A comparison of incidence and risk factors for serious adverse events in rheumatoid arthritis patients with etanercept or adalimumab in Korea and Japan

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Abstract

Objective. To compare the incidence and risk factors of serious adverse events (SAEs) in rheumatoid arthritis (RA) patients treated with etanercept (ETN) or adalimumab (ADA) between Korean and Japanese registries.

Methods. We recruited 416 RA patients [505.2 patient-years (PYs)] who started ETN or ADA from Korean registry and 537 RA patients [762.0 PY] from Japanese registry. The patient background, incidence rate (IR) of SAE in 2 years, and risk factors for SAEs were compared.

Results. Korean patients were younger and used more nonbiologic DMARDs, higher doses of methotrexate, and lower doses of prednisolone (PSL). The IR of SAEs (/100 PY) was higher in the Japanese registry compared to the Korean [13.65 vs. 6.73]. In both registries, infection was the most frequently reported SAE. The only significant risk factor for SAEs in Korean registry was age by decade [1.45]. In Japanese registry, age by decade [1.54], previous use of nonbiologic DMARDs ≥ 4 [1.93], and concomitant use of oral PSL ≥ 5 mg/day [2.20] were identified as risk factors for SAEs.

Conclusions. The IR of SAE in Japan, especially infection, was higher than that of Korea, which was attributed to the difference of demographic and clinical characteristics of RA patients and treatment profiles.

Keywords

Epidemiology, Registry, Rheumatoid arthritis, Safety

Introduction

The introduction of biologic disease-modifying antirheumatic drugs (biologic DMARDs) in the past decade has revolutionized treatment of rheumatoid arthritis (RA). Efficacy and safety of treatment with biologic DMARDs have been demonstrated in a number of clinical trials, but cost and long-term effectiveness of treatment with biologic DMARDs and safety in older patients or those with comorbidities, who are generally excluded from clinical trials, have been of concern [1]. To complement the evidence obtained from clinical trials, observational cohorts for RA patients treated with biologic DMARDs have been established in many countries, and have provided indispensable evidence for the safety and effectiveness of biologic DMARDs in clinical practice. However, some cohorts have reported results with differing magnitudes or even discordance of risk for the same adverse events [2]. For example, the incidence of serious infections in European RA registries was comparable [3,4], whereas in the US, lower rates have been reported in some studies [5]. These discrepant results arise from methodological differences, such as case definition for adverse events, length of follow-up, or selection and structure of a comparator group. Difference in treatment profile and ethnicities may also account for the discrepancy. Therefore, a careful comparison of registries from various point of views including methodology is
imperative to understand similarities and differences in the results obtained from each registry [6].

Through international collaborations among countries, the comparison of data from RA patients treated with biologic DMARDs will allow us to investigate the impact of differences in patients’ characteristics and health care systems on efficacy and safety of the treatment. Curtis et al. [2] have conducted the qualitative comparison of RA biologics registries in US and Europe and reported that different patients’ demographics, patterns of comorbidities, and sociodemographic characteristics provide valuable information to address the comparative safety of treatments for RA. However, no international collaborative studies have yet been reported to investigate the same outcomes using harmonized methodologies. In Korea, the effectiveness and safety of biologic DMARDs in clinical practice have been reported using a retrospective biologic DMARDs registry (REEtrospective study for Safety and Effectiveness of Anti-RA treatment with biologics, RESEARCh) [7]. In Japan, the REnrygate and comorbidities: a prospective cohort study in Japan, the RESEARCh database was approved by the ethics committees of the Hanyang University Hospital and other participating institutions. The reason for selecting ADA and ETN for this study is that these two biologics were approved within two calendar years in both countries. The observation period for this study started at the first dose of one of these biologic DMARDs. Observation of each patient was stopped either 2 years after the start of the observation period, or on the date of discontinuation of these biologic DMARDs, death, loss-to-follow up, or enrollment in clinical trials, whichever came first. We defined discontinuation of treatment with ADA or ETN as stopping administration of these agents for more than 90 days. Reasons for discontinuation of these biologic DMARDs were retrieved from medical records and classified into adverse events (AEs), Lack of efficacy (LOE), or miscellaneous. When a patient had two or more reasons for drug discontinuation, site investigators assigned precedence and the primary reason contributing to drug discontinuation for the patient was used.

**Definition for comorbidity**

For qualitative comparison, comorbidity was defined as cardiovascular and cerebrovascular diseases, including angina, myocardial infarction, heart failure, and strokes; pulmonary diseases, including interstitial lung diseases, chronic obstructive pulmonary diseases, and asthma; or liver diseases, including abnormalities in liver function tests, liver cirrhosis, hepatitis B, and hepatitis C. Renal dysfunction was defined using the estimated glomerular filtration rate (eGFR). We used a modification of the diet in renal disease (MDRD) formula to calculate eGFR and categorized according to the stage of chronic kidney disease (CKD) [12]. Anemia was defined using the WHO criteria (hemoglobin level < 13 g/dl for men and < 12 g/dl for women) [13].

**Patients and methods**

**Database and patients**

**RESEARCh**

The retrospective registry of Korean patients with RA, the RESEARCh, was established to evaluate the safety and effectiveness of biologic DMARDs by Clinical Research Center of Rheumatoid Arthritis (CRCRA) funded by Ministry of Health and Welfare, Republic of Korea [7]. All patients meeting the 1987 American College of Rheumatology criteria for RA who had ever been treated with biologic DMARDs from December 2000 to June 2011 were identified from the medical records of Hanyang University Hospital for Rheumatic Diseases. The RESEARCh study was approved by the ethics committee of the Hanyang University Hospital, and informed consent was not required because the data was deidentified and collected retrospectively.

Comprehensive chart reviews for all patients were undertaken by well-trained health professionals; and demographics, disease activity, comorbidities, medications, and laboratory data during the use of biologic DMARDs and their SAEs were collected. For the patients who were in use of biologic DMARDs at the time of data collection, the observational period was defined from the starting point of current agent to assessment date. For the other patients who had stopped biologic DMARDs before data collection, the agent with longest use for each patient was included in this database. Demographic features of RA patients and the persistence of TNF inhibitors in the RESEARCh database were quite similar to those of a previously reported study using nation-wide claims database of Korea: mean age (50.5 ± 13.2 in the RESEARCh vs. 50.6 ± 14.9 in the nation-wide database), proportion of female (86.1% vs. 84.9%), and persistence of TNF inhibitors during one year (74% vs. 73%) [7,10].

**REAL**

REAL is a prospective cohort established to investigate the long-term safety of biologic DMARDs in RA patients. Twenty-seven institutions participate, including 16 university hospitals and 11 referring hospitals. Details of the REAL have been previously described [9,11]. Briefly, the criteria for patient enrollment in the REAL include meeting the 1987 American College of Rheumatology criteria for RA, written informed consent, and starting or switching treatment with biologic DMARDs or starting, adding, or switching nonbiologic DMARDs at the time of enrollment in the REAL. Demography, disease activity, comorbidities, treatments, and laboratory data at the time of enrollment in the REAL were recorded. A follow-up form was submitted every 6 months by 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. Each patient is followed for 5 years. Enrollment in the REAL database was started in June 2005 and closed in January 2012. Data were retrieved from the REAL database on August 24, 2011 for this study. The REAL study was approved by the ethics committee of the Tokyo Medical and Dental University Hospital and other participating institutions. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

**Patients and follow-up**

We first identified 416 Korean RA patients whose registered biologic DMARDs in the RESEARCh database were ADA or ETN and 537 Japanese patients with RA who used ADA or ETN as the first biologic DMARDs in the REAL database, and enrolled themselves in this study. The reason for selecting ADA and ETN for this study is that these two biologics were approved within two calendar years in both countries. The observation period for this study started at the first dose of one of these biologic DMARDs. Observation of each patient was stopped either 2 years after the start of the observation period, or on the date of discontinuation of these biologic DMARDs, switching to other biologic DMARD, death, loss-to-follow up, or enrollment in clinical trials, whichever came first. We defined discontinuation of treatment with ADA or ETN as stopping administration of these agents for more than 90 days. Reasons for discontinuation of these biologic DMARDs were retrieved from medical records and classified into adverse events (AEs), Lack of efficacy (LOE), or miscellaneous. When a patient had two or more reasons for drug discontinuation, site investigators assigned precedence and the primary reason contributing to drug discontinuation for the patient was used.
Definition of SAEs

Our definition of a SAE, including serious infection (SI), was based on the report by the International Conference on Harmonization. In addition, bacterial infections that required intravenous administration of antibiotics, as well as opportunistic infections, were also regarded as SAEs. SAEs were classified using the System Organ Class (SOC) of the medical dictionary for regulatory activities (MedDRA version 11.1). SAEs were attributed to ETN or ADA when they developed during treatment with these biologics and no risk window was applied.

Statistical analysis

The chi-square test was used for comparison of categorical variables and the Mann–Whitney test for continuous variables. Drug retention rates were compared using the Kaplan–Meier method and the log-rank test. Crude IRs per 100 PY and crude incidence rate ratios (IRRs) with their 95% confidence intervals (CI) comparing Japan to Korea were calculated for all SAEs occurring from the first dose of ADA or ETN to the end of the observation period. For multivariate analysis, the Cox regression model with the forced entry method was employed. These statistical analyses were performed using SPSS (version 20.0, SPSS Inc., Chicago, IL USA). All p values were 2-tailed and p < 0.05 was considered statistically significant.

Results

Demographic and clinical baseline characteristics of patients from the two registries

We first compared baseline demographic and clinical characteristics of RA patients who used ADA or ETN in each registry (Table 1 and Figure 1). Patients in the RESEARCH were younger (47.5 ± 15.8 years-old, p < 0.001) and had shorter disease duration (8.5 ± 6.7 years vs. 9.9 ± 9.0 years, p = 0.009) than those in the REAL. The proportions of patients without previous exposure to biologic DMARDs (i.e., biologic DMARD-naïve patients) did not differ between the two registries, while 60.0% of the patients in the RESEARCH, but only 29.4% in the REAL, experienced four or more nonbiologic DMARDs (p < 0.001). The mean numbers of previous nonbiologic DMARDs were 4.1 in the RESEARCH and 2.6 in the REAL; the distribution is shown in Figure 1A. The mean Disease Activity Score calculated based on three variables including 28-swollen and tender joints count and C-reactive protein at starting biologic DMARDs did not differ between the registries.

The rates for concomitant metformin (MTX) more frequently and at higher dosage than those in the REAL (75.9% vs. 67.2%, p < 0.001) and had shorter disease duration (10.8% vs. 6.7%, p < 0.001), liver disease (21.9% vs. 15.8%, p = 0.044), and anemia (73.8% vs. 60.5%, p = 0.001) were significantly higher in the RESEARCH compared to the REAL. However, the rates for pulmonary disease (5.3% vs. 20.3%) and diabetes mellitus (9.4% vs. 13.6%) were significantly higher in the REAL than in the RESEARCH (Table 1).
Table 2. Reasons for drug discontinuation of patients with RA treated with ETN or ADA in Korean (RESEARCh) and Japanese (REAL) registries.*

| Reasons for drug discontinuation | RESEARCh (n = 124)† | REAL (n = 144)‡ |
|----------------------------------|----------------------|-----------------|
| Adverse events, n (%)            | 41 (33.1)            | 56 (38.9)       |
| Infection, n (%)                 | 11 (8.9)             | 19 (13.2)       |
| Pulmonary disease except infection, n (%) | 4 (3.2) | 6 (4.2)       |
| Allergy reaction, n (%)          | 10 (8.1)             | 12 (8.3)        |
| Malignancy, n (%)                | 0 (0)                | 4 (2.8)         |
| Cardiovascular system disease, n (%) | 2 (1.6) | 3 (2.1)       |
| Others, n (%)                    | 14 (11.3)            | 12 (8.3)        |
| Lack of efficacy, n (%)          | 31 (25.0)            | 53 (36.8)       |
| Miscellaneous*, n (%)            | 52 (41.9)            | 35 (24.3)       |

Chi-square test was applied to assess differences in the proportion of causes for discontinuation (i.e., adverse event, lack of efficacy, and miscellaneous), and the adjusted residuals were calculated. A significant difference among the two groups (p = 0.007) was observed. The adjusted residuals indicated that significantly higher percentage of patients in the REAL stopped the treatment due to lack of efficacy compared to the RESEARCh and significantly more patients in the RESEARCh stopped the treatment due to miscellaneous.

*Values are the number (percentage) of patients who discontinued ETN or ADA because of each reason.
†Number of patients who discontinued ETN or ADA for any reason.
‡Pulmonary diseases except for infection included interstitial pneumonia and other pulmonary diseases.
§Miscellaneous included good control, patients’ preference, financial reasons, and pregnancy.

The median interquartile range treatment period for each registry was 1.3 (0.5–2.0) years for the RESEARCh and 2.0 (0.8–2.0) years for the REAL. The numbers of patients who discontinued ADA or ETN for any reasons during the observation period were 124 (29.8%) for the RESEARCh and 144 (26.8%) for the REAL (p = 0.308 by chi-square). The reasons for discontinuation of ETN or ADA in each registry are shown in Table 2. The development of AEs was the most frequent reason for the discontinuation in both the RESEARCh (n = 41, 33.1%) and the REAL (n = 56, 38.9%). The two major AEs leading to discontinuation of the biologic DMARDs were infection and allergic reaction for both registries. There was no significant difference in the retention rates of ETN and ADA for 2 years between the registries (64.6% in the RESEARCh, 70.1% in the REAL, p = 0.060 by Kaplan–Meier analysis and log-rank test [supplementary Figure 2A available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695]), and no significant differences for treatment discontinuation due to AEs (p = 0.848 by log-rank test [supplementary Figure 2B available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695]).
are summarized in Table 3. The crude IRR comparing the REAL with the RESEARCH for all SAEs was 2.03 (95% CI, 1.38–2.99). The IRR for infections and respiratory diseases were 1.68 (95% CI, 0.92–3.05) and 1.44 (95% CI, 0.55–3.78), respectively (Table 3).

Factors influencing development of SAEs

To determine factors influencing development of SAEs, we compared patients who had and had not experienced SAEs using a univariate analysis and selected variables with p value < 0.05 or those with medical importance for the multivariate analysis. In the RESEARCH, age per decade (hazard ratio [HR] 1.45, 95% CI 1.23–1.74) and with previous use of nonbiologic DMARDs (HR 1.94, 95% CI 1.09–3.37) were identified as risk factors for development of SAEs using the multivariate Cox regression model. In the REAL, age per decade (HR 1.54, 95% CI 1.22–1.93), previous use of nonbiologic DMARDs ≥ 4 (HR 1.93, 95% CI 1.20–3.10), concomitant use of oral CSs (PSL-equivalent dose) ≥ 5 mg/day (HR 2.20, 95% CI 1.11–4.35) were identified as risk factors for SAEs using the multivariate Cox regression model. We then combined the patients from the two registries and performed the multivariate Cox regression analysis. In this analysis, the risk for SAEs was significantly higher in older patients (HR 1.47 per decade, 95% CI 1.23–1.74), and with previous use of nonbiologic DMARDs ≥ 4 (HR 1.64, 95% CI 1.09–2.47) and concomitant use of oral CSs (0 < PSL-equivalent dosage < 5 mg/day; HR 1.91, 95% CI 1.04–3.49, ≥ 5 mg/day; HR 2.04, 95% CI 1.18–3.53) (Table 4).

Discussion

This is the first study to directly compare safety of biologic DMARDs using harmonized methods between two registries from two countries.
countries in Asia. This study provides unique findings about safety of ADA and ETN because the two registries have different demographic and clinical characteristics of patients, as well as treatment profiles before starting biologic DMARDs. Some of these differences are identified as factors influencing the development of SAEs.

We found significant differences in demographic and clinical characteristics of RA patients between the two registries. First, in the RESEARCh, significantly more patients had experienced four or more nonbiologic DMARDs before starting ETN or ADA than the REAL, although patients in the RESEARCh were significantly younger with shorter disease durations than the REAL. In Korea, according to strict reimbursement guidelines, rheumatologists are required to treat a patient with at least two nonbiologic DMARDs, including MTX, for six months before confirming inadequate response to the treatment and starting TNF inhibitors. Japanese guidelines in 2007 recommend treatment with TNF inhibitors for patients who had inadequate response to treatment with at least one DMARD for 3 months [14]. Second, patients in the RESEARCh used concomitant MTX more frequently and higher dosages than those in the REAL. The maximum approved dosage for MTX in these countries apparently affects the use of the anchor drug in the two registries; i.e., 8 mg/week until February 2011, allowed up to 16 mg/week now in Japan and 20 mg/week in Korea.

The unadjusted IR of overall SAEs in the REAL was significantly higher than in the RESEARCh (IRR 2.03, 95% CI 1.38–2.99), explained at least in part by the numerically higher IR of SI in the REAL compared to the RESEARCh. The incidence of SIs in the REAL of 4.99/100 PY was comparable to Western registries incidence of 5.4–6.6/100 PY, whereas a lower incidence in the RESEARCh of 2.97/100 PY was observed [3,4,15]. We suppose that demographic features including age structure and comorbidity profiles of the two cohorts contributed to the difference. The proportion of elderly (≥65) in the general population in Japan was higher than in Korea in 2009 (22.7% in Japan vs. 10.4% in Korea) [16,17]. Compatible with these figures, the prevalence of elderly RA (≥65-year-olds) was 36.2% in a Japanese RA cohort [18] and 21.8% in Korean RA cohort [19]. Increased percentage of patients with pulmonary comorbidities, cardiovascular diseases, and diabetes mellitus in Japan may be explained by higher prevalence of elderly RA patients and longer disease duration. The prevalence of infection-related comorbidities such as pulmonary diseases, diabetes mellitus, and renal dysfunction is significantly higher in the REAL compared to the RESEARCh. It is plausible that the higher prevalence of comorbidities could be associated with the higher IR of SIs in the REAL. This association was supported by a previous comparative study showing that the difference in incidence of SIs between the American and European registries could be derived from differing comorbidity profiles of the registries [2].

Difference in the use of CSs between the two countries needs to be mentioned. It has been reported that the frequent usage of CSs at higher dosages was significantly associated with development of SIs in cohort studies from Western countries [20–22]. Japanese post marketing surveillance for ETN (HR 2.03, 95% CI 1.46–2.84) [23] and tocilizumab [24] (odds ratio 2.17, 95% CI 1.25–3.74) also revealed that concomitant use of CSs was one of the risk factors for SIs. Moreover, higher dosages of CSs significantly increased the risk for SIs in the REAL and its relative risk was the highest among the identified risk factors (2.49, 95% CI 1.08–5.50) [9]. Overall, it is apparent that use of CSs leads to a higher risk for SIs. In this study, the mean dosage of CSs at baseline was significantly higher in the REAL compared to the RESEARCh, which also explains the difference in incidence of SIs between the two registries. Furthermore, frequent usage of CSs at higher dosages may also be responsible for the higher prevalence of diabetes mellitus in Japanese RA patients, which in turn makes them more susceptible to infection. These data emphasize the importance of minimizing exposure to CSs in RA patients to decrease the risk for SIs.

Age, previous use of nonbiologic DMARDs ≥4, and concomitant use of CSs were significantly associated with occurrence of SAEs in the REAL as well as in the combined data, while the latter two factors were not in the RESEARCh. It has been reported that RA patients with larger number of previously used DMARDs have increased risk for SIs [20,22], which could explain the association between nonbiologic DMARDs ≥4 and SAE in this study because SIs account for about 40% of the SAEs (Table 3). In general, larger numbers of previously used DMARDs suggest long-standing and/or intractable disease. This may not be the case, however, for Korean patients given biologics because the patients have to be treated at least with DMARDs ≥2 beforehand by strict reimbursement guidelines. Such difference could lead to lack of association between previous use of nonbiologic DMARDs ≥4 and SAE in the RESEARCh. Weak trend toward positive association between the concomitant use of CS and SAE was observed in the RESEARCh. The small number of SAEs in the RESEARCh probably contributed to wide 95% confidence interval of the HR for the concomitant use of CS (Table 4) and the factor did not reach statistical significance.

There are certain limitations in our study. First, the difference of study design between the two registries should be mentioned. The data were obtained retrospectively from the RESEARCh registry and prospectively from the REAL registry [25], which could affect the results of this comparative study. To compensate for this difference in collecting data, we standardized the definition of SAEs, reasons for drug discontinuation, and variables such as comorbidities in two registries in this study as described in Patients and Methods. We discussed ambiguous SAE cases through regular meetings as well. A second limitation is that we did not investigate the patients with other biologics except for ETN and ADA. The safety and tolerance of a biologic DMARD can be affected by the approval status of other biologic and nonbiologic DMARDs [26]. The difference in approval status of biologic and nonbiologic DMARDs should be considered when we compare the use of biologic DMARDs between two countries. In this study, therefore, we focused on ADA and ETN, which were approved for treatment of RA within two calendar years in Korea and Japan (see Supplementary Figure S1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695). Third limitation is that RESEARCh was performed in a single institution, whereas REAL is comprised of 27 institutions, which may create selection bias in the study.

In conclusion, the differences in the demographic and clinical characteristics such as age structures, patterns of comorbidity, and treatments profile for RA between the two countries affect types and incidences of SAEs. This international collaborated study facilitates our understanding of similarity and discrepancy in the results from various biological registries, and may help applying the evidence to clinical management of patients with RA.

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Supplementary material available online

Supplementary Figures 1 and 2.