Drug retention of 7 biologics and tofacitinib in biologics-naïve and biologics-switched patients with rheumatoid arthritis -The ANSWER cohort study-

CURRENT STATUS: Under Review

Arthritis Research & Therapy  •  BMC

Kosuke Ebina, Toru Hirano, Yuichi Maeda, Wataru Yamamoto, Motomu Hashimoto, Koichi Murata, Tohru Takeuchi, Hideyuki Shiba, Yonsu Son, Hideki Amuro, Akira Onishi, Kengo Akashi, Ryota Hara, Masaki Katayama, Keiichi Yamamoto, Atsushi Kumanogoh, Makoto Hirao

Kosuke Ebina
Osaka University, Graduate School of Medicine
✉ k-ebina@umin.ac.jp Corresponding Author
ORCiD: https://orcid.org/0000-0002-2426-1024

Toru Hirano
Osaka University, Graduate School of Medicine

Yuichi Maeda
Osaka University, Graduate School of Medicine

Wataru Yamamoto
Krashiki Sweet Hospital

Motomu Hashimoto
Graduate School of Medicine, Kyoto University

Koichi Murata
Graduate School of Medicine, Kyoto University

Tohru Takeuchi
Osaka Medical College

Hideyuki Shiba
Osaka Medical College

Yonsu Son
Kansai Medical University

Hideki Amuro
Kansai Medical University

Akira Onishi
Kobe University Graduate School of Medicine

Kengo Akashi
Kobe University Graduate School of Medicine
Ryota Hara
Nara Medical University

Masaki Katayama
Osaka Red Cross Hospital

Keiichi Yamamoto
Wakayama Medical University Hospital

Atsushi Kumanogoh
Osaka University, Graduate School of Medicine

Makoto Hirao
Osaka University, Graduate School of Medicine

Subject Areas

*Rheumatology*

Keywords

*ANSWER cohort, biological disease-modifying antirheumatic drugs, drug retention, rheumatoid arthritis*
Abstract

Background: This multi-center, retrospective study aimed to clarify retention rates and reasons for discontinuation of 7 biological disease-modifying antirheumatic drugs (bDMARDs) and tofacitinib (TOF), one of the janus kinase inhibitors, in bDMARDs-naïve and bDMARDs-switched patients with rheumatoid arthritis (RA).

Methods: This study assessed 3,897 patients and 4,415 treatment courses with bDMARDs and TOF from 2001 to 2019 (2,737 bDMARDs-naïve patients and 1,678 bDMARDs-switched patients [59.5% switched to their second agent], female 82.3%, baseline age 57.4 years, disease duration 8.5 years; rheumatoid factor positivity 78.4%; Disease Activity Score in 28 joints using erythrocyte sedimentation rate 4.3; concomitant prednisolone [PSL] dose 6.1 mg/day [42.4%], and methotrexate [MTX] dose 8.5 mg/week [60.9%]). Treatment courses included abatacept (ABT; n=663), adalimumab (ADA; n=536), certolizumab pegol (CZP; n=226), etanercept (ETN; n=856), golimumab (GLM; n=458), infliximab (IFX; n=724), tocilizumab (TCZ; n=851), and TOF (n=101/only bDMARDs-switched cases). Drug discontinuation reasons (categorized into lack of effectiveness, toxic adverse events, non-toxic reasons, or remission) and rates were estimated at 36 months using the Gray’s test, and statistically evaluated after adjusted by potential clinical confounders (age, sex, disease duration, concomitant PSL and MTX usage, starting date, and number of switched bDMARDs) using the Fine-Gray model.

Results: Cumulative incidence of drug discontinuation for each reason was as follows: lack of effectiveness in the bDMARDs-naïve group (from 13.7% [ABT] to 26.9% [CZP]; P<0.001 between agents) and the bDMARDs-switched group (from 18.9% [TCZ] to 46.1% [CZP]; P<0.001 between agents). Toxic adverse events in the bDMARDs-naïve group (from 4.6% [ABT] to 11.2% [ETN]; P<0.001 between agents) and the bDMARDs-switched group (from 5.0% [ETN] to 15.7% [TOF]; P=0.004 between agents). Remission in the bDMARDs-naïve group (from 2.9% [ETN] to 10.0% [IFX]; P=0.001 between agents) and the bDMARDs-switched group (from 1.1% [CZP] to 3.3% [GLM]; P=0.9 between agents).

Conclusions: Remarkable differences were observed in drug retention of 7 bDMARDs and TOF between bDMARDs-naïve and bDMARDs-switched cases.

Introduction

Tumor necrosis factor inhibitors (TNFi) such as infliximab (IFX), etanercept (ETN), and adalimumab (ADA), were the first biological disease-modifying anti-rheumatic drugs (bDMARDs) used for rheumatoid arthritis (RA) that had accumulated evidence of drug retention [1-5]. Other TNFi such as golimumab (GLM) (2011) and certolizumab pegol (CZP) (2013), and the first Janus kinase inhibitor (JAKi), tofacitinib (TOF) (2013), were recently approved in Japan. The European League against Rheumatism (EULAR) provided recommendations in 2016 regarding the management of RA with bDMARDs, in which CTLA4-Ig (abatacept [ABT]), anti-interleukin (IL)-6 receptor antibody (tocilizumab [TCZ]), and JAKi are considered equivalent to TNFi [6]. They also mentioned that there is no difference in outcomes among these bDMARDs and JAKi, irrespective of their mechanism of action. Moreover, Smolen et al. reported that these bDMARDs have similar efficacy in previously TNFi-experienced patients, although efficacy may decrease compared with bDMARDs-naïve patients [7]. However, cohort-based studies revealed that in patients who showed inadequate response to TNFi, switching to a non-TNFi agent (such as ABT, rituximab, or TCZ) showed significantly higher drug retention rates compared with switching to another TNFi [8, 9]. Taken together, it is evident that this drug retention (reflecting both safety and effectiveness) may differ between bDMARDs-naïve and bDMARDs-switched cases.

Randomized controlled trials (RCTs) often recruit patients with fewer comorbidities who are different from those in real-world settings [10], and cohort-based observational studies have increasingly been used to investigate the performance of bDMARDs [1-4, 9, 11, 12]. In particular, drug retention is considered as a major index of both safety and effectiveness [4, 13-15]. To the best of our knowledge, there are no reports comparing drug retention rates of 7 bDMARDs and TOF, especially in both bDMARDs-naïve and bDMARDs-switched cases.
We recently reported drug retention rates among bDMARDs used in all age [16, 17] as well as among the elderly population [18], factors associated with the achievement of bDMARDs-free remission [19], and the correlation of treatment response with family history of RA [20] from our cohort. Since then, we are continuously accumulating new data. The aim of this multi-center, retrospective study was to clarify the retention rates of 7 bDMARDs and TOF in both bDMARDs-naïve and bDMARDs-switched cases in a real-world setting.

Materials And Methods

Patients

The Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort is an observational multicenter registry of patients with RA in the Kansai district of Japan. Data from RA patients who fulfilled the 1987 RA classification criteria of the American College of Rheumatology [21] or the 2010 ACR/EULAR RA classification criteria [22] at 6 universities and one university-affiliated hospital (Kyoto University, Osaka University, Osaka Medical College, Kansai Medical University, Kobe University, Nara Medical University, and Osaka Red Cross Hospital) were included [23]. In this study, patients who were newly treated with at least 1 of 7 bDMARDs (ABT, ADA, CZP, ETN, GLM, IFX, and TCZ; including both intravenous and subcutaneous agents, but excluding bio-similar agents) or TOF from 2001 to 2019, with data on starting and discontinuation dates and reasons for discontinuation, were included. In addition, baseline demographic data such as age, sex, duration of disease, disease activity (Disease Activity Score in 28 joints using erythrocyte sedimentation rate [DAS28-ESR]), clinical disease activity index (CDAI), number of previously administered bDMARDs, concomitant doses and ratio of methotrexate (MTX) and prednisolone (PSL) (other glucocorticoids were calculated as equivalent dose to PSL; MTX or PSL dose was not considered when agents were not combined), rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) positivity, and Health Assessment Questionnaire [HAQ] disability index [DI] score were also collected [16-18].

Treatments were administered by the attending rheumatologists in accordance with guidelines of the Japan College of Rheumatology [24-26]. The starting date of each biologic was classified into 3 groups: 2001-2009, 2010-2013, and 2014-2019, according to the released date [IFX (2003), ETN (2005), ADA (2008), TCZ (2008), / ABT (2010), GLM (2011), CZP (2013), TOF (2013), / Sarilumab (2017), Baricitinib (2017), Peficitinib (2019), and ETN biosimilar (2019) (some of them were used as investigational agents before commercially released)] to equalize the released agents’ number and possible influence of other agents on physicians’ prescription decision in each duration. Drug retention was retrospectively evaluated as the duration until definitive treatment interruption. Reasons for discontinuation were analyzed and classified into 4 major categories: 1) lack of effectiveness (including primary and secondary); 2) toxic adverse events (infection, skin or systemic reaction, and other toxic events, including hematologic, pulmonary, renal, cardiovascular complications, and malignancies, etc.); 3) non-toxic reasons (patient preference, change in hospital, desire for pregnancy, etc.); and 4) disease remission [16-18]. Physicians were allowed to cite only one reason for discontinuation. Then, treatment cases were separated into bDMARDs-naïve cases (without TOF) and bDMARDs-switched cases (all cases of TOF were switched from bDMARDs).

Statistical analysis

The estimated cumulative incidence curves and discontinuation ratio of each agent defined by specific reasons at 36 months were examined by the Gray’s test [27, 28]. The discontinuation ratio of the agents at 36 months was analyzed and statistically compared using Fine-Gray hazard competing risk regression model [27, 28], adjusted by potential confounders that may influence drug retention as previously described (age, sex, disease duration, concomitant PSL and MTX usage, starting date and number of switched bDMARDs) [1, 9, 11, 12, 29]. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [30]. P<0.05 was considered statistically significant.
Results

Baseline characteristics

Baseline clinical characteristics of the bDMARDs-naïve cases are shown in Table 1. Overall, mean age was 57.0 years, 81.8% of participants were female, mean disease duration was 7.3 years, RF positivity was 78.6%, ACPA positivity was 81.4%, mean DAS28-ESR score was 4.4, mean CDAI was 17.8, and mean HAQ-DI score was 1.0. Mean doses and ratio of concomitant medications were PSL 6.3 mg/day (39.6%) and MTX 8.6 mg/week (65.4%).

Baseline clinical characteristics of the bDMARDs-switched cases are shown in Table 2. Overall, mean age was 58.1 years, 83.3% of participants were female, mean disease duration was 10.5 years, RF positivity was 78.1%, ACPA positivity was 83.4%, mean DAS28-ESR score was 4.2, mean CDAI was 15.7, and mean HAQ-DI score was 1.1. Mean doses and ratio of concomitant medications were PSL 5.7 mg/day (49.3%) and MTX 8.3 mg/week (57.1%). The bDMARDs were administered as the second agent in 59.5% of patients, and as the third or latter agent in 40.5% of patients.

Drug retention and causes for discontinuation

Cause-specific cumulative discontinuation rates were assessed using Gray's test, and statistically compared using Fine-Gray hazard competing risk regression model at 36 months (Figs. 1-4 and Supplementary Fig. 1).

Drug discontinuation rates due to lack of effectiveness in the bDMARDs-naïve cases were as follows (Fig. 1a): ABT (13.7%), GLM (16.1%), TCZ (16.6%), ADA (20.6%), IFX (21.8%), ETN (22.4%), and CZP (26.9%) (P<0.001). These rates in the bDMARDs-switched cases were as follows (Fig. 1b): TCZ (18.9%), TOF (22.8%), ABT (28.7%), ETN (30.3%), GLM (33.3%), ADA (38.4%), IFX (39.4%), and CZP (46.1%) (P<0.001).

Drug discontinuation rates due to toxic adverse events in the bDMARDs-naïve cases were as follows (Fig. 2a): ABT (4.6%), CZP (5.5%), TCZ (6.8%), ADA (7.9%), GLM (9.3%), IFX (9.7%), and ETN (11.2%) (P<0.001). These rates in the bDMARDs-switched cases were as follows (Fig. 2b): ETN (5.0%), CZP (6.6%), ABT (9.2%), GLM (9.9%), IFX (12.2%), TCZ (13.2%), ADA (14.3%), and TOF (15.7%) (P=0.004).

Drug discontinuation rates due to remission in the bDMARDs-naïve cases were as follows (Fig. 3a): ETN (2.9%), ABT (4.0%), CZP (8.4%), GLM (9.0%), ADA (9.8%), TCZ (9.8%), and IFX (10.0%) (P<0.001). These rates in the bDMARDs-switched cases were as follows (Fig. 3b): CZP (1.1%), TCZ (1.2%), ABT (1.4%), ADA (2.1%), TOF (2.3%), ETN (2.5%), IFX (2.8%), and GLM (3.3%) (P=0.9).

Drug discontinuation rates due to non-toxic events in the bDMARDs-naïve cases were as follows (Supplementary Fig. 1a): CZP (3.8%), IFX (9.0%), ABT (10.8%), TCZ (11.4%), ADA (12.3%), ETN (13.5%), and GLM (17.2%) (P=0.07). These rates in the bDMARDs-switched cases were as follows (Supplementary Fig. 1b): CZP (4.1%), GLM (7.0%), ETN (7.4%), TOF (7.7%), IFX (8.5%), TCZ (9.4%), ABT (11.3%), and ADA (14.6%) (P=0.5).

Finally, drug discontinuation rates due to all adverse events (including lack of effectiveness and toxic adverse events) in the bDMARDs-naïve cases were as follows (Fig. 4a): ABT (18.3%), TCZ (23.5%), GLM (25.3%), ADA (28.4%), IFX (31.5%), CZP (32.4%), and ETN (33.6%) (P<0.001). These rates in the bDMARDs-switched cases were as follows (Fig. 4b): TCZ (32.1%), ETN (35.2%), ABT (37.9%), TOF (38.5%), GLM (43.2%), IFX (51.6%), ADA (52.7%), and CZP (52.7%) (P<0.001).

Hazard ratios (HRs) and 95% confidence intervals (CI) for discontinuation due to each specific cause were calculated using Fine-Gray hazard competing risk regression model adjusted for confounders (Tables 3 and 4).

In the bDMARDs-naïve cases (Table 3), HRs for discontinuation due to lack of effectiveness were significantly higher with CZP (HR=2.4, P<0.001), ETN (HR=1.7, P<0.01), and IFX (HR=1.5, P<0.05) compared with ABT (P<0.001 between agents). In terms of toxic adverse events, ADA (HR=2.8, P<0.001), ETN (HR=4.0, P<0.001),
GLM (HR=2.5, P<0.01), IFX (HR=4.3, P<0.001), and TCZ (HR=2.2, P<0.05) showed a significantly higher rate compared with ABT (P<0.001 between agents). HR for discontinuation due to non-toxic reasons was significantly lower with CZP (HR=0.3, P<0.05) compared with ABT, although no significant difference was observed between agents (P=0.07). HRs for discontinuation due to remission were significantly higher with ADA (HR=2.9, P<0.001), GLM (HR=2.4, P<0.05), IFX (HR=3.1, P<0.001), and TCZ (HR=2.5, P<0.01) compared with ABT (P<0.001 between agents). Finally, HRs for all adverse events (including lack of effectiveness and toxic adverse events) were significantly higher with ADA (HR=1.8, P<0.001), CZP (HR=2.5, P<0.001), ETN (HR=2.3, P<0.001), GLM (HR=1.5, P<0.05), IFX (HR=2.1, P<0.001), and TCZ (HR=1.4, P<0.05) compared with ABT (P<0.001 between agents).

In the bDMARDs-switched cases (Table 4), HRs for discontinuation due to lack of effectiveness were significantly higher with CZP (HR=1.5, P<0.05), although significantly lower with TCZ (HR=0.6, P<0.001) compared with ABT (P<0.001 between agents). As for all toxic adverse events, ETN (HR=0.4, P<0.05) showed a significantly lower rate compared with ABT (P=0.004 between agents). There were no significant differences in HRs for discontinuation due to non-toxic reasons (P=0.5) and remission (P=0.9) between agents. Finally, HRs for all adverse events (including lack of effectiveness and toxic adverse events) were significantly higher with ADA (HR=2.7, P<0.001), CZP (HR=2.2, P<0.01), and IFX (HR=2.0, P<0.05) compared with ABT (P<0.001 between agents).

Discussion

This multi-center, retrospective study was designed to evaluate retention rates and reasons for discontinuation for 7 bDMARDs and TOF, especially in bDMARDs-naïve and bDMARDs-switched cases.

Factors affecting bDMARDs retention rates have been reported. Higher age [3], female sex [5], concomitant PSL [3], high DAS28 or HAQ scores [3, 11, 31], absence or low dose of combined MTX [3, 11], and the number of previously used bDMARDs [11] were negative predictors of retention rates in previous studies. With reference to these previous reports, we selected age, sex, disease duration, concomitant PSL and MTX, starting date, and number of switched bDMARDs as adjustment confounders [16-18].

In terms of serious infections or malignancies across bDMARDs [32]. However, cohort-based studies revealed that among TNFi, ETN showed a lower rate of adverse events compared with IFX [3, 5] and ADA [3]. Another report showed that toxic adverse events such as lupus-like events and vasculitis-like events tended to be lowest with CZP compared with other TNFi [33]. In terms of non-TNFi, ABT showed a lower risk of hospitalized infection rates compared with all other bDMARDs [34], and possible increased safety of ABT compared with other agents in RA-associated interstitial lung disease is also reported [35].

Regarding total retention of TNFi, GLM showed a higher retention rate compared with other TNFi when clinical backgrounds were matched [36]. On the other hand, previous studies showed that ETN showed a higher total retention rate compared with ADA and IFX [3, 5]. With respect to differences between TNFi and non-TNFi agents, Jones et al. reported that ABT or TCZ showed higher retention rates compared with TNFi [37]. Moreover, we previously reported that TCZ showed a higher retention rate compared with ADA and IFX [38], and both ABT and TCZ showed higher retention compared with TNFi [16, 17].

Patients with first TNFi failure, switching to non-TNFi bDMARDs showed higher retention rates due to lack of effectiveness compared with patients switched to a second TNFi [9]. In such cases, both ABT and TCZ resulted in substantial improvement in clinical disease activity [39] along with good retention rates [40]. In terms of a JAK inhibitor, TOF showed a lower discontinuation rate due to lack of efficacy and an equivalent rate of adverse events compared with ABT, GLM, and TCZ [41]. However, another report demonstrated that TCZ showed the highest clinical response in such cases, followed by ABT or TOF [42]. Taken together, among the TNFi, ETN and GLM may show good retention, and in bDMARDs-switched cases, non-TNFi such as ABT, TCZ, and TOF may show good retention compared to TNFi. These results are comparable to this study, although discontinuation rate of ETN due to toxic adverse events was relatively high in bDMARDs-naïve cases (especially within 5 months).
Considering patients’ background, patients who were treated by ETN as first bDMARDs were combined with relatively low rate of MTX (39.4%), which may suggest the existence of comorbidities leading to MTX intolerance and high rate of toxic adverse events. Interestingly, there were remarkable differences between bDMARDs-naïve and bDMARDs-switched cases in terms of drug retention in this study. Most of the agents’ retention due to lack of effectiveness decreased in bDMARDs-switched cases compared with bDMARDs-naïve cases, although TCZ and ETN showed similar retention rates.

The efficacy of low-dose MTX in Japanese populations compared with western populations should be mentioned. Intraerythrocyte MTX-polyglutamate concentrations, which are considered a useful biomarker of MTX efficacy, were 65 nmol/L with 13.4 mg/week of MTX in the United States, compared with 94 nmol/L with 10.3 mg/week of MTX in Japanese [43]. Thus, a relatively low dose of MTX may have positive effects on bDMARD retention in Japanese populations.

Some limitations to this study need to be considered. First, the backgrounds of patients differed between agents, which may affect results even after adjustment for potential confounders (e.g., MTX may strongly affect the retention of TNFi compared to that of non-TNFi); in addition, comorbidities that may affect drug retention could not be evaluated. Second, the judgment and reasons for discontinuation (such as lack of effectiveness or remission) depended on the decisions of each physician, without standardized criteria. Third, the difference between intravenous and subcutaneous bDMARDs and the use of other conventional synthetic DMARDs could not be determined. Fourth, dose changes of bDMARDs, MTX, and PSL could not be monitored. Fifth, among agents available in Japan, CZP and TOF were licensed most recently (2013), which may have led to a small number of prescriptions (i.e., we could not collect enough data for TOF in bDMARDs-naïve cases), which may have affected results. However, the strength of this study is that it is the first study comparing drug retention and discontinuation reasons of 7 bDMARDs and TOF between bDMARDs-naïve and bDMARDs-switched cases, based on a real-world setting. These results may provide important evidences for the precision medicine, especially for appropriate use of bDMARDs and TOF in both situations of daily clinical practice.

Conclusions

Remarkable differences were observed in drug retention rates of 7 bDMARDs and TOF between bDMARDs-naïve and bDMARDs-switched cases. Overall retention rates excluding non-toxic reasons and remission were highest with ABT among the bDMARDs-naïve cases (not including TOF), while TCZ showed the highest total retention rate in the bDMARDs-switched cases.

Declarations

Acknowledgments

We wish to thank all medical staff at all institutions participating in the ANSWER cohort for providing the data.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Authors’ contributions

KE was responsible for conception and design. KE, TH, YM, MH, KM, TT, HS, YS, HA, AO, KA, RH, and MK contributed to data extraction and interpretation. KE, WY, and KY contributed to the design and conduction of
statistical analysis. KE and MH prepared the manuscript. AK and MH supervised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The representative facility of this registry is Kyoto University, and this observational study was conducted in accordance with the Declaration of Helsinki, with approval by each ethics committee of seven institutes (Kyoto University, Osaka University, Osaka Medical College, Kansai Medical University, Kobe University, Nara Medical University, and Osaka Red Cross Hospital). This study was approved by the Institutional Ethical Review Board of Osaka University Graduate School of Medicine (approval number: 15300), and the board waived the requirement for patients’ informed consent because of the anonymous nature of the data. Written informed consent was obtained from participants in other institutes.

Consent for publication

Not applicable.

Competing interests

KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, which is supported by Taisho. KE has received research grants from Abbie, Asahi-Kasei, Astellas, Chugai, Eisai, Ono Pharmaceutical, and UCB Japan. KE has received payments for lectures from Abbie, Asahi-Kasei, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Janssen, Mitsubishi-Tanabe, Ono Pharmaceutical, Sanofi, and UCB Japan. TH received a research grant and/or speaker fee from Astellas, Chugai, Nippon Shinyaku, Abbvie, Eisai, and Ono Pharmaceutical. YM received a research grant and/or speaker fee from Eli Lilly, Chugai, Pfizer, Bristol-Myers Squibb, and Mitsubishi-Tanabe. MHashimoto and KM are affiliated with a department that is financially supported by four pharmaceutical companies (Mitsubishi-Tanabe, Chugai, Ayumi, and UCB Japan) and the city government (Nagahama City). MHashimoto received a research grant and/or speaker fee from Astellas, Mitsubishi-Tanabe, Eisai, Eli Lilly, and Bristol-Myers Squibb. KM received a speaking fee, and/or consulting fee from Eisai. TT is affiliated with a department that is financially supported by six pharmaceutical companies (Mitsubishi-Tanabe, Chugai, Ayumi, Astellas, Eisai, and Takeda). TT received a research grant from Chugai, CoverLetter and a speaker fee from Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Abbvie, Bristol-Myers Squibb, Ayumi, Daiichi Sankyo, Eisai, Takeda, and Asahi-Kasei. AO received a speaker fee from Chugai, Ono Pharmaceutical, Eli Lilly, Mitsubishi-Tanabe, Asahi-Kasei, and Takeda. RH received a speaker fee from AbbVie. M Hirao received a speaker fee from Astellas, Ono Pharmaceutical, Eli Lilly, Mitsubishi-Tanabe, Pfizer, Ayumi, and Takeda. AK received a research grant and/or speaker fee from Mitsubishi-Tanabe, Chugai, Eisai, Asahi-Kasei, Astellas, Abbvie, Bristol-Myers Squibb, Ono Pharmaceutical, and Pfizer. WY, HS, YS, HA, KA, MK, and KY have no financial conflicts of interest to disclose concerning this manuscript. These companies had no role in the study design, data collection, data analysis, data interpretation, and preparation of the manuscript.

Funding

The study reported in this publication uses ANSWER Cohort supported by grants from eight pharmaceutical companies (AbbVie, Asahi Kasei, Ayumi, Chugai, Eisai, Janssen, Ono and Sanofi) and an information technology services company (CAC). This study is conducted as investigator-initiated study, and these companies had no role in the study design, data collection, data analysis, data interpretation, and preparation of the manuscript.
References

1. Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A: Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009, 61(5):560-568.

2. Favalli EG, Pregnolato F, Biggioggero M, Becciolini A, Penatti AE, Marchesoni A, Meroni PL: Twelve-Year Retention Rate of First-Line Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: Real-Life Data From a Local Registry. Arthritis Care Res (Hoboken) 2016, 68(4):432-439.

3. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, Poulsen UE et al: Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010, 62(1):22-32.

4. Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, Askling J: Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015, 74(2):354-360.

5. Souto A, Maneiro JR, Gomez-Reino JJ: Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford) 2016, 55(3):523-534.

6. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R et al: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017, 76(6):960-977.

7. Smolen JS, Aletaha D: Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol 2015, 11(5):276-289.

8. Du Pan SM, Scherer A, Gabay C, Finckh A: Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients. Ann Rheum Dis 2012, 71(6):997-999.

9. Favalli EG, Biggioggero M, Marchesoni A, Meroni PL: Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. Rheumatology (Oxford) 2014, 53(9):1664-1668.

10. Wolfe F, Michaud K, Dewitt EM: Why results of clinical trials and observational studies of antitumour necrosis factor (anti-TNF) therapy differ: methodological and interpretive issues. Ann Rheum Dis 2004, 63 Suppl 2:ii13-ii17.

11. Gabay C, Riek M, Scherer A, Finckh A: Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. Rheumatology (Oxford) 2015, 54(9):1664-1672.

12. Jorgensen TS, Kristensen LE, Christensen R, Bliddal H, Lorenzen T, Hansen MS, Ostergaard M, Jensen J, Zanjani L, Laursen T et al: Effectiveness and drug adherence of biologic monotherapy in routine care of patients with rheumatoid arthritis: a cohort study of patients registered in the Danish biologics registry. Rheumatology (Oxford) 2015, 54(12):2156-2165.

13. Hjardem E, Hetland ML, Ostergaard M, Krogh NS, Kvien TK: Prescription practice of biological drugs in rheumatoid arthritis during the first 3 years of post-marketing use in Denmark and Norway: criteria are becoming less stringent. Ann Rheum Dis 2005, 64(8):1220-1223.

14. Hyrich KL, Watson KD, Lunt M, Symmons DP: Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. Rheumatology (Oxford) 2011, 50(1):117-123.

15. Simard JF, Arkema EV, Sundstrom A, Geborek P, Saxne T, Baecklund E, Coster L, Dackhammar C, Jacobsson L, Feltelius N et al: Ten years with biologics: to whom do data on effectiveness and safety apply? Rheumatology (Oxford) 2011, 50(1):204-213.

16. Ebina K, Hashimoto M, Yamamoto W, Hirano T, Hara R, Katayama M, Onishi A, Nagai K, Son Y, Amuro H et al: Drug tolerability and reasons for discontinuation of seven biologics in 4466 treatment courses of
rheumatoid arthritis-the ANSWER cohort study. Arthritis Res Ther 2019, 21(1):91.

17. Ebina K, Hashimoto M, Yamamoto W, Ohnishi A, Kabata D, Hirano T, Hara R, Katayama M, Yoshida S, Nagai K et al: Drug retention and discontinuation reasons between seven biologics in patients with rheumatoid arthritis -The ANSWER cohort study. PLoS One 2018, 13(3):e0194130.

18. Ebina K, Hashimoto M, Yamamoto W, Hirano T, Hara R, Katayama M, Onishi A, Nagai K, Son Y, Amuro H et al: Drug tolerability and reasons for discontinuation of seven biologics in elderly patients with rheumatoid arthritis -The ANSWER cohort study. PLoS One 2019, 14(5):e0216624.

19. Hashimoto M, Furu M, Yamamoto W, Fujimura T, Hara R, Katayama M, Ohnishi A, Akashi K, Yoshida S, Nagai K et al: Factors associated with the achievement of biological disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: the ANSWER cohort study. Arthritis Res Ther 2018, 20(1):165.

20. Murata K, Hashimoto M, Yamamoto W, Son Y, Amuro H, Nagai K, Takeuchi T, Katayama M, Maeda Y, Ebina K et al: The family history of rheumatoid arthritis in anti-cyclic citrullinated peptide antibody-positive patient is not a predictor of poor clinical presentation and treatment response with modern classification criteria and treatment strategy: the ANSWER cohort study. Rheumatol Int 2019.

21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS et al: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988, 31(3):315-324.

22. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD et al: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010, 69(9):1580-1588.

23. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, Takeuchi T, Nagai K, Son Y, Amuro H et al: Drug retention of secondary biologics or JAK inhibitors after tocilizumab or abatacept failure as first biologics in patients with rheumatoid arthritis -the ANSWER cohort study. Clin Rheumatol 2020.

24. Kawaihito Y: [Guidelines for the management of rheumatoid arthritis]. Nihon Rinsho 2016, 74(6):939-943.

25. Koike R, Harigai M, Atsumi T, Amano K, Kawai S, Saito K, Saito T, Yamamura M, Matsubara T, Miyasaka N: Japan College of Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis. Mod Rheumatol 2009, 19(4):351-357.

26. Koike R, Takeuchi T, Eguchi K, Miyasaka N: Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. Mod Rheumatol 2007, 17(6):451-458.

27. Dutz A, Lock S: Competing risks in survival data analysis. Radiother Oncol 2019, 130:185-189.

28. Scrucca L, Santucci A, Aversa F: Competing risk analysis using R: an easy guide for clinicians. Bone Marrow Transplant 2007, 40(4):381-387.

29. Greenberg JD, Reed G, Decktor D, Harrold L, Forst D, Gibofsky A, Dehoratius R, Kishimoto M, Kremer JM: A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis 2012, 71(7):1134-1142.

30. Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013, 48(3):452-458.

31. Forsblad-d’Elia H, Bengtsson K, Kristensen LE, Jacobsson LT: Drug adherence, response and predictors thereof for tocilizumab in patients with rheumatoid arthritis: results from the Swedish biologics register. Rheumatology (Oxford) 2015, 54(7):1186-1193.

32. Ramiro S, Sepriano A, Chatzidiyonysiou K, Nam JL, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, Bijlsma JW, Burmester GR et al: Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2017, 76(6):1101-1136.

33. Jani M, Dixon WG, Kersley-Fleet L, Bruce IN, Chinoy H, Barton A, Lunt M, Watson K, Symmons DP, Hyrich KL: Drug-specific risk and characteristics of lupus and vasculitis-like events in patients with rheumatoid arthritis treated with TNFi: results from BSRBR-RA. RMD Open 2017, 3(1):e000314.

34. Yun H, Xie F, Delzell E, Levitan EB, Chen L, Lewis JD, Saag KG, Beukelman T, Winthrop KL, Baddley JW et al: Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare. Arthritis Rheumatol 2016, 68(1):56-66.

35. Fernandez-Diaz C, Loriceria J, Castaneda S, Lopez-Mejias R, Ojeda-Garcia C, Olive A, Rodriguez-Muguruza
S, Carreira PE, Perez-Sandoval T, Retuerto M et al: Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum 2018, 48(1):22-27.

36. Sruamsiri R, Kameda H, Mahlich J: Persistence with Biological Disease-modifying Antirheumatic Drugs and Its Associated Resource Utilization and Costs. Drugs Real World Outcomes 2018, 5(3):169-179.

37. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, Siri DA, Tomsic M, Alecock E, Woodworth T et al: Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITIOn study. Ann Rheum Dis 2010, 69(1):88-96.

38. Hishitani Y, Ogata A, Shima Y, Hirano T, Ebina K, Kunugiza Y, Shi K, Narazaki M, Hagihara K, Tomita T et al: Retention of tocilizumab and anti-tumour necrosis factor drugs in the treatment of rheumatoid arthritis. Scand J Rheumatol 2013, 42(4):253-259.

39. Harrold LR, Reed GW, Solomon DH, Curtis JR, Liu M, Greenberg JD, Kremer JM: Comparative effectiveness of abatacept versus tocilizumab in rheumatoid arthritis patients with prior TNFi exposure in the US Corrona registry. Arthritis Res Ther 2016, 18(1):280.

40. Leffers HC, Ostergaard M, Glintborg B, Krogh NS, Foged H, Tarp U, Lorenzen T, Hansen A, Hansen MS, Jacobsen MS et al: Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 2011, 70(7):1216-1222.

41. Vieira MC, Zwillich SH, Jansen JP, Smiechowski B, Spurden D, Wallenstein GV: Tofacitinib Versus Biologic Treatments in Patients With Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors: Results From a Network Meta-analysis. Clin Ther 2016, 38(12):2628-2641 e2625.

42. Lee YH, Bae SC: Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. Int J Rheum Dis 2016, 19(11):1103-1111.

43. Takahashi C, Kaneko Y, Okano Y, Taguchi H, Oshima H, Izumi K, Yamaoka K, Takeuchi T: Association of erythrocyte methotrexate-polyglutamate levels with the efficacy and hepatotoxicity of methotrexate in patients with rheumatoid arthritis: a 76-week prospective study. RMD Open 2017, 3(1):e000363.

**Tables**

Table 1. Clinical characteristics at initiation of 7 bDMARDs (bDMARDs-naïve cases)
| Variable                        | ABT (n=390) | ADA (n=374) | CZP (n=135) | ETN (n=616) | GLM (n=208) | IFX (n=650) | TCZ (n=364) |
|--------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Age (years)                    | 65.5±12.4   | 55.3±12.8   | 58.1±16.8   | 55.5±15.9   | 62.0±14.8   | 52.9±13.4   | 56.6±14.4   |
| Female sex (%)                 | 81.2        | 79.4        | 88.8        | 86.7        | 86.1        | 78.0        | 78.2        |
| Disease duration (years)       | 9.2±12.4    | 5.0±7.5     | 4.7±7.6     | 8.3±8.7     | 7.3±10.0    | 6.9±8.4     | 7.4±9.4     |
| RF positivity (%)              | 86.6        | 73.8        | 86.2        | 83.1        | 75.6        | 74.2        | 74.0        |
| ACPA positivity (%)            | 84.3        | 75.9        | 85.7        | 83.2        | 73.2        | 82.9        | 82.1        |
| DAS28-ESR                      | 4.4±1.2     | 4.1±1.2     | 4.6±1.4     | 4.4±1.4     | 4.3±1.2     | 4.5±1.6     | 4.6±1.5     |
| CDAI                           | 17.7±9.6    | 14.7±9.1    | 22.2±12.9   | 17.3±8.8    | 17.2±11.5   | 18.5±12.4   | 18.1±9.8    |
| HAQ-DI                         | 1.2±0.8     | 0.7±0.6     | 1.2±0.8     | 0.9±0.8     | 1.1±0.8     | 1.1±0.9     | 1.1±0.8     |
| PSL usage (%)                  | 44.2        | 32.8        | 44.8        | 39.2        | 38.9        | 36.4        | 45.7        |
| PSL dose (mg/day)              | 3.1±7.3     | 2.9±4.9     | 1.7±2.6     | 2.8±3.6     | 2.3±3.6     | 3.1±5.9     | 2.8±3.9     |
| MTX usage (%)                  | 49.1        | 72.0        | 76.1        | 39.4        | 76.0        | 100.0       | 51.2        |
| MTX dose (mg/week)             | 8.1±2.8     | 9.4±3.1     | 9.4±2.9     | 8.0±2.8     | 9.2±2.9     | 8.2±2.5     | 8.8±3.0     |
| Starting date 2001-2009 (%)    | 0.0         | 13.6        | 0.0         | 40.4        | 1.0         | 60.9        | 11.5        |
| Starting date 2010-2013 (%)    | 35.9        | 53.7        | 12.6        | 42.0        | 40.4        | 30.2        | 47.3        |
| Starting date 2014-2019 (%)    | 64.1        | 32.7        | 87.4        | 17.6        | 58.7        | 8.9         | 41.2        |

Values are mean ± standard deviation or percentages. bDMARDs = biological disease-modifying antirheumatic drugs, ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, RF = rheumatoid factor, ACPA = anti-cyclic citrullinated peptide antibody, DAS28-ESR = Disease Activity Score in 28 joints using erythrocyte sedimentation rate, CDAI = clinical disease activity index, HAQ-DI = Health Assessment Questionnaire disability index, PSL = prednisolone, MTX = methotrexate.

Table 2. Clinical characteristics at initiation of 7 bDMARDs and tofacitinib (bDMARDs-switched cases)
| Variable                  | ABT (n=273) | ADA (n=162) | CZP (n=91) | ETN (n=240) | GLM (n=250) | IFX (n=74) | TCZ (n=487) | TOF (n=101) |
|---------------------------|-------------|-------------|------------|-------------|-------------|------------|------------|-------------|
| Age (years)               | 61.5±13.2   | 55.4±14.8   | 54.1±15.4  | 55.5±15.7   | 60.5±14.6   | 53.5±12.6  | 58.1±4.1   | 59.7±3.6    |
| Female sex (%)            | 81.3        | 87.7        | 85.7       | 82.1        | 88.0        | 79.5       | 82.5       | 77.2        |
| Disease duration (years)  | 11.2±9.3    | 9.7±9.0     | 9.9±9.0    | 9.4±8.1     | 12.0±10.2   | 10.9±16.0  | 10.0±8.9   | 11.0±8.6    |
| RF positivity (%)         | 77.8        | 78.2        | 77.2       | 75.6        | 78.1        | 72.7       | 79.9       | 80.0        |
| ACPA positivity (%)       | 84.4        | 80.9        | 84.8       | 86.5        | 82.9        | 82.4       | 83.3       | 73.3        |
| DAS28-ESR                 | 4.3±1.3     | 3.9±1.1     | 4.4±1.5    | 4.1±1.4     | 4.0±1.4     | 4.0±1.6    | 4.4±1.4    | 4.3±1.3     |
| CDAI                      | 14.7±9.5    | 11.9±8.8    | 16.3±10.8  | 13.7±10.0   | 14.6±10.2   | 18.9±13.0  | 16.3±1.0   | 19.3±1.3    |
| HAQ-DI                    | 1.1±0.8     | 0.8±0.7     | 1.2±0.9    | 0.9±0.8     | 1.1±0.8     | 1.0±1.0    | 1.2±0.8    | 1.0±0.8     |
| PSL usage (%)             | 55.1        | 44.1        | 40.7       | 47.0        | 46.0        | 42.5       | 52.2       | 54.5        |
| PSL dose (mg/day)         | 6.4±4.1     | 5.9±4.3     | 4.9±2.9    | 5.6±3.8     | 5.1±3.5     | 5.6±3.1    | 6.1±3.9    | 4.1±3.1     |
| MTX usage (%)             | 47.8        | 57.1        | 62.6       | 50.0        | 66.1        | 100.0      | 54.9       | 51.5        |
| MTX dose (mg/week)        | 8.4±3.0     | 8.0±2.9     | 8.4±3.1    | 8.3±2.7     | 8.0±3.1     | 8.7±2.8    | 8.4±3.1    | 9.0±3.3     |
| Starting date 2001-2009 (%)| 0.0         | 25.3        | 0.0        | 27.5        | 0.0         | 20.3       | 10.9       | 0.0         |
| Starting date 2010-2013 (%)| 43.2        | 49.4        | 26.4       | 37.5        | 48.8        | 51.4       | 45.8       | 2.0         |
| Starting date 2014-2019 (%)| 56.8        | 25.3        | 73.6       | 35.0        | 51.2        | 28.4       | 43.3       | 98.0        |
| 2nd bio or TOF (%)        | 54.6        | 75.9        | 41.8       | 74.6        | 58.8        | 70.3       | 57.3       | 31.7        |
| 3rd bio or TOF (%)        | 45.4        | 24.1        | 58.2       | 25.4        | 41.2        | 29.7       | 42.7       | 68.3        |

Values are mean ± standard deviation or percentages. bDMARDs = biological disease-modifying antirheumatic drugs, ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib, RF = rheumatoid factor, ACPA = anti-cyclic citrullinated peptide antibody, DAS28-ESR = Disease Activity Score in 28 joints using erythrocyte sedimentation rate, CDAI = clinical disease activity index, HAQ-DI = Health Assessment Questionnaire disability index, PSL = prednisolone, MTX = methotrexate, bio = biologic agent.
Table 3. Hazard ratio of treatment discontinuation in the bDMARDs-naïve cases (Fine-Gray hazard competing risk regression model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX usage, and starting date of bDMARDs)

| Variable                                | Reference | ABT (n=390) | ADA (n=374) | CZP (n=135) | ETN (n=616) | GLM (n=208) | IFX (n=650) | TCZ (n=364) |
|-----------------------------------------|-----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Lack of effectiveness                   | 1         | 1.4 (1.0-2.1) | 2.4 (1.5-3.8)** | 1.7 (1.2-2.4)** | 1.1 (0.7-1.7) | 1.5 (1.1-2.2)* | 1.1 (0.8-1.7) |
| All toxic adverse events                | 1         | 2.8 (1.5-5.2)** | 1.7 (0.7-4.0) | 4.0 (2.3-6.9)** | 2.5 (1.3-4.8)** | 4.3 (2.5-7.3)** | 2.2 (1.2-4.2)* |
| Non-toxic reasons                       | 1         | 0.8 (0.5-1.3) | 0.3 (0.1-0.9)* | 1.1 (0.7-1.6) | 1.5 (0.9-2.5) | 1.0 (0.7-1.5) | 1.1 (0.7-1.8) |
| Remission                               | 1         | 2.9 (1.5-5.4)** | 1.8 (0.8-4.4) | 1.0 (0.5-2.0) | 2.4 (1.2-5.0)* | 3.1 (1.7-5.6)** | 2.5 (1.3-4.8)** |
| All adverse events (including lack of effectiveness and toxic adverse events) | 1         | 1.8 (1.3-2.5)** | 2.5 (1.6-3.7)** | 2.3 (1.7-3.1)** | 1.5 (1.0-2.2)* | 2.1 (1.6-2.9)* | 1.4 (1.0-2.0)* |

bDMARDs = biological disease-modifying antirheumatic drugs, PSL = prednisolone, MTX = methotrexate, HR = hazard ratio; 95% CI = 95% confidence interval, ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab.

* P<0.05, **P<0.01, *** P<0.001.

Table 4. Hazard ratio of treatment discontinuation in the bDMARDs-switched cases (Fine-Gray hazard competing risk regression model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX usage, starting date, and number of switched bDMARDs)
| Variable                                      | Reference | HR (95% CI) |
|-----------------------------------------------|-----------|-------------|
|                                               | ABT (n=273) | ADA (n=162) | CZP (n=91) | ETN (n=240) | GLM (n=250) | IFX (n=74) | TCZ (n=487) | TOI (n=1) |
| Lack of effectiveness                         | 1         | 1.3 (0.9-1.8) | 1.5 (1.0-2.2)* | 1.1 (0.8-1.5) | 1.0 (0.7-1.3) | 1.3 (0.9-2.0) | 0.6 (0.4-0.8)** | 0.8 (0.6-1.2) | 1.2 |
| All toxic adverse events                      | 1         | 1.8 (1.0-3.1) | 0.8 (0.3-2.0) | 0.4 (0.2-0.9)* | 1.0 (0.6-1.9) | 1.2 (0.5-2.7) | 1.4 (0.9-2.3) | 1.8 (0.6-3.5) |
| Non-toxic reasons                             | 1         | 1.2 (0.6-2.2) | 0.3 (0.1-1.1) | 0.8 (0.4-1.4) | 0.8 (0.4-1.5) | 0.9 (0.4-2.4) | 0.8 (0.5-1.3) | 0.6 (0.4-1.5) |
| Remission                                     | 1         | 0.8 (0.1-5.0) | 0.9 (0.1-9.2) | 1.4 (0.3-6.1) | 1.8 (0.4-7.7) | 1.9 (0.4-10.7) | 1.5 (0.4-5.4) | 2.3 (0.6-13.8) |
| All adverse events (including lack of         |           | 2.7 (1.6-4.3)*** | 2.2 (1.4-3.4)** | 1.2 (0.8-2.0) | 1.4 (1.0-2.1) | 2.0 (1.0-3.7)* | 0.9 (0.6-1.4) | 1.1 (0.6-1.9) |
| effectiveness and toxic adverse events)       |           |             |            |             |             |             |             |             |

bDMARDs = biological disease-modifying antirheumatic drugs, PSL = prednisolone, MTX = methotrexate, HR = hazard ratio; 95% CI = 95% confidence interval, ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib.

* P<0.05, **P<0.01, *** P<0.001.
a) Estimated cumulative incidence with discontinuation due to lack of effectiveness (bDMARDs-naïve cases)

- ABT
- ADA
- CZP
- ETN
- GLM
- IFX
- TCZ

P < 0.001

Continued months

|     | 0  | 5  | 10 | 15 | 20 | 25 | 30 | 35 |
|-----|----|----|----|----|----|----|----|----|
| ABT | 390| 337| 303| 269| 240| 192| 144| 116|
| ADA | 374| 311| 276| 235| 204| 176| 149| 133|
| CZP | 135| 101| 86 | 82 | 66 | 47 | 29 | 14 |

b) Estimated cumulative discontinuation due to lack of effectiveness (bDMARDs-switch cases)

- ABT
- ADA
- CZP
- ETN
- GLM
- IFX
- TCZ
- TOF

Continued

|     | 0  | 5  | 10 | 15 | 20 | 25 | 30 |
|-----|----|----|----|----|----|----|----|
| ABT | 273| 199| 169| 145|
| ADA | 162| 108| 85 | 73 |
| CZP | 91 | 63 | 56 | 49 |
Figure 1

Estimated cumulative incidence with discontinuation due to lack of effectiveness in the bDMARDs-naïve cases (a) and the bDMARDs-switched cases (b). ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib, bDMARDs = biological disease-modifying antirheumatic drugs.
Figure 2

Estimated cumulative incidence with discontinuation due to toxic adverse events in the bDMARDs-naïve cases (a) and the bDMARDs-switched cases (b). ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib, bDMARDs = biological disease-modifying antirheumatic drugs.
Figure 3

Estimated cumulative incidence with discontinuation due to remission in the bDMARDs-naïve cases (a) and the bDMARDs-switched cases (b). ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib, bDMARDs = biological disease-modifying antirheumatic drugs.
Figure 4

Estimated cumulative incidence with discontinuation due to all adverse events (including lack of effectiveness and toxic adverse events) in the bDMARDs-naïve cases (a) and the bDMARDs-switched cases (b). ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib, bDMARDs = biological disease-modifying antirheumatic drugs.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- `reviseARTnaiveswitchsupplementaryfigure1no1.pptx`
- `reviseANSWERNaiveswitchARTsupplementaryfigurelegend.docx`