, the tocilizumab group had a significantly lower percentage of biological-naive patients, which may be associated with a less favourable response to treatment.[47 48] In the tocilizumab group, we confirmed that the discontinuation rate due to LOE was numerically lower in the biological-naive patients compared with biological agent non-naive patients (see supplementary figure S3, available online only).

In this study, we limited our multivariate analyses to the risk factors associated with discontinuation due to AE. Some previous studies identified risk factors for overall discontinuation in patients treated with TNF inhibitors.[6 17 26] Because treatments with biological agents are discontinued for various reasons, as shown in table 1, we postulated that it would not be appropriate to build a multivariate model for overall discontinuation from a medical point of view. In REAL, we did not collect measures of patients' disease activity, such as the disease activity score in 28 joints (DAS28), when patients stopped treatment with biological agents, and we could not define discontinuation due to LOE by using objective criteria. Therefore, we opted not to analyse risk factors for discontinuation due to LOE. The number of patients who discontinued the agents due to good control was too small to analyse associated factors using multivariate analysis.

Increasing age was also identified as a risk factor associated with the discontinuation of biological agents due to AE, data supported by a previous report.[16] In all three groups, infections were most frequent among AE leading to drug discontinuation (table 2). It is plausible that increasing age contributes to discontinuation because of an increasing risk of RA patients for infection[29 49] with age. Higher numbers of previous non-biological DMARD use suggests cases difficult to treat, with high disease activity or long-standing disease. Compatible with this possibility, patients who had been treated with three or more non-biological DMARD before enrolment in REAL had a significantly longer disease duration with more advanced disease stages and classes than those receiving less than three non-biological DMARD (data not shown). It has been reported that advanced stage or higher disease activity was reported as a risk for infections.[8 29 50]

Our study has limitations. First, we have to mention the possibility of selection bias in this study. However, because almost all patients who were registered from the participating hospitals of our study to the all-cases postmarketing surveillance programmes for each biological DMARD were enrolled in REAL, selection bias was substantially decreased. Second, we analysed the first biological agent administered to each patient at or after enrolment in REAL. However, these biological agents were not necessarily truly the first one used for each patient; rates of biological-naive patients were significantly different among the three groups (table 1), indicating the presence of channelling bias. Therefore, we adjusted for the previous use of biological agents in the multivariate analysis.

In conclusion, we have presented the first epidemiological data that directly compare TNF inhibitors and tocilizumab in a single cohort. We demonstrated that reasons for discontinuation were significantly different among the biological agents and that the use of infliximab and tocilizumab had a significantly higher risk of treatment discontinuation due to AE compared with etanercept after adjusting for various confounding factors.

Values are the mean±SD, unless otherwise stated. For univariate analysis, the χ^2 test for categorical variables and the Student's t test or Mann–Whitney test were used to compare continuous variables among groups.

Steinbrocker's classification[30] was used to definite RA disease stages and classes.

The immunosuppressive drugs used were tacrolimus, leflunomide, mizoribine and ciclosporin.

The oral corticosteroid dose was converted to the equivalent prednisolone dosage. Methotrexate and corticosteroid doses are shown as the mean±SD among users of these drugs.

Chronic pulmonary diseases include interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, previous pulmonary tuberculosis and bronchiectasis.

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Author affiliations [1]Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
[2]Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
[3]Clinical Research Center, Tokyo Medical and Dental University Hospital, Tokyo, Japan
[4]Department of Rheumatology/Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan
[5]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[6]Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan
[7]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[8]Department of Internal Medicine II, Hokkaido University, Graduate School of Medicine, Sapporo, Japan
[9]Department of Rheumatology, Tokyo Metropolitan Police Hospital, Tokyo, Japan
[10]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan
[11]Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[12]Department of Internal Medicine, Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan
[13]Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan
[14]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan
[15]Rheumatic and Collagen Disease Center, Sasebo Chuo Hospital, Nagasaki, Japan
[16]Department of Rheumatology, Kobe University Graduate School of Medicine, Kobe, Japan
[17]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
[18]Department of Allergy and Rheumatology, The University of Tokyo, Tokyo, Japan
[19]Global Center of Excellence (GCOE) Program; International Research Center for Molecular Science in Tooth and Bone Diseases, Tokyo Medical and Dental University, Tokyo, Japan

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ARD

Drug retention rates and relevant risk factors for drug discontinuation due to adverse events in rheumatoid arthritis patients receiving anticytokine therapy with different target molecules

Ryoko Sakai, Michi Tanaka, Toshihiro Nanki, et al.

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ORIGINAL ARTICLE

Time-Dependent Increased Risk for Serious Infection From Continuous Use of Tumor Necrosis Factor Antagonists Over Three Years in Patients With Rheumatoid Arthritis

RYOKO SAKAI,[1] YUKIKO KOMANO,[1] MICHI TANAKA,[1] TOSHIHIRO NANKI,[1] RYUJI KOIKE,[1] HAYATO NAGASAWA,[2] KOICHI AMANO,[2] ATSUO NAKAJIMA,[3] TATSUYA ATSUMI,[4] TAKAO KOIKE,[4] ATSUSHI IHATA,[5] YOSHIAKI ISHIGATSUBO,[5] KAZUYOSHI SAITO,[6] YOSHIYA TANAKA,[6] SATOSHI ITO,[7] TAKAYUKI SUMIDA,[7] SHIGETO TOHMA,[8] NAOTO TAMURA,[9] TAKAO FUJII,[10] TAKAHIKO SUGIHARA,[11] ATSUSHI KAWAKAMI,[12] NOBORU HAGINO,[13] YUKITAKA UEKI,[14] AKIRA HASHIRAMOTO,[15] KENJI NAGASAKA,[16] NOBUYUKI MIYASAKA,[1] AND MASAYOSHI HARIGAI,[1] FOR THE REAL STUDY GROUP

Objective. To investigate associations between continuous treatments with tumor necrosis factor (TNF) antagonists and risk for developing serious infections (SIs) over 3 years in Japanese patients with rheumatoid arthritis (RA) enrolled in the Registry of Japanese RA Patients for Long-Term Safety (REAL) database.

Methods. We analyzed 727 RA patients who had started either infliximab or etanercept (the anti-TNF group; 1,480.1 patient-years [PY]) and 571 RA patients who had started conventional nonbiologic disease-modifying antirheumatic drugs (the unexposed group; 1,104.1 PY) at the time of enrollment in the REAL. We assessed the occurrence of SIs within a 3-year observation period, including the period after switching to other TNF antagonists, and all SIs, unlimited to the first one in each patient as reported in other studies, to evaluate the real safety of TNF antagonists in daily practice.

Results. The incidence rate of SIs per 100 PY was 5.54 (95% confidence interval [95% CI] 4.44–6.84) in the anti-TNF group and 2.72 (95% CI 1.87–3.83) in the unexposed group. Poisson regression analysis revealed that the relative risk (RR) of continuous use of TNF antagonists for SIs after adjusting for baseline and time-dependent covariates was significantly elevated both overall (1.97, 95% CI 1.25–3.19) and for the first year (2.40, 95% CI 1.20–5.03), but not for the second and third years combined (1.38, 95% CI 0.80–2.43). The adjusted RR for SIs of etanercept compared to infliximab was not significantly elevated.

Conclusion. Continuous anti-TNF therapy was significantly associated with increased risks for developing SIs during, but not after, the first year.

INTRODUCTION

Biologic disease-modifying antirheumatic drugs (DMARDs) have been widely used to treat patients with rheumatoid arthritis (RA) whose response to conventional DMARD therapy was inadequate (1–4). In Japan, 6 biologic DMARDs (infliximab, etanercept, adalimumab, tocilizumab, abatacept, and golimumab) have been approved and widely used in clinical practice. The criterion for indication for

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[1]Ryoko Sakai, MPharm, Yukiko Komano, MD, PhD, Michi Tanaka, MD, PhD, Toshihiro Nanki, MD, PhD, Ryuji Koike, MD, PhD, Nobuyuki Miyasaka, MD, PhD, Masayoshi Harigai, MD, PhD: Tokyo Medical and Dental University, Tokyo, Japan; [2]Hayato Nagasawa, MD, PhD, Koichi Amano, MD, PhD: Saitama Medical University, Saitama, Japan; [3]Atsuo Nakajima, MD, PhD: Tokyo Metropolitan Police Hospital, Tokyo, Japan; [4]Tatsuya Atsumi, MD, PhD, Takao Koike, MD, PhD;

Significance & Innovations

- Using a Japanese rheumatoid arthritis (RA) patient registry, we show for the first time in Asia that the continuous use of tumor necrosis factor (TNF) antagonists over a 3-year observation period was associated with a 2-fold increased risk for serious infections (SIs) compared to nonbiologic disease-modifying antirheumatic drugs (DMARDs). This elevation, however, was time dependent and significant only for the first year, not for the second and third years combined.
- To redeem methodologic shortcomings in previous reports, we examined all SIs occurring during treatment with TNF antagonists, including those after switching to other TNF antagonists. We used not only baseline but also time-dependent variables as candidates for risk factors for SIs in multivariate analysis because disease activity of RA and the dose of drugs such as corticosteroids and methotrexate are subject to change during treatment.
- Over 3 years, the incidence rate of SIs in the etanercept group was numerically higher than that of the infliximab group, but the risk for SIs from treatment with etanercept was not significantly different from that of infliximab after adjusting for covariates.

infliximab or the other 5 biologic DMARDs, according to Japanese labeling, consists of inadequate response to methotrexate (MTX) or nonbiologic DMARDs, respectively. In addition, Japanese rheumatologists follow the guidelines proposed by the Japan College of Rheumatology (5,6).

Hokkaido University, Sapporo, Japan; [5]Atsushi Ihata, MD, PhD, Yoshiaki Ishigatsubo, MD, PhD: Yokohama City University, Yokohama, Japan; [6]Kazuyoshi Saito, MD, PhD, Yoshiya Tanaka, MD, PhD: University of Occupational and Environmental Health, Kitakyushu, Japan; [7]Satoshi Ito, MD, PhD, Takayuki Sumida, MD, PhD: University of Tsukuba, Tsukuba, Japan; [8]Shigeto Tohma, MD: Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan; [9]Naoto Tamura, MD, PhD: Juntendo University School of Medicine, Tokyo, Japan; [10]Takao Fujii, MD, PhD: Kyoto University, Kyoto, Japan; [11]Takahiko Sugihara, MD, PhD: Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan; [12]Atsushi Kawakami, MD, PhD: Nagasaki University, Nagasaki, Japan; [13]Noboru Hagino, MD: University of Tokyo, Tokyo, Japan; [14]Yukitaka Ueki, MD, PhD: Sasebo Chuo Hospital, Nagasaki, Japan; [15]Akira Hashiramoto, MD, PhD: Kobe University, Kobe, Japan; [16]Kenji Nagasaka, MD, PhD: Ome Municipal General Hospital, Ome, Japan.

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Address correspondence to Masayoshi Harigai, MD, PhD, Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan. E-mail: mharigai.mpha@tmd.ac.jp.

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Although biologic DMARDs have superior clinical efficacy for patients with RA, there are concerns about increased risk for infection (7). Prevention of infections in RA patients who are treated with immunosuppressive drugs is relevant because the incidence rate (IR) of infections is already higher in patients with RA than in the general population, and infection is a major factor hampering proper management of the disease and influencing prognosis (8–10). Infection was the most frequent serious adverse event (SAE) reported in postmarketing surveillance programs for infliximab and etanercept in Japan: the most prevalent infectious disease was pneumonia, and higher IRs of tuberculosis and *Pneumocystis jiroveci* pneumonia (PCP) were reported compared to Western countries (11–13). We established the Registry of Japanese RA Patients for Long-Term Safety (REAL) in 2005 and, utilizing this database, recently reported that treatment with either tumor necrosis factor (TNF) antagonist infliximab or etanercept for up to 1 year was associated with increased risk for serious infections (SIs) compared to treatment with nonbiologic DMARDs (14). Recent data from prospective observational studies in Europe and the US also suggest that the risk for infection was higher in RA patients treated with biologic DMARDs, at least in the short term (15–18), and disappeared with increasing treatment duration (15,16,18–20).

In clinical practice, rheumatologists often switch from the initial TNF antagonist to an alternative TNF antagonist when the patient shows insufficient efficacy or develops an adverse event. Some patients also experience more than one adverse event during treatment with TNF antagonists. In previous reports from prospective cohort studies, observation was stopped after switching to another TNF antagonist or after the first adverse event (18,21–23); therefore, second or third adverse events and those occurring after switching TNF antagonists were not analyzed (18,21–23). In addition, the time dependency of covariates such as corticosteroid dose and disease activity was not included in some studies (14,15,19–24). To understand the real safety of TNF antagonists for patients with RA, it is essential to design an epidemiologic study that evaluates all adverse events during continuous treatment with these agents. However, in Japan, as well as in Asia overall, there are no safety data from prospective cohort studies with an observation period longer than 1 year in RA patients receiving TNF antagonists. Because differences in genetic, environmental, and medical factors in each geographic region may influence the safety of biologic DMARDs (25), it is prudent to compare the safety of biologic DMARDs from various countries or regions. The primary purpose of this study was to assess the risk for SIs associated with continuous use of infliximab or etanercept for 3 years, including the period after switching to other TNF antagonists, and its trend over time, and to identify independent risk factors after adjusting for time-dependent covariates. In a secondary analysis, we focused on the first TNF antagonist used in each patient to investigate differences in the risk for SIs among the agents.

PATIENTS AND METHODS

Database. The REAL is an ongoing prospective cohort established to investigate the long-term safety of biologic DMARDs in patients with RA. Details of the REAL have been previously described (14,26). In brief, 27 institutions participated in the REAL, including 16 university hospitals and 11 referring hospitals. The criteria for enrollment in the REAL include those patients meeting the 1987 American College of Rheumatology criteria for RA (27) with written informed consent and starting or switching treatment with biologic DMARDs (the biologics exposed group) or starting, adding, or switching nonbiologic DMARDs (the biologics unexposed group) at the time of study entry. Until the end of 2007, patients already receiving treatment with nonbiologic DMARDs at the time of study entry were also enrolled in the unexposed group. To facilitate enrollment in the REAL, participating physicians were asked to enroll their patients already registered to postmarketing surveillance programs previously implemented by pharmaceutical companies for biologic DMARDs (11,12). In addition, our investigators were also encouraged to enroll as many patients as possible who fulfilled the inclusion criteria (14). For this study, data were retrieved from the REAL database on November 30, 2009. This study was in compliance with the Declaration of Helsinki (revised in 2008). The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and the other participating institutions (see Appendix A for members of the REAL Study Group and their affiliates).

Data collection. Each patient's recorded baseline data included demography, disease activity, comorbidities, treatments, and laboratory data at the start of the observation period. A followup form was submitted every 6 months by the participating physicians to the REAL Data Center at the Department of Pharmacovigilance of Tokyo Medical and Dental University to report the occurrence of SAEs, current RA disease activity, treatments, and clinical laboratory data. We collected the Steinbrocker class (28) as the measurement for patient physical disability instead of the Health Assessment Questionnaire disability index at baseline (29). Using this protocol, SAEs were reported at regular followup times every 6 months. The REAL Data Center checked all of the data sent by attending physicians to improve the quality of data, and the participating physicians in each hospital confirmed them on the web site of the REAL.

Anti-TNF group. In the biologics exposed group, there were 727 patients with RA who started infliximab or etanercept at enrollment in the REAL (anti-TNF group; 1,480.1 patient-years [PY]); 335 started infliximab (infliximab group) and 392 started etanercept (etanercept group). In the infliximab group, 67 patients were switched to either etanercept (58 patients), tocilizumab (8 patients), or adalimumab (1 patient), and 74 patients stopped treatment with infliximab during the study observation period. The remaining patients continued treatment with infliximab

throughout. In the etanercept group, 60 patients were switched to either infliximab (27 patients), tocilizumab (25 patients), or adalimumab (8 patients), and 62 patients stopped administration of etanercept during the study observation period. The remaining patients continued etanercept treatment throughout. The overall survival rates of the first biologic agent at year 3 were 0.48 (95% confidence interval [95% CI] 0.41–0.55) for infliximab and 0.61 (95% CI 0.55–0.66) for etanercept. Our analysis was restricted to infliximab or etanercept because few patients receiving adalimumab or tocilizumab were registered in the REAL database and golimumab and certolizumab pegol were not approved in Japan at the time this study was conducted.

Unexposed group. Among 574 RA patients in the biologics unexposed group, 3 patients had received biologic DMARDs within 90 days before their enrollment in the REAL. These 3 patients were excluded from our analysis in consideration of the pharmacokinetic and pharmacodynamic property of biologic DMARDs and their possible effects on development of infection. Fifteen patients who had received biologic DMARDs and stopped them over 90 days before their enrollment in the REAL were included in this analysis. Therefore, 571 RA patients who initiated or were receiving nonbiologic DMARDs and not receiving biologic DMARDs at enrollment in the REAL were included in the unexposed group (1,104.1 PY). At enrollment, 347 patients (60.8%) of the patients in the unexposed group were being treated with MTX, 127 patients (22.4%) with sulfasalazine, 103 patients (18.0%) with tacrolimus, 95 patients (16.6%) with bucillamine, and 29 patients (5%) with other nonbiologic DMARDs.

Followup. For those patients who initiated nonbiologic DMARDs or biologic DMARDs at entry, the start of the observation period was the date these agents were first administered. For those patients enrolled in the unexposed group already receiving treatment with nonbiologic DMARDS at the time of study entry, the observation period started from the date of their enrollment in the REAL database.

Observation was stopped either 3 years after the start of the observation period, the day a patient died or met the exclusion criteria (14), or on November 30, 2009, whichever came first. For the unexposed group, stopping all nonbiologic DMARDs or starting any biologic DMARDs stopped followup. For the anti-TNF group, stopping therapy with either infliximab or etanercept ended observation. Patients were followed even after development of SAEs, as long as they did not meet the above criteria for stopping observation. The date of the last administration of infliximab or etanercept was retrieved from medical records and reported by the participating physicians. The mean ± SE followup was 2.04 ± 0.92 years for the anti-TNF group and 1.93 ± 0.99 years for the unexposed group. Figure 1 shows the number of patients for each year and the number who dropped out from each group during observation. Four hundred forty-two patients (34%) of all patients (n = 1,298) were followed up for 3 years.

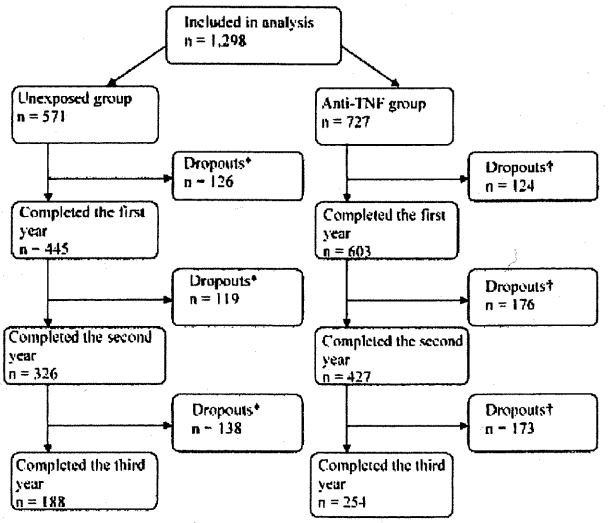

Figure 1. Distribution of numbers of patients with rheumatoid arthritis during the 3-year observation period. * = dropouts from the unexposed group include patients who started biologic disease-modifying antirheumatic drugs (DMARDs) or patients whose observation did not complete the next 1 year; † = dropouts from the anti–tumor necrosis factor (anti-TNF) group include patients who stopped infliximab or etanercept or switched to biologic DMARDs, except infliximab and etanercept, or patients whose observation did not complete the next 1 year.

Definition of SAEs. Our definition of an SAE, including an SI, was based on the report by the International Conference on Harmonisation (30). In addition, bacterial infections that required intravenous administration of antibiotics, as well as opportunistic infections, were also regarded as SAEs (14) (see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Statistical analysis. Crude IRs per 100 PY and crude IR ratios (IRRs) with their 95% CIs were calculated. We conducted 2 analyses in this study. In the primary analysis (analysis 1), risk factors for SIs during continuous treatment with infliximab or etanercept for up to 3 years were identified. We also calculated the risk of TNF antagonists for SIs in the first year and in the second and third years combined to investigate time dependence of the risk. In the secondary analysis (analysis 2), the risks for SIs were compared between treatment with infliximab and etanercept.

Analysis 1. We included both patient groups and the entire observation period for each patient as described above for analysis 1 and added risk windows as follows. When a patient no longer received either infliximab or etanercept, the patient was excluded from the study on the day of the last administration of the agents and a 90-day postdiscontinuation risk window was applied (14). Any SAEs occurring within the risk window were attributed to the effects of the TNF antagonists. No risk window was needed for the unexposed group. For multivariate analysis, Poisson regression models were employed to estimate

Table 1. Comparison of RA patients treated with or without TNF antagonists infliximab or etanercept at the start of the observation period*

	Unexposed group (n = 571)	All anti-TNF groups (n = 727)	Infliximab group (n = 335)	Etanercept group (n = 392)	P†
Age, years	59.3 ± 13.1	56.3 ± 13.4‡	53.7 ± 13.9	58.5 ± 12.7	< 0.001
Women, %	83.2	82.0	79.3	85.1	0.045
Disease duration, years	8.9 ± 9.3	9.5 ± 8.6‡	8.1 ± 8.0	10.6 ± 9.0	< 0.001
Steinbrocker class 3 or 4, %§	10.7	30.7‡	28.4	32.7	0.211
Steinbrocker stage III or IV, %§	39.6	53.0‡	45.1	59.7	< 0.001
DAS28-CRP	3.4 ± 1.2	4.5 ± 1.2‡	4.6 ± 1.1	4.5 ± 1.3	0.197
N	567	723	335	388	
MTX use, %	60.8	68.8‡	99.1	42.9	< 0.001
MTX dosage, mg/week	6.4 ± 2.0	7.6 ± 2.2‡	7.9 ± 2.2	7.0 ± 2.1	< 0.001
MTX dosage >8 mg/week, %	4.4	10.6‡	18.2	4.1	< 0.001
Use of immunosuppressive drugs except for MTX, %¶	20.1	4.3‡	1.2	6.9	< 0.001
Oral corticosteroid use, %	58.3	71.5‡	69.0	73.7	0.16
Prednisolone or equivalent dosage of corticosteroids, mg/day	4.6 ± 2.1	5.7 ± 3.0‡	5.3 ± 2.7	6.0 ± 3.2	0.006
Prednisolone or equivalent dosage of corticosteroids ≥10 mg/day, %	1.9	9.1‡	5.7	12.0	0.003
No. of previous DMARDs	2.2 ± 1.2	2.5 ± 1.2‡	2.3 ± 1.1	2.7 ± 1.2	< 0.001
Chronic pulmonary disease, %#	18.7	21.6	11.9	29.8	< 0.001
Diabetes mellitus, %	5.8	12.0‡	8.7	14.8	0.011

* Values are the mean ± SD unless otherwise indicated. For univariate analysis, the chi-square test for categorical variables and the Student's *t*-test or Mann-Whitney test were used to compare continuous variables among groups. RA = rheumatoid arthritis; TNF = tumor necrosis factor; DAS28-CRP = 3-variable Disease Activity Score including 28-joint counts using the C-reactive protein level; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs.
† Between the 2 anti-TNF antagonists.
‡ $P < 0.05$ versus the unexposed group.
§ Steinbrocker classification (28) was used to define RA disease stages and classes.
¶ Immunosuppressive drugs include tacrolimus, leflunomide, mizoribine, and cyclosporine.
# Chronic pulmonary diseases include interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, prior pulmonary tuberculosis, and bronchiectasis.

the risk for SIs with TNF antagonist treatment. To analyze the time-dependent risk for SIs, observation periods were divided into the first year and the second and third years combined.

Analysis 2. To compare the risk for SIs between the use of infliximab and etanercept in the anti-TNF group, the treatment period with the first TNF inhibitor for each patient was evaluated without setting a risk window because most of the patients who had stopped the first biologic agent started treatment with the second one immediately. We applied propensity score (PS) methodology to calculate the likelihood of being treated with TNF antagonists. First, we made a multivariate logistic regression model with the use of TNF antagonists as the dependent variable and the following as independent variables: age, sex, the 3-variable Disease Activity Score including 28-joint counts using the C-reactive protein level (DAS28-CRP), the presence of chronic pulmonary comorbidity, diabetes mellitus, calendar year of entry in the REAL, Steinbrocker stage (III or IV), MTX (≤8 or >8 mg/week), and oral corticosteroid (prednisolone or equivalent dosage <10 or ≥10 mg/day) at enrollment. We applied the Hosmer-Lemeshow goodness-of-fit test to assess how effectively the model described the outcome variable (i.e., the use of TNF antagonist: yes/no). We used the PS to select representative patients receiving TNF antagonist treatment: the patients with a PS >0.4 were included in analysis 2 and different cutoff values for PS were used for sensitivity analyses (31). To compare the risk for SIs between etanercept and infliximab, we employed Poisson regression models in the anti-TNF group patients with various combinations of adjusting factors, including the PS, to calculate the relative risks (RRs) of etanercept with 95% CIs, using infliximab as the reference.

These statistical analyses were conducted using SPSS, version 16.0, and R statistical language software, version 2.8.1. All *P* values were 2-tailed and *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of patients. This study included a total of 1,298 patients: 727 in the anti-TNF group and 571 in the unexposed group. Baseline data for the patients are shown in Table 1. Compared to the unexposed group, the anti-TNF group was younger ($P < 0.001$), had more severe disease activity ($P < 0.001$), and was treated with higher doses of MTX ($P < 0.001$) and oral corticosteroids ($P < 0.001$). Significantly more patients with diabe-

Table 2. Number and IRs of SAEs in RA patients treated with and without the TNF antagonists infliximab or etanercept*

	Unexposed group (n = 571)	Anti-TNF group			Etanercept vs. infliximab, crude IRR (95% CI)	Anti-TNF vs. unexposed group, crude IRR (95% CI)
		All (n = 727)†	Infliximab (n = 335)‡	Etanercept (n = 392)§		
Patient-years (PY)	1,104.1	1,480.1	583.31	787.94		
All SAEs					1.49 (1.10–2.03)	1.67 (1.31–2.13)
No. of events	95	213	61	123		
IR/100 PY (95% CI)	8.60 (7.00–10.47)	14.39 (12.55–16.42)	10.46 (8.07–13.34)	15.61 (13.03–18.56)		
Serious infection					1.16 (0.72–1.87)	2.04 (1.34–3.10)
No. of events	30	82	28	44		
IR/100 PY (95% CI)	2.72 (1.87–3.83)	5.54 (4.44–6.84)	4.80 (3.26–6.84)	5.58 (4.11–7.42)		
Serious respiratory tract infection					1.20 (0.65–2.24)	1.96 (1.10–3.48)
No. of events	17	42	16	26		
IR/100 PY (95% CI)	1.45 (0.86–2.30)	2.84 (2.07–3.80)	2.74 (1.63–4.35)	3.30 (2.21–4.76)		
Serious infection leading to death					NA	0.75 (0.15–3.69)
No. of events	3	3	0	3		
IR/100 PY (95% CI)	0.27 (0.08–0.72)	0.20 (0.06–0.54)	0	0.38 (0.11–1.02)		

* Note that the number of severe adverse events (SAEs) in the All column is not the sum of the Infliximab and Etanercept columns. IRs = incidence rates; TNF = tumor necrosis factor; IRR = IR ratio; 95% CI = 95% confidence interval; NA = not applicable.
† The continuous treatment period with infliximab or etanercept for each patient was evaluated.
‡ Patients with rheumatoid arthritis (RA) given infliximab as the first TNF inhibitor in the Registry of Japanese RA Patients for Long-Term Safety (REAL) were included. The treatment period with infliximab for each patient was evaluated.
§ Patients with RA given etanercept as the first TNF inhibitor in the REAL were included. The treatment period with etanercept for each patient was evaluated.

tes mellitus ($P < 0.001$) were seen in the anti-TNF group compared to the unexposed group. In the anti-TNF group, the etanercept group compared to the infliximab group was older ($P < 0.001$), had a longer disease duration ($P < 0.001$), used MTX less frequently ($P < 0.001$), was treated with higher doses of oral corticosteroids ($P = 0.006$), and had higher percentages of chronic pulmonary comorbidity ($P < 0.001$) (see Table 1 for definition) and diabetes mellitus ($P = 0.011$) (Table 1).

Types and occurrence of SAEs. Among the 1,298 patients, 308 SAEs were reported during the observation period, 95 in the unexposed group and 213 in the anti-TNF group. The crude IRR comparing the anti-TNF group with the unexposed group for SAEs was 1.67 (95% CI 1.31–2.13) and for SIs was 2.04 (95% CI 1.34–3.10); both of these IRRs were significantly elevated. The IRs of SAEs, SIs, and serious respiratory tract infections in the infliximab group and the etanercept group are shown in Table 2. The crude IRR comparing the infliximab group with the etanercept group for SAEs was 1.49 (95% CI 1.10–2.03) and for SIs was 1.16 (95% CI 0.72–1.87). The IRs of SAEs, SIs, serious respiratory tract infections, and SIs leading to death are summarized in Table 2.

In the anti-TNF group, there were 82 SIs, including 21 opportunistic (14 cases of herpes zoster, 4 PCP, 3 pulmonary cryptococcosis, and 1 pulmonary nontuberculous mycobacterial infection) and 61 other infections. In the unexposed group, 30 SIs occurred, including 12 opportunistic (4 cases of herpes zoster, 3 PCP, 2 pulmonary tuberculosis, and 3 pulmonary nontuberculous mycobacterial infections) and 18 other infections. The names of the SIs in each site of infection are listed in Table 3. The respiratory system was the most frequent site of infection (n = 59), followed by skin and subcutaneous tissue (n = 24), gastrointestinal (n = 6), urinary tract (n = 5), and bone and joints (n = 5). Four of the latter 5 patients had histories of joint surgery. Three patients in each group died from SIs.

Continuous treatment with TNF antagonists and other risk factors contributing to the development of SIs (analysis 1). We initially performed univariate analyses to compare patients who did and did not develop SIs (data not shown) and selected the following variables for multivariate analysis: age, sex, chronic pulmonary comorbidity, diabetes mellitus, disease duration, calendar year, the number of previous DMARDs, Steinbrocker class, the use of immunosuppressive drugs, mean DAS28-CRP, and the mean dose of MTX and oral corticosteroids during the observation period. We used Poisson regression models and identified continuous use of TNF inhibitors as an independent risk factor for the development of SIs (RR 1.97, 95% CI 1.25–3.19; $P = 0.0045$) (Table 4). Among the confounding factors, we found that increasing age (RR 1.45 per 10-year increment, 95% CI 1.20–1.77; $P < 0.001$), chronic pulmonary comorbidity (RR 1.77, 95% CI 1.15–2.70; $P = 0.009$), mean DAS28-CRP score (RR 1.33, 95% CI 1.05–1.66; $P = 0.015$), mean dosage of MTX >8 mg/week (RR 2.14, 95% CI 1.15–3.87; $P = 0.013$), and mean dosage of oral prednisolone ≥10 mg/day (RR 2.49, 95% CI 1.08–5.50; $P = 0.027$) were significantly associated with SIs. The

Table 3. Classification of serious infections*

Site and name of infection	No. of infections		No. of deaths	
	Anti-TNF group	Unexposed group	Anti-TNF group	Unexposed group
Pulmonary				
Bacterial pneumonia	27	9	1	2
Fungal pneumonia†	7	3	0	1
Bronchitis	4	0	0	0
Nontuberculous mycobacterial infection	1	3	0	0
Empyema	1	0	0	0
Tuberculosis	0	2	0	0
Aspiration pneumonia	1	0	1	0
Infectious pneumatocele	1	0	0	0
Total	42	17	2	3
Skin				
Herpes zoster	14	4	0	0
Cellulitis	4	2	0	0
Total	18	6	0	0
Gastrointestinal				
Infectious gastroenteritis	3	0	0	0
Acute suppurative cholangitis	1	0	0	0
Appendicitis	1	0	0	0
Infection due to drain replacement‡	0	1	0	0
Total	5	1	0	0
Urinary				
Pyelonephritis	3	1	0	0
Urinary tract infection	1	0	0	0
Total	4	1	0	0
Bone and joints				
Infectious arthritis	3	1	0	0
Osteomyelitis	0	1	0	0
Total	3	2	0	0
Others				
Sepsis	4	1	0	0
Surgical wound infection	0	2	0	0
Bacteremia	1	0	0	0
Bacterial meningitis	1	0	1	0
Sinusitis	1	0	0	0
Viral meningitis	1	0	0	0
Unidentified	2	0	0	0
Total	10	3	1	0

* Anti-TNF = anti–tumor necrosis factor.
† Fungal pneumonia included *Pneumocystis jiroveci* pneumonia and cryptococcal pneumonia.
‡ For the treatment of cholangiocellular carcinoma.

Poisson regression analysis also revealed that the RR of TNF inhibitors in the first year was significantly elevated (RR 2.40, 95% CI 1.20–5.03), but not in the second and third years combined (RR 1.38, 95% CI 0.80–2.43).

Comparison of risk for SIs between infliximab and etanercept (analysis 2). We next investigated possible differences between the TNF inhibitors in their contribution to risk for development of SIs. The PS of each patient was calculated by logistic regression model as described in the Methods. The model fit well; the Hosmer-Lemeshow goodness-of-fit statistics did not show a significant difference between observed and predicted frequencies (P = 0.164). The patients with a PS of <0.4 (17.6% of the infliximab group and 20.9% of the etanercept group) were considered not representing those receiving TNF antagonists and we excluded them from the following analysis. We constructed 3 Poison regression models to calculate the RR from the use of etanercept for the development of SIs compared to infliximab. In the first model, we adjusted for age, sex, Steinbrocker class, chronic pulmonary comorbidity, diabetes mellitus, observation period, and the PS. The second model added the mean dosage of MTX (≤8 or >8 mg/week) and the mean dosage of oral corticosteroids (<10 or ≥10 mg prednisolone or equivalent/day) to the adjusting factors in the first model. The third model added the calendar year and the number of previous nonbiologic DMARDs to the adjusting factors in the second

Table 4. Multivariate analysis of independent risk factors for serious infections during continuous use of TNF antagonists in the Registry of Japanese Rheumatoid Arthritis Patients for Long-Term Safety database*

	RR (95% CI)†	P
TNF antagonist (infliximab or etanercept)	1.97 (1.25–3.19)	0.0045
Age by decade	1.45 (1.20–1.77)	< 0.001
Chronic pulmonary disease	1.77 (1.15–2.70)	0.009
Diabetes mellitus	1.20 (0.69–1.97)	0.49
Mean DAS28-CRP (per 1.0 increment)	1.33 (1.05–1.66)	0.015
Mean MTX dosage >8.0 mg/week‡	2.14 (1.15–3.87)	0.013
Mean prednisolone dosage ≥10 mg/day‡	2.49 (1.08–5.50)	0.027

* TNF = tumor necrosis factor; RR = relative risk; 95% CI = 95% confidence interval; DAS28-CRP = 3-variable Disease Activity Score including 28-joint counts using the C-reactive protein level; MTX = methotrexate.
† The RRs of biologic agents for development of serious infection for up to 3 years of the observation period were calculated using the Poisson regression model after adjusting for confounding factors of age, sex, disease duration, chronic pulmonary disease, diabetes mellitus, Steinbrocker class (28), calendar year, number of previous disease-modifying antirheumatic drugs, observation period, disease activity, immunosuppressive drugs, corticosteroid dose, and MTX dose.
‡ Mean dosage during the observation period.

model. The RR for using etanercept compared to infliximab in the first model was 1.28 (95% CI 0.73–2.30, $P = 0.41$), for the second model was 1.39 (95% CI 0.69–2.76, $P = 0.35$), and for the third model was 1.32 (95% CI 0.65–2.66, $P = 0.44$). We performed sensitivity analyses using different cutoffs for PS and observed essentially the same results.

DISCUSSION

This is the first epidemiologic study of patients with RA that uses a prospective cohort from an Asian country to investigate the association of SIs and use of TNF antagonists during 3 years and includes patients that changed to a second agent. In addition, we performed a head-to-head comparison of the risk for SIs between infliximab and etanercept. We demonstrated that the continuous use of TNF antagonists for up to 3 years was an independent risk factor for SIs (RR 1.97, 95% CI 1.25–3.19), but the risk was time dependent. We also revealed that the RR for SIs comparing the etanercept group with the infliximab group after adjusting for covariates was not significantly different.

Studies from European biologics registries analyzed the association of TNF antagonists with infections in patients with RA (32,33). There are some reports indicating that the risk for SIs was not increased by TNF antagonists (21–24), but other studies show significant associations between the use of these agents and development of SIs (14–20,34–36). Several of the latter studies revealed time dependence of the risk for SIs (15,16,18–20,34), which is compatible with our results where the risk for SIs was significantly elevated only in the first year and declined in the second and third years combined. The decrease in risk might be explained in part by the effect of dropout patients who developed SIs and stopped the TNF antagonist (34). Of 68 patients who developed SIs in the anti-TNF group, 22 discontinued the biologic agents. Patients who were not susceptible to SIs were more likely to remain in the cohort, which could contribute to reduced risk with increasing observation period.

Increasing age, presence of chronic pulmonary comorbidity, higher mean DAS28-CRP, mean dosage of MTX >8 mg/week, and mean dosage of oral prednisolone ≥10 mg/day were identified as independent risk factors for SIs in this study. Most previous studies have reported that increasing age, pulmonary comorbidity, and use of oral prednisolone were risk factors for infections (14,21–23,35,36) and for PCP (37) in RA patients treated with TNF antagonists. Conflicting results, however, have been reported regarding the association of disease activity and risk for SIs (23,36). Because disease activity is often improved rapidly and significantly by treatment with biologic agents, including TNF antagonists, it seems reasonable that baseline disease activity may not accurately predict infectious events. Mean disease activity during the observation period may serve as a better predictor, as our study indicates.

In Japan, the data from postmarketing surveillance programs conducted by pharmaceutical companies showed that the IRs of pneumonia, PCP, and tuberculosis occurring during the first 6 months of treatment with infliximab were numerically higher than those of etanercept (11–13). In the present study, however, we show that the risk for SIs of treatment with etanercept during the longer observation period was not significantly different from that of infliximab after adjusting for covariates. Some observational studies directly (23) or indirectly (17,20) compared the risk for SIs between treatment with infliximab and etanercept, and found no statistically significant difference. A recent meta-analysis including randomized controlled trials and their extension studies also supports the results of our study; the odds ratio of etanercept treatment for SIs indirectly compared with infliximab was 0.73 (95% CI 0.46–1.15), which was not statistically significant (38).

There are a number of limitations to our study. First, we have to consider possible selection bias in our study. All of

the patients were enrolled from university hospitals or referral hospitals that are dedicated to the treatment of RA. The number of the unexposed group was smaller than that of the anti-TNF group in this study, which did not reflect the real world and may indicate unidentified selection bias. Although we estimated the risk of SIs after adjusting for variables that were clinically important, we had to interpret our data under these conditions. A second limitation is the effect of prevalent users on the analyses. In the exposed group, there were 273 prevalent nonbiologic DMARD users who had already been receiving the nonbiologic DMARDs at enrollment in the REAL database, and the rest were incident nonbiologic DMARD users. Inclusion of these prevalent nonbiologic DMARD users in our cohort might lead to the underestimation of the incidence of SIs. However, the majority of these patients started new nonbiologic DMARDs or underwent dose escalations of nonbiologic DMARDs during the observation period (data not shown), reducing the degree of underestimation. Third, the mean observation periods for both groups were approximately 2 years; it is possible that we underestimated the rate of SIs in the third year. Fourth, the mean dose of MTX of our database is lower than those of Western cohorts. In Japan, the maximum approved dosage of MTX for RA has been increased since February 2011 and Japanese rheumatologists can now officially prescribe MTX up to 16 mg/week for patients with RA. Therefore, in the future, we will be able to conduct further studies to examine the risk of TNF antagonists in patients receiving a higher dose of MTX.

In conclusion, we have shown that the continuous use of TNF therapy for up to 3 years in Japanese patients with RA, including cases where a clinical switch to a second TNF antagonist was employed, time dependently increased the risk for SIs compared to treatment with nonbiologic conventional DMARDs. A comparison of actual long-term safety among different classes of biologic DMARDs using registry data will be necessary for choosing the appropriate treatment of RA and needs to be performed.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Harigai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sakai, Komano, Michi Tanaka, Nanki, Ryuji Koike, Miyasaka, Harigai.

Acquisition of data. Komano, Michi Tanaka, Nanki, Ryuji Koike, Nagasawa, Amano, Nakajima, Atsumi, Takao Koike, Ihata, Ishigatsubo, Saito, Yoshiya Tanaka, Ito, Sumida, Tohma, Tamura, Fujii, Sugihara, Kawakami, Hagino, Ueki, Hashiramoto, Nagasaka, Miyasaka, Harigai.

Analysis and interpretation of data. Sakai, Komano, Michi Tanaka, Nanki, Ryuji Koike, Miyasaka, Harigai.

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APPENDIX A: MEMBERS OF THE REAL STUDY GROUP AND THEIR AFFILIATES

Members of the Registry of Japanese Rheumatoid Arthritis Patients for Long-Term Safety (REAL) Study Group and their affiliates who contributed to this work were as follows: Hideto Kameda (Saitama Medical University), Shinsuke Yasuda (Hokkaido University), Mitsuhiro Takeno (Yokohama City University), Shintaro Hirata (University of Occupational and Environmental Health), Taichi Hayashi (University of Tsukuba), Yoshinari Takasaki (Juntendo University), Tsuneyo Mimori (Kyoto University), Hiroaki Ida, Katsumi Eguchi (Nagasaki University), Kazuhiko Yamamoto (University of Tokyo), Shunichi Shiozawa, Yasushi Miura (Kobe University), Tetsuji Sawada (Tokyo Medical University Hospital), Hiroaki Dobashi (Kagawa University Hospital), Sae Ochi (Tokyo Metropolitan Bokutoh Hospital), Ayako Nakajima, Hisashi Yamanaka (Tokyo Women's Medical University), Kiyoshi Migita (National Hospital Organization Nagasaki Medical Center), and Hayato Yamazaki, Kaori Watanabe (Tokyo Medical and Dental University).

The following university and hospitals are also members of the REAL Study Group, but were not involved in the present study: Keio University, Kurashiki Kohsai Hospital, Tokyo Kyosai Hospital, and Yokohama City Minato Red Cross Hospital.

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ORIGINAL ARTICLE

Pneumocystis jirovecii pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors

Michi Tanaka · Ryoko Sakai · Ryuji Koike · Yukiko Komano · Toshihiro Nanki · Fumikazu Sakai · Haruhito Sugiyama · Hidekazu Matsushima · Toshihisa Kojima · Shuji Ohta · Yoji Ishibe · Takuya Sawabe · Yasuhiro Ota · Kazuhisa Ohishi · Hajime Miyazato · Yoshinori Nonomura · Kazuyoshi Saito · Yoshiya Tanaka · Hayato Nagasawa · Tsutomu Takeuchi · Ayako Nakajima · Hideo Ohtsubo · Makoto Onishi · Yoshinori Goto · Hiroaki Dobashi · Nobuyuki Miyasaka · Masayoshi Harigai

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Abstract
Objectives The association of anti-tumor necrosis factor therapy with opportunistic infections in rheumatoid arthritis (RA) patients has been reported. The goal of this study was to clarify the clinical characteristics and the risk factors of RA patients who developed *Pneumocystis jirovecii* pneumonia (PCP) during etanercept therapy.
Methods We conducted a multicenter, case–control study in which 15 RA patients who developed PCP were compared with 74 RA patients who did not develop PCP during etanercept therapy.
Results PCP developed within 26 weeks following the first injection of etanercept in 86.7% of the patients. All PCP patients presented with a rapid and severe clinical course and the overall mortality was 6.7%. Independent risk factors were identified using multivariate analysis and included age ≥65 years [hazard ratio (HR) 3.35, $p = 0.037$], coexisting lung disease (HR 4.48, $p = 0.009$), and concomitant methotrexate treatment (HR 4.68, $p = 0.005$).

M. Tanaka · R. Sakai · R. Koike · T. Nanki · M. Harigai (✉)
Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: mharigai.mpha@tmd.ac.jp

M. Tanaka · R. Koike · Y. Komano · T. Nanki · Y. Nonomura · N. Miyasaka · M. Harigai
Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

R. Koike
Clinical Research Center, Tokyo Medical and Dental University Hospital, Tokyo, Japan

F. Sakai
Department of Diagnostic Radiology, International Medical Center, Saitama Medical University, Saitama, Japan

H. Sugiyama
National Center for Global Health and Medicine, Tokyo, Japan

H. Matsushima
Saitama Red Cross Hospital, Saitama, Japan

T. Kojima
Department of Orthopedic Surgery, Nagoya University School of Medicine, Nagoya, Japan

S. Ohta
Hitachi Ltd., Taga General Hospital, Hitachi, Japan

Y. Ishibe
Saijo Central Hospital, Saijo, Japan

T. Sawabe
Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan

Y. Ota
Yasuhiro Clinic, Hamamatsu, Japan

K. Ohishi
Hamamatsu Medical Center, Hamamatsu, Japan

H. Miyazato
Shunan Memorial Hospital, Yamaguchi, Japan

K. Saito · Y. Tanaka
The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

H. Nagasawa
Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

In patients having a larger number of risk factors, the cumulative probability of developing PCP was significantly higher ($p < 0.001$ for patients with two or more risk factors vs. those with no risk factor, and $p = 0.001$ for patients with one risk factor vs. those with no risk factor).
Conclusion Physicians must consider the possibility of PCP developing during etanercept therapy in RA patients, particularly if one or more risk factors are present.

Keywords *Pneumocystis jirovecii* pneumonia · Rheumatoid arthritis · Etanercept · Anti-TNF therapy · Opportunistic infection

Introduction

Tumor necrosis factor (TNF) plays an important role in the pathological mechanism of rheumatoid arthritis (RA) [1]. The excellent efficacy of TNF inhibitors for RA seen in various clinical trials has established TNF as a major pathogenic cytokine in RA [2–4]. TNF is one of the key molecules protecting the human body against microorganisms in vivo. The blockade of TNF with TNF inhibitors in RA patients has been associated with increased risks of opportunistic and serious infections [5–8].

In Japan, mandatory post-marketing surveillance (PMS) programs have been implemented, requiring registration and 6-month tracking of all RA patients who have received TNF inhibitors. Of 5,000 patients treated with infliximab, 13,894 patients treated with etanercept, and 3,000 patients treated with adalimumab tracked by these programs, 22 patients (0.4%) receiving infliximab, 25 patients (0.18%) treated with etanercept, and 9 patients (0.3%) treated with adalimumab developed *Pneumocystis jirovecii* pneumonia (PCP) [9–11], a rare opportunistic infectious disease seen in patients with human immunodeficiency virus (HIV) infection [12] and other immune-compromised states [13]. The incidence rate of PCP in the PMS programs in Japan was notably higher than that found in corresponding studies in the United States [14, 15].

The diagnosis of PCP in immunosuppressed patients without acquired immunodeficiency syndrome (AIDS) is challenging because of lower numbers of the organism in the lung [13]. In order to overcome this problem and to achieve prompt clinical diagnosis of PCP in non-AIDS patients who have a lower burden of *P. jirovecii* [16], several molecular techniques, such as the polymerase chain reaction (PCR) [17] and the use of serum markers, such as 1,3-β-D-glucan (BDG) [18, 19], have been developed. We, and other investigators, have performed several clinical studies of PCP using diagnostic criteria that involved these new diagnostic tools [9, 20–22].

Although the etanercept PMS program in Japan identified 25 patients with PCP, the diagnoses were based on reports from attending physicians and detailed analyses have not been implemented. Independent from the etanercept PMS program, we conducted a multicenter case–control study of PCP in RA patients treated with etanercept to delineate the clinical characteristics of PCP and identify risk factors in this population.

Patients, materials, and methods

Patients

In this study, we collected data from 21 hospitals on 28 RA patients suspected of having PCP; data were collected either through the PMS etanercept program or from voluntary case reports at scientific meetings, or from the relevant pharmaceutical company. Among these 28 patients, we identified one definitive PCP patient (patient 14) and 14 presumptive PCP patients (patients 1–13 and 15) based on the predefined criteria presented below. These 15 patients did not have other risk factors for PCP, such as malignancy, post-transplantation status, or other immunodeficiency states. We did not examine antibody for HIV because this laboratory test was not routinely conducted in clinical practice in Japan. These 15 patients were classified as the 'PCP group' in this study. The other 13 patients were not diagnosed with PCP because their data were incompatible with the diagnostic criteria for PCP and diagnoses including other infectious diseases or rheumatoid lung were considered more appropriate, and these patients were

T. Takeuchi
Division of Rheumatology, Department of Internal Medicine, Keio University, Tokyo, Japan

A. Nakajima
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

H. Ohtsubo
Japanese Red Cross Society Kagoshima Hospital, Kagoshima, Japan

M. Onishi
Center for Rheumatic Disease, Dohogo Spa Hospital, Matsuyama, Japan

Y. Goto
Goto Medical Clinic, Hamamatsu, Japan

H. Dobashi
Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Department of Internal Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

excluded from further evaluation. The data of 74 RA patients who did not develop PCP within 12 months after the beginning of etanercept treatment were collected and these patients were termed the 'non-PCP' group. These patients' were randomly extracted from consecutive RA patients receiving etanercept at hospitals that participated in this study. All patients in this study fulfilled the 1987 American College of Rheumatology (formerly the American Rheumatism Association) diagnostic criteria for RA [23].

Diagnostic criteria for PCP

For this study, we used previously established diagnostic criteria for PCP [22, 24]. A diagnosis of PCP was considered definitive if: (1) *P. jirovecii* was found on microscopic analysis of respiratory samples from patients with concurrent clinical manifestations (fever, dry cough, or dyspnea), (2) the patients presented with hypoxemia, and (3) radiographic findings were indicative of PCP. The diagnosis of PCP was considered presumptive if a patient fulfilled the clinical and radiographic conditions [i.e., criteria (2) and (3)] in the absence of evidence of other infectious diseases and in the presence of either a positive PCR test for *P. jirovecii* DNA (qualitative PCR analysis by SRL, Tokyo, Japan, or Mitsubishi Chemical Medicine Corporation, Tokyo, Japan) or increased serum BDG levels above the upper limit of normal (ULN) (Fungitec *G* test MK; Seikagaku, Tokyo, Japan, or Wako β-D-glucan test; Wako Pure Chemical Industries, Tokyo, Japan) and responded to standard treatments for PCP with trimethoprim/sulfamethoxazole (TMP/SMX) or pentamidine isethionate. Both the PCR test for *P. jirovecii* DNA and the serum BDG test are commercially available, validated, and officially approved as clinical laboratory tests by the Ministry of Health, Labour, and Welfare in Japan.

Collection and analysis of clinical data

Data were collected from medical records using a standardized format including demographic information, comorbidities, concomitant drugs, laboratory data, radiographic data, treatments, and outcomes. Chest radiographs and computed tomography (CT) scans of the thorax were evaluated by a radiologist (F.S.) and a pulmonologist (H.S.).

Ethics

The guidelines of the Helsinki Declaration and the ethical guidelines for epidemiological research in Japan were followed. The study protocol was approved by the Institutional Ethics Committee of the Tokyo Medical and Dental University Hospital (#545 in 2008). The ethical guidelines for epidemiological studies in Japan required notifying eligible RA patients of this study and allowed us to implement this study without obtaining individual written informed consent. Patients were notified of this study by leaflets or posters at the outpatients clinics of each participating institution and on the website of the Department of Pharmacovigilance of the Tokyo Medical and Dental University. Patients were excluded from the study when they expressed their unwillingness to participate in this study.

Statistical analyses

Fisher's exact test was used for categorical variables and the Mann–Whitney *U*-test was used for continuous variables, with the Bonferroni correction for multiple pair comparisons. To identify risk factors for PCP, the Cox proportional-hazards regression model was used. The cumulative probability of PCP was calculated using the Kaplan–Meier method and the comparison among groups was performed using the log-rank test. All analyses were performed using SPSS software, version 17.0 (SPSS Japan, Tokyo, Japan).

Results

Demographics and treatment of RA patients who developed PCP

The demographics and treatment of RA patients at the onset of PCP are summarized in Table 1. The mean age of the PCP group was 66 years. The median interval between the first injection of etanercept and the onset of PCP was 14 weeks. Thirteen patients (86.7%) developed PCP within 26 weeks after the first injection of etanercept. All patients were treated with 50 mg/week of etanercept, except for patient 14, who was given 25 mg/week. At the onset of PCP, ten patients (66.7%) were receiving concomitant methotrexate (MTX) and 12 patients (80%) were receiving concomitant corticosteroids with etanercept. The median dosage of MTX was 8 mg/week and the median dosage of prednisolone (PSL) was 5 mg/day. Patient 8 received concomitant cyclophosphamide. None of the patients received chemoprophylaxis for PCP. Seven patients had pulmonary comorbidities, including interstitial pneumonia (IP) ($n = 4$), prior pleuritis ($n = 1$), pneumoconiosis ($n = 1$), and prior pulmonary tuberculosis ($n = 1$). Three patients had diabetes mellitus.

Table 1 Demographics and treatment of rheumatoid arthritis patients at the onset of *Pneumocystis jirovecii* pneumonia (PCP)

Pt	Age (years)	Number of injections[a]	Duration of ETN (weeks)[b]	MTX (mg/week)	PSL (mg/day)	Lung disease	Diabetes mellitus
1	66	38	21	8	3	–	–
2	32	8	7	12	0	–	+
3	74	55	27	8	0	–	–
4	61	35	19	6	8	–	–
5	79	51	27	0	2.5	IP	–
6	74	80	43	10	1	IP	+
7	72	28	13	0	10	Old pleuritis	–
8	73	25	14	0	30	Pneumoconiosis	–
9	72	29	13	8	5	IP	–
10	61	13	10	10	5	–	–
11	63	7	3	0	25	IP	–
12	72	12	11	0	4	Prior tbc	–
13	61	33	9	10.5	7.5	–	–
14	79	17	17	4	17.5	–	+
15	58	6	3	10	0	–	–
Median (IQR)	72 (61–73)	28 (12.5–36.5)	14 (9.5–20)	8 (0–10)	5 (1.75–9)		

Pt patient, *M* male, *F* female, *ETN* etanercept, *MTX* methotrexate, *PSL* prednisolone, *IP* interstitial pneumonia, *tbc* tuberculosis, *IQR* interquartile range

[a] Number of etanercept injections prior to the diagnosis of PCP

[b] Duration of treatment with etanercept before the onset of PCP

Clinical characteristics of RA patients who developed PCP

The clinical characteristics of each patient at the onset of PCP are summarized in Table 2. All had fever, 14 patients (93%) showed dyspnea on effort, and seven patients (46.7%) had a dry cough. Hypoxemia was observed in all patients at the onset of PCP; most had either severe hypoxemia with oxygen partial pressure in arterial blood (PaO_2) <60 mmHg on room air or required immediate oxygen therapy. Chest radiographs and CT scans were performed for all patients. On CT scans, ground-glass opacity (GGO) was observed in all patients. Six patients had GGO with sharp demarcation by interlobular septa (type A), while eight patients had GGO without interlobular septal boundaries (type B) (Fig. 1). One patient showed a combination of consolidation and GGO without interlobular septal boundaries. These thoracic CT findings in RA patients receiving etanercept who developed PCP were essentially the same as those in RA patients receiving infliximab who developed PCP [22, 24].

Serum levels of BDG, a reliable serum marker for PCP [18], were elevated above the ULN in 10 patients, with marked elevation (BDG >100 pg/ml) observed in 3 patients (Table 2). The PCR test for detection of *P. jirovecii* was utilized for 11 patients, using either induced sputum (nine patients) or bronchoalveolar lavage (BAL) fluid (two patients). All test results were positive. *P. jirovecii* was microscopically identified in BAL samples from patient 14 (Table 2).

Laboratory test results for PCP patients

Laboratory data from each patient at the onset of PCP are summarized in Table 3. Severe lymphopenia (<500 cells/μl) was observed in only 3 patients, while 4 patients had 500–1,000 cells/μl, and 8 patients had >1,000 cells/μl. The median serum level of C-reactive protein (CRP) was 9.5 mg/dl ($n = 15$); that of IgG was 1,341 mg/dl ($n = 9$); that of albumin (Alb) was 3.1 g/dl ($n = 15$); and that of the KL-6 antigen was 666 U/ml ($n = 13$). The KL-6 antigen is produced by type II alveolar epithelial cells and is reported to be elevated in patients with active IP [25], as well as in those with PCP [26].

Clinical course of PCP in RA patients treated with etanercept

All patients developed PCP rapidly and were hospitalized 3 or 4 days after the appearance of the clinical manifestations. Three patients required mechanical ventilation immediately upon admission because of progressive respiratory failure. Disease- modifying anti-rheumatic drugs (DMARDs), immunosuppressive drugs, and etanercept were discontinued in all patients. All patients received therapeutic doses of TMP/SMX immediately after the laboratory and radiographic examinations. Treatment with TMP/SMX was changed to pentamidine isethionate in three patients who had adverse drug reactions. Eight patients were treated with methylprednisolone (mPSL) pulse therapy, three with high-dose PSL, and five with increasing dosages of PSL within a few days after admission.