<table>
<thead>
<tr>
<th>English</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Sakai, Ryoko; Tanaka, Michi; Nanki, Toshihiro; Watanabe, Kaori; Yamazaki, Hayato; Koike, Ryuji; Nagasawa, Hayato; Amano, Koichi; Saito, Kazuyoshi; Tanaka, Yoshiya; Ito, Satoshi; Sumida, Takayuki; Ihata, Atsushi; Ishigatsubo, Yoshiaki; Atsumi, Tatsuya; Koike, Takao; Nakajima, Atsuo; Tamura, Naoto; Fujii, Takao; Dobashi, Hiroaki; Tohma, Shigeto; Sugihara, Takahiko; Ueki, Yukitaka; Hashiramoto, Akira; Kawakami, Atsushi; Hagino, Noboru; Miyasaka, Nobuyuki; Harigai, Masayoshi</td>
</tr>
<tr>
<td>Citation</td>
<td>Annals of the Rheumatic Diseases, 71(11), pp.1820-1826; 2012</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2012-11</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10069/30709">http://hdl.handle.net/10069/30709</a></td>
</tr>
<tr>
<td>Rights</td>
<td>© 2013 BMJ Publishing Group Ltd &amp; European League Against Rheumatism. All rights reserved.</td>
</tr>
</tbody>
</table>
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

Ryoko Sakai,1,2 Michi Tanaka,1,2 Toshihiro Nanki,1,2 Kaori Watanabe1,2 Hayato Yamazaki,1,2 Ryui Koike,1,2,3 Hayato Nagasawa,4 Koichi Amano,4 Kazuoyoshi Saito,5 Yoshiya Tanaka,5 Satoshi Ito,5 Takayuki Sumida,6 Atsushi Ihata,7 Yoshiaki Ishigatsubo,7 Tatsuya Atsumi,8 Takao Koike,8 Atsuo Nakajima,9 Naoto Tamura,10 Takao Fuji,11 Hiroaki Dobashi,12 Shigeto Tohma,13 Takahiko Sugihara,14 Yukitaka Ueki,15 Akira Hashiramoto,16 Atsushi Kawakami,17 Noboru Higino,18 Nobuyuki Miyasaka,2,19 Masayoshi Harigai1,2,3 for the REAL Study Group

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 Rheumatology3 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
Clinical and epidemiological research

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

<table>
<thead>
<tr>
<th></th>
<th>Infliximab group (n=412)</th>
<th>Etanercept group (n=442)</th>
<th>Tocilizumab group (n=168)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.6±13.5</td>
<td>58.5±13.0</td>
<td>59.8±13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, %</td>
<td>85.9</td>
<td>78.1</td>
<td>80.4</td>
<td>0.011</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7.9±7.8</td>
<td>10.3±8.9</td>
<td>10.3±9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steinbrocker's class (3 or 4), %</td>
<td>24.8</td>
<td>31.2</td>
<td>27.4</td>
<td>0.108</td>
</tr>
<tr>
<td>Steinbrocker’s stage (III or IV), %</td>
<td>43.9</td>
<td>57.0</td>
<td>46.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prednisolone-equivalent dose of corticosteroids (mg/day)</td>
<td>4.5±1.2 (n=411)</td>
<td>4.5±1.3 (n=440)</td>
<td>5.1±3.4 (n=167)</td>
<td>0.056</td>
</tr>
<tr>
<td>Use of ≥3 previous non-biological DMARD, %</td>
<td>41.0</td>
<td>54.5</td>
<td>31.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biological-naïve, %</td>
<td>96.4</td>
<td>83.9</td>
<td>46.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methotrexate use, %</td>
<td>99.3</td>
<td>44.6</td>
<td>44.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methotrexate dose, mg/week</td>
<td>8.0±2.1</td>
<td>7.0±2.0</td>
<td>8.2±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of immunosuppressive drugs, except for methotrexate, %</td>
<td>1.9</td>
<td>5.7</td>
<td>14.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral corticosteroid use, %</td>
<td>68.9</td>
<td>73.1</td>
<td>60.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Prednisolone-equivalent dose of corticosteroids (mg/day)</td>
<td>5.4±2.6</td>
<td>6.1±3.3</td>
<td>4.9±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic pulmonary disease, %</td>
<td>22.6</td>
<td>36.7</td>
<td>40.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>8.5</td>
<td>14.9</td>
<td>12.5</td>
<td>0.015</td>
</tr>
</tbody>
</table>

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

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

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

The χ² 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).

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

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

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 followed the STROBE statement for clear reporting 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 statement for clear reporting except for ‘the number and reasons for non-participation’ in this study.

The statistical analyses were conducted using SPSS (version 16.0Illinois, ). 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-naive patients (96.4% for the infliximab group, 85.9% 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 χ²). Table 2 shows the reasons for drug discontinuation for each group. A significant difference among the three groups (p=0.026 by χ²) 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
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

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.

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
Clinical and epidemiological research

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

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

*p Cox regression hazard model analysis, adjusted for the variables included in the table, gender and calendar year.

Inhibitors. 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 and the French registries. In this study, AE and LOE were the two major reported reasons for discontinuation, with similar percentages also for all in the 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 and tocilizumab without flare of RA, but the reported percentage of patients who could discontinue infliximab was higher compared with tocilizumab. In contrast, there was 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. The prevalence of antidrug antibodies in RA patients who were treated with infliximab is much higher compared with etanercept and tocilizumab. The tocilizumab group had a significantly lower percentage of biological-naive patients, which may be associated with a less favourable response to treatment. 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 S5, 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. 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. In all three groups, infections were more 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 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.

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 χ² 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 was used to define 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.

Acknowledgements The investigators of the REAL study group and their affiliates who contributed to this work were: Yukiko Komano (Tokyo Medical and Dental University; Shintaro Hirata (University of Occupational and Environmental Health); Taichi Hayashi (University of Tsukuba); Mitsuito Takeno (Yokohama City University); Shinshuke Yasuda (Hokkaido University); Yoshiharu Fukanuma (Juntendo University); Tsuneo Mimori (Kyoto University); Suneichi Shiozawa (Kobe University); Hiroaki Ida, Katsumi Eguchi (Nagasaki University); Kazuhiro Yamamoto (The University of Tokyo); Kazuhiko Eawaa (Kurashiki Kosei Hospital); Sae Ochi (Tokyo Metropolitan Bokubu Hospital); Kenji Nagasaki (One Municipal General Hospital); Yudito Kameda, Yaku Kaneko, Tatsunori Takeuchi (Keio University); Kiyoji Migtia (National Hospital Organization Nagasaki Medical Centre); Yasushi Murata (Kobe University); Tetsuji Sawada (Tokyo Medical University Hospital); Akayo Nakajima, Hisashi Yamanaoka (Tokyo Women's Medical University); Yoshinori Nonomura (Tokyo Kyosai Hospital). Yokohama City Minato Red Cross Hospital is also a member of the REAL study group, but was not involved in the present study. The authors sincerely thank all the rheumatologists and others caring for RA patients enrolled in REAL.

Funding This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare, Japan (H23-meneki-site-016 and H19-meneki-ippan-009 to NM, H22-meneki-ippan-D01 to MH) and by a grant-in-aid for scientific research from the Japan Society for the Promotion of Science (#20500958 to NH, #19500530 to RK, and #50277114 to MT). This work was also supported by grants for pharmacovigilance research on biological agents from Abbott Laboratories, Bristol-Myers Japan, Eisai, Chugai Pharmaceutical, Mitsubishi Tanabe Pharma Corp, Takeda Pharmaceutical and Pfizer Japan (to NH), and by a grant from the Japanese Ministry of Education, Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Diseases.

Competing interests KA has received research support from Chugai Pharmaceutical, Mitsubishi Tanabe Pharma and Astellas Pharma YT has received consulting fees, speaking fees, and/or honoraria from Mitsubishi-Tanabe Pharma, Chugai Pharmaceutical, Eisai, Takeda Pharmaceutical, Astellas Pharma and Abbott Japan, and has received research grant support from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical, MSD KK, Pfizer Japan, Astellas Pharma, Chugai Pharmaceutical, Abbott Japan and Eisai. TF has received grant/research support from Abbott Japan, Eisai, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Pfizer Japan, Astellas Pharma, Bristol-Myers Squibb KK. NM has received research grants from Abbott Japan, Astellas Pharma, MSD KK, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, and Teijin Pharma. MH has received research support from Abbott Laboratories, Bristol-Myers Japan, Eisai, Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Pfizer Japan, Astellas Pharma, Bristol-Myers Squibb KK, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Santen Pharmaceuticals, Takeda Pharmaceutical and Pfizer Japan.

Ethics approval The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and other participating institutions.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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

REFERENCES

Clinical and epidemiological research


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.

*Ann Rheum Dis* 2012 71: 1820-1826 originally published online April 13, 2012
doi: 10.1136/annrheumdis-2011-200838

Updated information and services can be found at:
http://ard.bmj.com/content/71/11/1820.full.html

These include:

**Data Supplement**
"Web Only Data"
http://ard.bmj.com/content/suppl/2012/04/12/annrheumdis-2011-200838.DC1.html

**References**
This article cites 48 articles, 19 of which can be accessed free at:
http://ard.bmj.com/content/71/11/1820.full.html#ref-list-1

Article cited in:
http://ard.bmj.com/content/71/11/1820.full.html#related-urls

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Connective tissue disease (2926 articles)
- Degenerative joint disease (3182 articles)
- Immunology (including allergy) (3434 articles)
- Musculoskeletal syndromes (3421 articles)
- Rheumatoid arthritis (2203 articles)
- Epidemiology (969 articles)

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/