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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

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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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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).

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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.

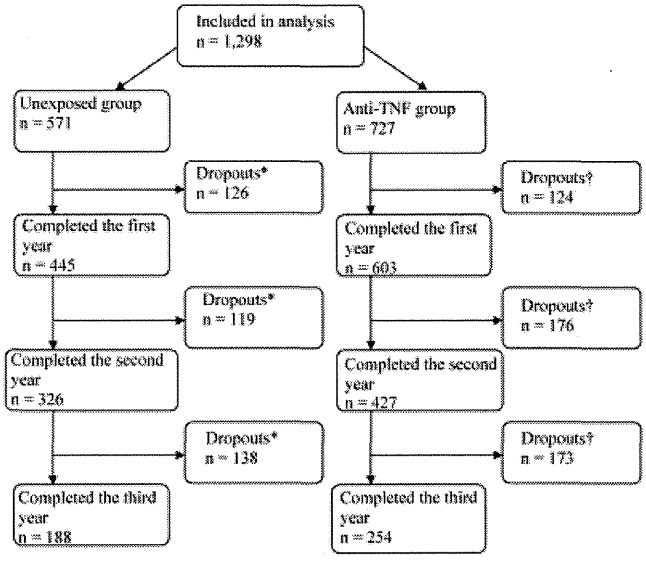

Figure 1. Distribution of numbers of patients with rheumatoid arthritis during the 3-year observation period. * = dropouts from the unexposed group include patients who started biologic disease-modifying antirheumatic drugs (DMARDs) or patients whose observation did not complete the next 1 year; † = 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.

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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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Successful Treatment of Refractory Takayasu Arteritis with Tacrolimus

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Successful Treatment of Refractory Takayasu Arteritis with Tacrolimus

To the Editor:

Takayasu arteritis (TA) is a systemic vasculitis that affects large-size vessels such as the aorta and/or its main branches. Persistent inflammation of TA leads to segmental stenosis, occlusion, dilatation, and/or aneurysm formation. TA is also accompanied by somatic symptoms, including fever, fatigue, and weight loss, and elevation of acute-phase reactants such as C-reactive protein (CRP) that correlate with disease activity. Although high-dose corticosteroid (CS) therapy is effective in TA, CS alone does not provide sustained remission in about half of patients[1]. CS-resistant patients with TA have been treated with immunosuppressants, including methotrexate (MTX) and azathioprine[1,2]. Anti-tumor necrosis factor (anti-TNF) therapy[3,4] and anti-interleukin 6 receptor antibody[5,6] are also promising treatments for TA. However, the new therapies for CS-resistant TA have yet to be standardized. We describe a patient with TA who was successfully treated with tacrolimus, a calcineurin inhibitor, after failed trial of conventional CS, MTX, and infliximab (IFX). This case suggests that tacrolimus is another potential alternative treatment option for refractory TA.

A 22-year-old woman was admitted to our hospital in August 2007 for persistent fever and neck pain. Examination showed tenderness around both carotid arteries, different blood pressures in the left and right upper extremities (right 109/54, left 90/47 mm Hg), weak left radial pulse, and murmur on the common carotid arteries and abdominal aorta. Blood analysis showed elevated CRP (10.3 mg/dl). Neck and chest magnetic resonance imaging (MRI) showed wall thickening and stenosis of the left common carotid artery and bilateral brachiocephalic arteries (Figure 1A, 1B). Based on these findings, she was diagnosed with TA. Treatment with 30 mg/day (0.6 mg/kg/day) prednisolone (PSL) relieved the symptoms and reduced CRP to within the normal range (< 0.05 mg/dl). The PSL dose was subsequently reduced to 10 mg/day.

However, in April 2008, the patient developed fever and tenderness at the same location around carotid arteries, with high CRP (1.57 mg/dl), suggesting relapse of TA. Accordingly, the dose of PSL was escalated to 30 mg/day and combined with MTX. The combination treatment induced remission of TA again. Nevertheless, the disease activity became exacerbated again after reduction of PSL dose to 12.5 mg/day despite continuation of MTX at 12.5 mg/week. IFX was added to the treatment in March 2009 (3 mg/kg at weeks 0, 2, and 6 and then at 8-week intervals). Although the dose of IFX was subsequently increased to 8.5 mg/kg and the administration interval was shortened to every 6 weeks, neck tenderness did not disappear and CRP levels remained positive (0.40–0.97 mg/dl), suggesting the arteritis was still active. Consequently, 3 mg/day tacrolimus was added in February 2010 and the dosage was increased to 4 mg/day to maintain an adequate serum trough level (~5 ng/ml). The CRP level decreased to normal range 5 weeks after start of tacrolimus, and remained within the normal range even after discontinuation of IFX in June 2010. The dose of PSL was subsequently tapered to 6 mg/day. MRI in February 2011 showed disappearance of the vascular wall thickening and absence of new stenosis of arteries (Figure 1C, 1D).

There is only limited evidence for the efficacy of immunosuppressants

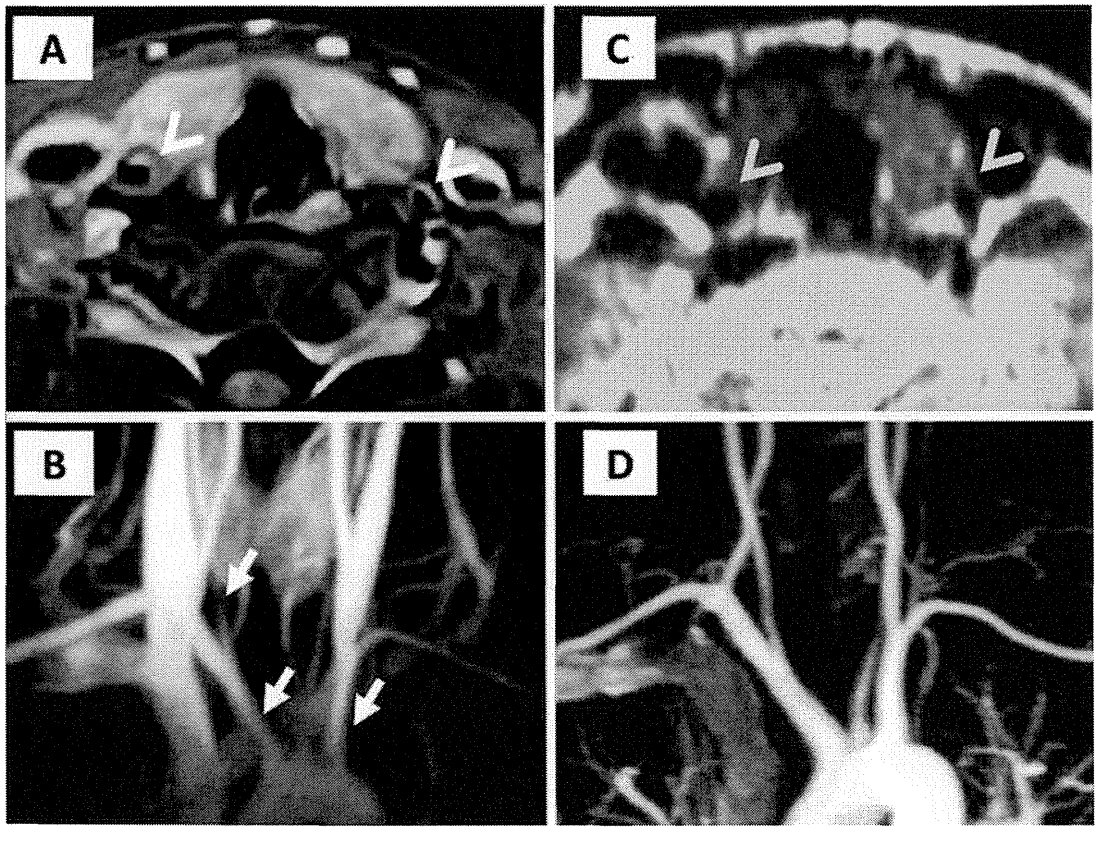

Figure 1. Neck and chest MRI findings. The left common carotid artery of this patient branches from the left brachiocephalic artery. A. T1-weighted image shows wall thickening of the left common carotid artery and right brachiocephalic artery (arrowheads). B. Magnetic resonance angiography shows stenosis of the right common carotid artery and bilateral brachiocephalic arteries (arrows) at diagnosis in August 2007. C. Magnetic resonance imaging in February 2011 during treatment with tacrolimus and subsequent sustained clinical remission shows normal vascular wall and (D) absence of new stenosis of arteries.

or biologics for CS-resistant TA[1,2]. Molloy, *et al*[4] reported an uncontrolled series of 25 patients with TA who received anti-TNF therapy; remission with discontinuation of PSL was achieved in 15 patients (60%) and remission with PSL ≤ 10 mg/day in an additional 7 patients (28%). Three patients did not respond to anti-TNF therapy, similar to our patient.

A thorough search of the PubMed database revealed that this is the first case of TA treated successfully with tacrolimus in spite of failure of anti-TNF therapy. In addition, we identified 2 patients with TA who improved significantly with calcineurin inhibitors. In the first patient, tacrolimus was effective in a patient resistant to CS and intolerant to MTX[7]. Cyclosporine was effective in another patient with CS- and MTX-resistant TA[8]. Cyclosporine is another calcineurin inhibitor that shares similar immunosuppressive action with tacrolimus. Studies in the field of organ transplantation suggest that tacrolimus is more efficacious than cyclosporine[9]. Therefore, for treatment of TA, tacrolimus may also be more useful, although there is not enough evidence to date to compare the efficacy between tacrolimus and cyclosporine.

Our case suggests that tacrolimus is a potential alternative therapy for patients with CS-resistant or anti-TNF-resistant TA; further studies with large number of patients are needed to confirm the efficacy of tacrolimus for TA.

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5 T細胞標的治療

T-cell target therapy

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1990年筑波大学医学部専門学群卒業，同年東京医科歯科大学　第一内科，'97年テキサス大学サウスウエスタンメディカルセンター，米国国立衛生研究所に留学，2000年東京医科歯科大学膠原病・リウマチ内科，'07年東京医科歯科大学薬学監視学講座。研究テーマ：膠原病における細胞遊走に関する分子の解析，生物学的製剤の安全性等の解析

Key words：関節リウマチ，T細胞，CTLA-4-Ig，アバタセプト，感染症

Abstract

関節リウマチ（RA）に対して生物学的製剤が用いられるようになり，RAの治療は大きく変化し，また予後も改善してきた。T細胞を標的としたアバタセプト（CTLA-4-Ig）も，2010年に本邦で承認された。国内での臨床試験，市販後全例調査，および海外での臨床試験より，アバタセプトのRAに対する有効性が報告されている。また，安全性に関しては，感染症の発現頻度は生物学的製剤の中では低い傾向を認めている。これらの報告はT細胞を標的とした治療がRAに有用であることを示しており，今後もさらなるT細胞標的治療薬の開発が期待される。

はじめに

2003年に抗TNF抗体が本邦で関節リウマチ（rheumatoid arthritis: RA）に対して承認されて以来，生物学的製剤が積極的にRAに用いられるようになり，RAの治療法は格段の進歩を遂げている。現在では，3種類の抗TNF抗体，およびTNF受容体Ig，抗IL-6受容体抗体，CTLA-4-Igの6種類の生物学的製剤が用いられている。

RAの病態形成には，T細胞，B細胞，マクロファージ，線維芽細胞様滑膜細胞などが関わっている。T細胞に関しては，RA滑膜組織に多数のCD4陽性T細胞が集簇していること，またCD4 T細胞に抗原提示をする主要組織適合抗原のHLA-DR4とRA発症に強い相関があることより，CD4 T細胞がRA病態に大きく寄与すると考えられてきた。

本稿では，T細胞の活性化抑制作用を持つCTLA-4-Igについて，その作用機序，RAに対する治療効果，安全性に関して概説する。

1. RAに対するT細胞を標的とした治療

T細胞を標的とした治療としては，1990年代に抗CD4抗体がRAに対する治療として試みられた。当初は良好な治療効果が期待されたが，臨床試験では有意な治療効果を認めず[1]，抗CD4抗体による治療開発は断念されている。しかしながら，抗TNF抗体と抗CD4抗体または抗CD3抗体の併用による有効性が動物モデルで報告されており[2,3]，今

後抗CD3抗体，抗CD4抗体などによる再度の試みも期待される。

一方，T細胞の副刺激を阻害するCTLA-4-Igは，RAに対する有効性が示され，2010年より本邦でも用いられている。

2. アバタセプト（CTLA-4-Ig，オレンシア®）

T細胞の活性化には，抗原提示を受けたT細胞受容体刺激とともに共刺激からのシグナルが必要である。T細胞上のCD28は抗原提示細胞上のCD80, CD86と結合し共刺激を受けることによりT細胞を活性化させる。CD80, CD86はT細胞上のcytotoxic T-lymphocyte antigen 4（CTLA-4）にも結合し，共刺激の抑制効果もある。アバタセプトはCTLA-4とヒト免疫グロブリンIgG1のFc部分を結合させた融合蛋白（CTLA-4-Ig）である。アバタセプト（CTLA-4-Ig）は抗原提示細胞上のCD80, CD86に結合し，T細胞上のCD28への刺激を阻害することにより，T細胞の共刺激を阻害してT細胞の活性化を抑制する。

3. アバタセプトの有効性

国内における臨床試験，市販後全例調査の結果を紹介する。第Ⅱ相臨床試験ではメトトレキサート（MTX: methotrexate）効果不十分の患者に対して，アバタセプト（10mg/kg，または2mg/kg）+MTX，プラセボ+MTXの3群で治療効果が比較された[4]。その結果，治療開始24週時点でのACRコアセット，DAS28-CRPにおいて，アバタセプト用量依存性に治療効果がみられた（図1A, B）。長期継続試験（第Ⅲ相試験）では，第Ⅰ相，第Ⅱ相試験からの継続投与に加えて，アバタセプト単剤投与群（体重別固定用

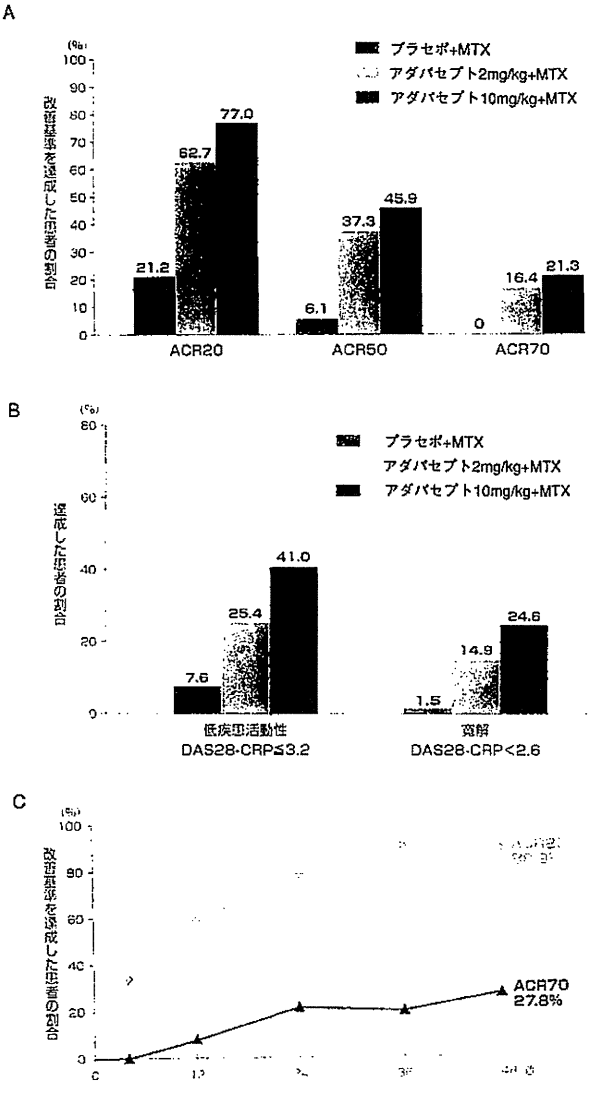

図1　国内臨床試験の結果
A，B：国内第Ⅱ相試験の結果。
アバタセプト（10mg/kg,または2mg/kg）+MTX，プラセボ+MTX，24週時での比較。
ACRコアセット（A），DAS28-CRPの低疾患活動性，寛解（B）の達成率を示す。
C：第Ⅲ相試験（国内長期継続試験）の結果。
アバタセプト単剤投与によるACRコアセット基準達成率。
（文献4，5より引用改変）

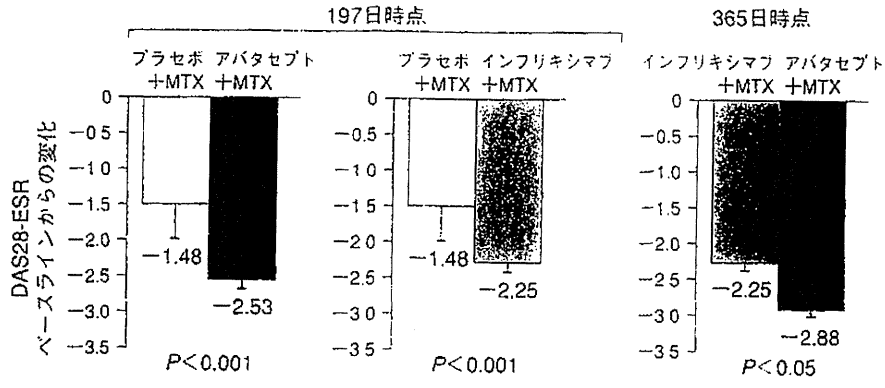

図2　MTX抵抗性RA患者にアバタセプト，インフレキシマブ，プラセボをMTXと併用した無作為化二重盲検比較試験（ATTEST試験）
治療開始197日と365日でのDAS28-ESRのベースラインからの比較。（文献8より引用改変）

量：体重 <60kg: 500mg，60-100kg: 750mg，>100kg: 1000mg）が組み入れられ，アバタセプト単剤投与群においても有効な結果が得られた（図1C）[5]。またアバタセプトは承認時より市販後全例調査が行われており，1000例の時点での中間報告では，DAS28，SDAI，CDAIにおいて投与開始24週後に有意な治療効果を認めている[6]。これらの結果は日本人RA患者におけるアバタセプトの有用性を示すものである。

海外では，MTX抵抗性のRA患者にアバタセプト+MTX，またはプラセボ+MTXによる治療効果が比較された（AIM試験）[7]。アバタセプトの投与によりACRコアセット，HAQ，シャープスコアにおいて有意な治療効果が認められた。さらに，MTX抵抗性患者にアバタセプト+MTX，インフリキシマブ（3mg/kg）+MTX，プラセボ+MTXが投与され，治療効果が比較された（ATTEST試験）[8]。その結果，アバタセプトはインフリキシマブと同等以上の効果がみられた（図2）。また，TNF阻害薬に不応性患者に対してアバタセプト+DMARDs，またはプラセボ+DMARDsの投与が行われた（ATTAIN試験）[9]。TNF阻害薬不応性のRAにおいてもアバタセプトの投与によりACRコアセットの改善達成率の上昇がみられた。さらに，DAS28が3.2以下の低疾患活動性，および2.6未満の寛解患者の割合もプラセボ投与群と比較してアバタセプト投与群で優位に上昇した。これら国内および海外からの報告より，アバタセプトはMTX抵抗性，TNF阻害薬抵抗性のRA患者に対して有用な治療法と考えられる。

4．アバタセプトの安全性

アバタセプトの投与による有害事象としては，他の生物学的製剤と同様に肺炎などの感染症や投与時反応などが報告されている。ATTEST試験では，アバタセプト投与1年間での重篤な有害事象の発症は9.6％，重篤な感染症は1.9％にみられたが，インフリキシマブでは各々18.2％，8.5％であった[8]。アバタセプトの方が有害事象の発生率が低い可能性が示唆された。

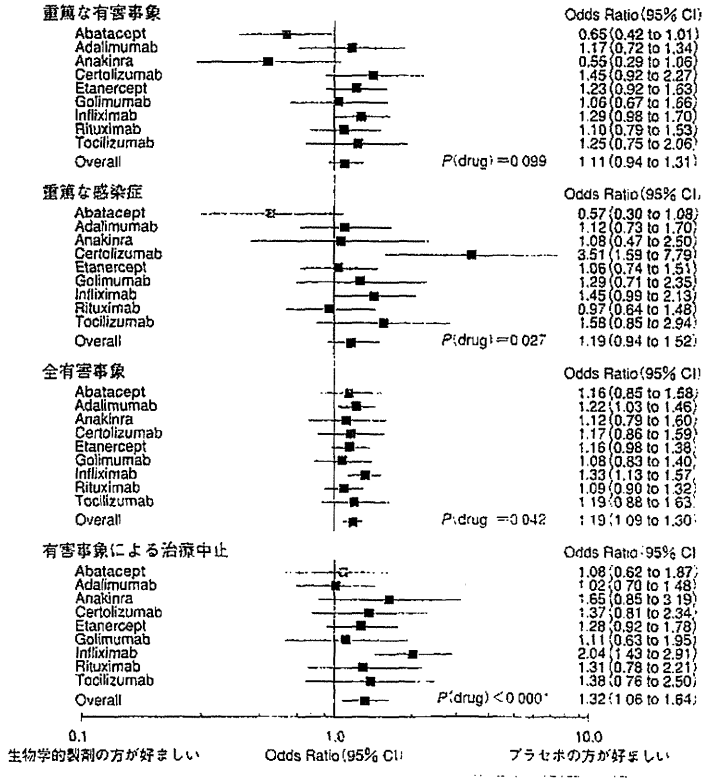

図3　生物学的製剤ごとの重篤な有害事象，重篤な感染症，全有害事象，有害事象による治療中止のforest plots（串刺し図）
（文献10より引用改変）

昨年Cochrane Libraryに，これまでの生物学的製剤を用いた163の無作為化比較試験，46のオープンラベル長期継続試験によるメタアナリシスの結果が報告された[10]。アバタセプト，アダリムマブ，アナキンラ，セルトリズマブ ペゴル，エタネルセプト，ゴリムマブ，インフリキシマブ，リツキシマブ，トシリズマブが解析の対象となり，対象疾患はRA，癌，乾癬，炎症性腸疾患，強直性脊椎炎，乾癬性関節炎などが含まれている。すべての生物学的製剤の使用をコントロール治療と比較すると，全有害事象，有害事象による治療中止，結核の再活性化の頻度が優位に上昇した。重篤な有害事象および重篤な感染症の発症頻度は高い傾向にあったが，統計学的に優位差は認めなかった。生物学的製剤ごとのforest plotsを図3に示すが，アバタセプトでは統計学的有意差は認めないものの重篤な有害事象，重篤な感染症の発現はむしろ低い傾向にあった。

アバタセプトと各製剤とを間接的に比較した結果では，同一の試験内での比較ではないことに留意する必要があるが，重篤な有害事象の発現はアバタセプトでは，セルトリズマブ ペゴル，エタネルセプト，インフリキシマブ，リツキシマブ，トシリズマブより優位に低く，また重篤な感染症はアバタセプトでは，セルトリズマブ ペゴル，インフリキシマブ，トシリズマブより低い結果であった。

国内のインフリキシマブ，エタネルセプト，トシリズマブ，アダリムマブ，アバタセプトの市販後全例調査による副作用，感染症の発現頻度を表に示す。生物学的製剤一般に，重篤な有害事象の約半数，有害事象全体の約3分の1を感染症で占める。アバタセプトは市販後全例調査の途中であり，未確定例も含まれるため，他の生物学的製剤との比較はできないが，Cochrane reviewの結果も合わせ考えると，アバタセプトは他の生物学的製剤よりも重篤な感染症の発現頻度は低い傾向にある。しかし，同一試験内での比較ではないため，患者背景が違う可能性もあり，今後，直接比較した臨床研究が待たれる。

表　生物学的製剤ごとの副作用，感染症の発現頻度

	インフリキシマブ(5000 例)		エタネルセプト(13894 例)		トシリズマブ(6424 例)	
	*重篤	**総数	*重篤	**総数	*重篤	**総数
副作用	308 例(6.2%)	1401 例(28.0%)	636 例(4.6%)	3714 例(26.7%)	450 例(7.0%)	2319 例(36.1%)
感染症	202 例(4.0%)	433 例(8.7%)	334 例(2.4%)	1206 例(8.7%)	233 例(3.6%)	615 例(9.6%)

	アダリムマブ(7740 例)		アバタセプト(9150 例)	
	*重篤	**総数	*重篤	**総数
副作用	348 例(4.5%)	1857 例(24.0%)	155 例(1.7%)	757 例(8.3%)
感染症	182 例(2.4%)	538 例(7.0%)	70 例(0.8%)	278 例(3.0%)

各生物学的製剤の市販後全例調査からの結果(アバタセプトは途中経過かつ未確定症例も含む)。
製剤ごとの総副作用発症例数、感染症発症例数について、*重篤なものの例数、**重篤および非重篤を合わせた例数。

おわりに

T細胞を標的とした治療として，アバタセプト（CTLA-4-Ig）がRAに対して用いられるようになり良好な治療成績が報告されている。また，T細胞を標的とした治療がRAに有用であることが示されたことより，今後T細胞を標的とした他の治療薬の開発も期待される。

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Retention of tocilizumab and anti-tumour necrosis factor drugs in the treatment of rheumatoid arthritis

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Objectives: The retention of the anti-rheumatic agent tocilizumab (TCZ) has not been well documented in patients with rheumatoid arthritis (RA). We conducted an observational study to compare the retention of TCZ and anti-tumour necrosis factor (TNF) drugs in the treatment of patients with RA.

Method: We reviewed continuation rates and causes of discontinuation of biological agents (biologics) by assessing medical records of patients with RA who were administered biologics at our institute from September 1999 to April 2012, using the Osaka University Biologics for Rheumatic Diseases (BiRD) registry.

Results: A total of 401 patients were included. TCZ, infliximab (IFX), etanercept (ETN), and adalimumab (ADA) were administered to 97, 103, 143, and 58 patients, respectively. There were some differences between the baseline characteristics of the groups. The median duration (range) of TCZ, IFX, ETN, and ADA administration was 2.5 (0.1–12.6), 1.9 (0.0–7.7), 2.9 (0.0–11.3), and 1.3 (0.0–3.4) years, respectively. Continuation rates for TCZ and ETN were significantly higher than those for IFX and ADA. Multivariate analyses showed that discontinuation due to lack or loss of efficacy was significantly less common in the TCZ group than in the other groups. Discontinuation due to overall adverse events was not significantly different between treatment groups.

Conclusion: TCZ and ETN show better retention than IFX or ADA in the treatment of RA.

Many biological agents (biologics) have been developed and used for the treatment of rheumatoid arthritis (RA) (1–3). In Japan, six different biologics are currently available for the treatment of RA (4): the anti-tumour necrosis factor (TNF) drugs infliximab (IFX), etanercept (ETN), adalimumab (ADA), and golimumab; the interleukin (IL)-6 receptor blocker tocilizumab (TCZ); and the T-cell activation blocker abatacept. The retention of a drug compositely reflects efficacy, safety, and patient satisfaction with daily clinical practice. However, the retention characteristics of these biologics have not been established in clinical trials. Although continuation rates of each drug have been reported (5–7), there are few comparative studies that have evaluated their continuation in clinical practice (8–13). In particular, comparative studies that include TCZ are rare, despite its considerable efficacy in patients with RA (14–22). Thus, we conducted an observational study of daily clinical practice to assess and compare the retention of TCZ and the three anti-TNF drugs IFX, ETN, and ADA.

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Method

Study design and approval

This observational retrospective cohort study was approved by the ethics committee of Osaka University Hospital.

The Osaka University Biologics for Rheumatic Diseases (BiRD) registry

The Osaka BiRD registry includes all patients who were administered one of the six biologics TCZ, IFX, ETN, ADA, abatacept, or golimumab for the treatment of rheumatic diseases in Osaka University Hospital between September 1999 and April 2012. Patients who were initiated with biologics before entering the registry are included. In this study, we analysed patients with RA in the Osaka BiRD registry who were treated with TCZ, IFX, ETN, or ADA. Diagnosis of RA was made

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