

EXTENDED REPORT

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

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► Additional supplementary data are published online only. To view these files please visit the journal online (<http://ard.bmj.com/content/early/recent>)

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ABSTRACT

Objective To compare reasons for discontinuation and drug retention rates per reason among anticytokine therapies, infliximab, etanercept and tocilizumab, and the risk of discontinuation of biological agents due to adverse events (AE) in patients with rheumatoid arthritis (RA).

Method This prospective cohort study included Japanese RA patients who started infliximab (n=412, 636.0 patient-years (PY)), etanercept (n=442, 765.3 PY), or tocilizumab (n=168, 206.5 PY) as the first biological therapy after their enrolment in the Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety (REAL) database. Drug retention rates were calculated using the Kaplan–Meier method. To compare risks of drug discontinuation due to AE for patients treated with these biological agents, the Cox proportional hazard model was applied.

Results The authors found significant differences among the three therapeutic groups in demography, clinical status, comorbidities and usage of concomitant drugs. Development of AE was the most frequent reason for discontinuation of biological agents in the etanercept and tocilizumab groups, and the second most frequent reason in the infliximab group. Discontinuation due to good control was observed most frequently in the infliximab group. Compared with etanercept, the use of infliximab (HR 1.69; 95% CI 1.14 to 2.51) and tocilizumab (HR 1.98; 95% CI 1.04 to 3.76) was significantly associated with a higher risk of discontinuation of biological agents due to AE.

Conclusions Reasons for discontinuation are significantly different among biological agents. The use of infliximab and tocilizumab was significantly associated with treatment discontinuation due to AE compared with etanercept.

Biological disease-modifying antirheumatic drugs (biological agents) are a standard treatment for rheumatoid arthritis (RA).^{1,2} A number of clinical trials have demonstrated that biological agents significantly improve signs and symptoms of RA patients with both early and established disease, and that remission of RA can be achieved with

biological agents not only in early RA patients, but also in established RA patients who have shown inadequate responses to conventional non-biological disease-modifying antirheumatic drugs (DMARD).

In Japan, six biological agents have been approved for the treatment of RA, infliximab in 2002, etanercept in 2005, tocilizumab and adalimumab in 2008, abatacept in 2010 and golimumab in 2011. These drugs are widely used in clinical practice according to treatment guidelines for biological agents by the Japan College of Rheumatology^{3,4} and Japanese drug package inserts. Postmarketing surveillance and some clinical studies have shown short-term effectiveness and safety of these biological agents for Japanese RA patients.^{5–8} The European League Against Rheumatism recommendations for the management of RA state that a tumour necrosis factor (TNF) antagonist should be administered as the first biological DMARD for patients who fail to respond to non-biological DMARD, including methotrexate,⁹ whereas Japanese guidelines do not clearly specify the precedence of biological agents.

Some RA patients treated with biological agents are compelled to stop the administration of these drugs because of lack of efficacy (LOE), adverse events (AE), or financial reasons. In addition, some RA patients discontinue biological agents in the hope of a biological-free remission or biological-free low disease activity status.^{10–12} In general, drugs with high retention rates have a good balance between long-term effectiveness and tolerability, reflecting the satisfaction of patients and doctors with the treatment. Because treatment for RA continues for many years or is life-long in the majority of patients, the examination of long-term drug retention rates using a prospective cohort study is important for the evaluation of biological agents.

To establish better treatment strategies for RA, it is important to identify reasons and risk factors causing the discontinuation of a drug, especially for biological agents. Several studies have shown that

Table 1 Characteristics of RA patients treated with infliximab, etanercept or tocilizumab at the start of the observation period

	Infliximab group (n=412)	Etanercept group (n=442)	Tocilizumab group (n=168)	p Value
Age, years	53.6±13.5	58.5±13.0	59.8±13.4	<0.001
Female, %	85.9	78.1	80.4	0.011
Disease duration, years	7.9±7.8	10.3±8.9	10.3±9.6	<0.001
Steinbrocker's class (3 or 4), %	24.8	31.2	27.4	0.108
Steinbrocker's stage (III or IV), %	43.9	57.0	46.4	<0.001
DAS28 (3/CRP)	4.5±1.2 (n=411)	4.5±1.3 (n=440)	5.1±3.4 (n=167)	0.056
Use of ≥3 previous non-biological DMARD, %	41.0	54.5	31.5	<0.001
Biological—naive, %	96.4	83.9	46.4	<0.001
Methotrexate use, %	99.3	44.6	44.0	<0.001
Methotrexate dose, mg/week	8.0±2.1	7.0±2.0	8.2±2.9	<0.001
Use of immunosuppressive drugs, except for methotrexate, %	1.9	5.7	14.9	<0.001
Oral corticosteroid use, %	68.9	73.1	60.1	0.008
Prednisolone-equivalent dose of corticosteroids (mg/day)	5.4±2.6	6.1±3.3	4.9±2.2	<0.001
Chronic pulmonary disease, %	22.6	36.7	40.5	<0.001
Diabetes mellitus, %	8.5	14.9	12.5	0.015

CRP, C-reactive protein; DAS28, disease activity score including 28-joint count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis

a frequent reason for the discontinuation of biological agents is the development of AE.^{5–7 13–16} Mid to long-term tolerability of TNF inhibitors^{6 13 14 16–24} and tocilizumab^{7 15 25} has been reported, and some studies have directly compared drug retention rates among TNF inhibitors or between TNF inhibitors and other biological agents.^{14 16 17 25–27} To summarise, infliximab had the lowest overall retention rate among infliximab, etanercept and adalimumab^{14 16 17} and among infliximab, etanercept and anakinra.²⁶ A recent report from the CORONA registry demonstrated the highest retention rate of infliximab compared with etanercept and adalimumab.²⁷ However, drug retention rates have not been compared between TNF inhibitors and the interleukin-6 receptor inhibitor, tocilizumab, in the real world. In addition, the risk factors causing drug discontinuation due to AE for patients given these biological agents have not been thoroughly evaluated.

The purpose of this study was to compare drug retention rates and reasons for discontinuation of infliximab, etanercept and tocilizumab among Japanese RA patients, and to investigate the association of the use of these biological agents and other clinical characteristics with drug discontinuation due to AE.

PATIENTS AND METHODS

Database

The Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety (REAL) is an ongoing prospective cohort established to investigate the long-term safety of biological agents in RA patients. Twenty-seven institutions participate, including 16 university hospitals and 11 referring hospitals. Details of REAL have previously been described.^{28 29} Briefly, the criteria for enrolment in REAL include patients meeting the 1987 American College of Rheumatology criteria for RA, written informed consent, and starting or switching treatment with biological agents or starting, adding or switching non-biological DMARD at the time of enrolment in the study. Enrolment in the REAL database was started in June 2005 and closed in January 2012. To facilitate enrolment to the REAL registry, participating physicians were asked to enrol their patients already registered in postmarketing surveillance programmes previously implemented by pharmaceutical companies for biological agents.^{5 8} In addition, our investigators were also encouraged to enrol as many patients as possible who fulfilled the inclusion criteria.²⁹

Data were retrieved from the REAL database on 4 April 2011 for this study. The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and other participating institutions.

Data collection

Each patient's recorded baseline data included demography, disease activity, physical disability, comorbidities, treatments and laboratory data at the beginning of the observation period. A follow-up form was submitted by the site investigators every 6 months to the REAL data centre at the Department of Pharmacovigilance of Tokyo Medical and Dental University to report the occurrence of serious AE, current RA disease activity, treatments and clinical laboratory data.^{28 29} We collected the Steinbrocker class³⁰ as the baseline measurement for each patient's physical disability, instead of the health assessment questionnaire disability index.³¹ The investigators in each hospital confirmed the accuracy of their data submitted to the REAL data centre. The centre examined all the data sent by site investigators and sent queries if necessary to verify the accuracy of the data.

Patients

By April 2011, 2067 RA patients were registered in REAL, of these 1044 patients started treatment with infliximab, etanercept or tocilizumab at the time of enrolment or after enrolment in REAL. Four patients were excluded from this study because the reason for discontinuation of the initial biological agents was not identified. Eighteen patients who were enrolled in another clinical study requiring the discontinuation of infliximab were also excluded. We did not include patients who used adalimumab, abatacept or golimumab as the first biological agent in REAL because we did not have sufficient numbers of patients on adalimumab in the database (n=98) compared with infliximab and etanercept and had no patients given abatacept or golimumab in the database at the time our data were compiled. Our analysis included 412 patients who started infliximab, 442 patients who started etanercept and 168 patients who started tocilizumab.

Follow-up

For patients who initiated biological agents (infliximab, etanercept, or tocilizumab) at enrolment in REAL, the start date

Clinical and epidemiological research

Table 2 Reasons for drug discontinuation in RA patients treated with infliximab, etanercept or tocilizumab*

Reason for discontinuation	Infliximab (n=157)†	Etanercept (n=130)†	Tocilizumab (n=51)†
Adverse events	57 Cases (36.3%)	57 Cases (43.8%)	23 Cases (45.1%)
Infection	20 Cases (12.7%)	22 Cases (16.9%)	8 Cases (15.7%)
Pulmonary diseases except infection‡	7 Cases (4.5%)	7 Cases (4%)	3 Cases (5.9%)
Infusion reaction	6 Cases (3.8%)	NA	0 Case (0%)
Allergy except infusion reaction	7 Cases (4.5%)	12 Cases (9.2%)	6 Cases (11.8%)
Malignancy	6 Cases (3.8%)	3 Cases (2.3%)	1 Case (2%)
Cardiovascular system disease	2 Cases (1.3%)	2 Cases (1.5%)	2 Cases (3.9%)
Others	9 Cases (5.7%)	11 Cases (8.5%)	3 Cases (5.9%)
Lack of efficacy	68 Cases (43.3%)	47 Cases (36.2%)	23 Cases (45.1%)
Good control	21 Cases (13.4%)	7 Cases (5.4%)	2 Cases (3.9%)
Miscellaneous§	11 Cases (7.0%)	19 Cases (14.6%) §	3 Cases (5.9%)

The χ^2 test was applied to assess differences in the proportion of causes for discontinuation (ie, adverse event, lack of efficacy, good control and miscellaneous), and the adjusted residuals were calculated. A significant difference among the three groups ($p=0.026$) was observed. The adjusted residuals indicated that significantly higher percentages of patients in the infliximab group stopped the treatment due to good disease control compared with the other two groups ($p<0.05$).

*Values are the number (percentage) of patients who discontinued use because of each reason.

†Number of patients who discontinued their first biological DMARD for any reason.

‡Pulmonary diseases except for infection included interstitial pneumonia (three cases for infliximab, five for etanercept, two for tocilizumab) and other pulmonary diseases (four for infliximab, two for etanercept, one for tocilizumab).

§Miscellaneous reasons for drug discontinuation include patients' preference, financial reasons, and pregnancy.

DMARD, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.

NA, not applicable

of the observation period was the date these agents were first administered. For patients who started non-biological DMARD at the time of entry in REAL and who later started treatment with biological agents, the start of the observation period was the date of the first administration of biological agents in REAL. Observation was stopped either at 2.5 years after the start of the observation period, on the date of death of a patient, loss to follow up, enrolment in clinical trials, or when therapy was stopped with the first biological agent in REAL for more than 90 days, or on 4 April 2011, whichever came first. The period following switching to a second biological agent was excluded from this study. We defined termination of treatment with biological agents as stopping treatment with the agent for more than 90 days. The date of the last administration of each biological DMARD was retrieved from medical records and reported by the site investigators. Reasons for drug discontinuation were obtained from case report forms of REAL supplemented by medical records, if necessary, and classified into AE, good control, LOE or miscellaneous. We did not discriminate between a primary and secondary LOE. Note that we collected only serious AE in REAL, but also collected AE in this study if it was the main reason for the discontinuation of a biological agent. When a patient had two or more reasons for drug discontinuation, site investigators assigned precedence and we used the primary reason contributing to drug discontinuation for that patient.

Statistical analysis

The primary outcome of this study was the investigation of the association of the use of infliximab, etanercept and tocilizumab with drug discontinuation due to AE. We also sought to identify other risk factors for drug discontinuation due to AE. Drug retention rates were calculated by the Kaplan–Meier method and compared using the log-rank test among groups. For univariate analysis, the χ^2 test was used for comparison of categorical variables and the Kruskal–Wallis test was used for continuous variables among the three agents. For multivariate analysis, the Cox regression hazard model with the forced entry method was employed to compare risks for drug discontinuation due to AE. The validity of the proportional hazards assumption was confirmed by the log-minus-log survival function. We followed the STROBE statement³² for clear reporting

except for 'the number and reasons for non-participation' in this study.

These statistical analyses were conducted using SPSS (version 16.0 Illinois,). All p values were two-tailed and $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the patients

This analysis included 412 patients in the infliximab group (636.0 patient-years (PY)), 442 in the etanercept group (765.3 PY) and 168 in the tocilizumab group (206.5 PY). Table 1 shows the baseline characteristics of the groups. There were significant differences in age, gender, disease duration and clinical status of the patients. The etanercept and tocilizumab groups had longer disease duration ($p<0.001$) and higher percentages of comorbidities than the infliximab group ($p<0.001$ for chronic pulmonary disease, $p=0.011$ for diabetes mellitus). The rates of biological-naïve patients (96.4% for the infliximab group, 83.9% for the etanercept group and 46.4% for the tocilizumab group) ($p<0.001$) and of the use of three or more non-biological DMARD ($p<0.001$) in the tocilizumab group were the lowest among the three groups. The rate of the use ($p=0.007$) and dose ($p<0.001$) of oral corticosteroids of the etanercept group were higher than those for the other two groups. Disease activity did not differ significantly among the groups.

Occurrence of treatment termination

The median IQR of the observation period for each group was 1.50 (0.74–2.50) years for the infliximab group, 2.1 (0.98–2.50) years for the etanercept group and 1.0 (0.5–2.0) years for the tocilizumab group. The number of patients who discontinued biological agents for any reason during the observation period was 157 (38.1%) for the infliximab group, 130 (29.4%) for the etanercept group and 51 (30.4%) for the tocilizumab group ($p=0.019$ by χ^2). Table 2 shows the reasons for drug discontinuation for each group. A significant difference among the three groups ($p=0.026$ by χ^2) was seen in the proportions of reasons for discontinuation, and the adjusted residuals indicated that significantly higher percentages of patients in the infliximab group stopped treatment due to good disease control compared with the other two groups ($p<0.05$). The most frequently reported

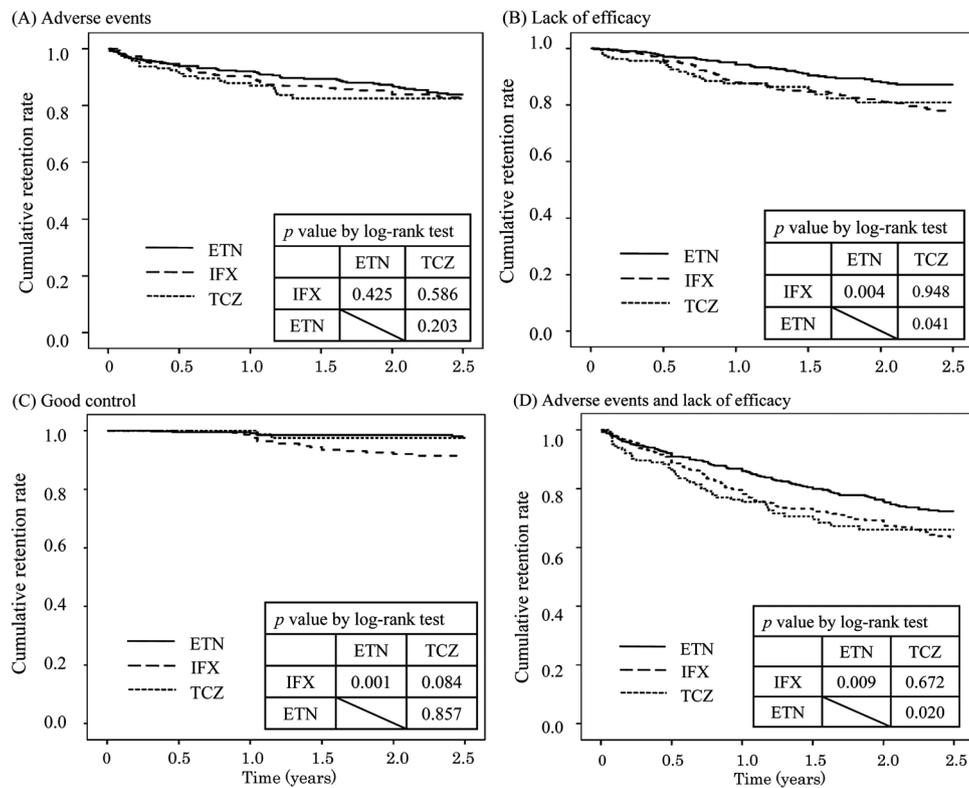


Figure 1 Kaplan-Meier curves for time to discontinuation for each biological agent (etanercept (ETN); infliximab (IFX); tocilizumab (TCZ)). Withdrawal for adverse events (A), lack of efficacy (B), good control (C), and adverse events and lack of efficacy (D) are presented separately. Drug retention rates are compared using the log-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-naïve and non-naïve patients (see supplementary figures, available online only). In both groups, there was no significant difference in drug retention rates between biological-naïve and non-naïve patients. However, we found a numerically higher discontinuation rate of biological agent non-naïve 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 Swiss¹⁴ and the French¹⁶ 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 tocilizumab⁴¹ 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-naïve 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-naïve patients compared with biological agent non-naïve 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-naïve 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 classification⁵⁰ 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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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

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