Original Article

Title:

Drug retention of sarilumab, baricitinib, and tofacitinib in patients with rheumatoid arthritis: The ANSWER cohort study

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Abstract

Objectives: The aim of this multicenter, retrospective study was to clarify the retention rates of sarilumab (SAR), baricitinib (BAR), and tofacitinib (TOF) in patients with rheumatoid arthritis (RA).

Methods: Patients treated with either SAR (n = 62), BAR (n = 166), or TOF (n = 185) (females, 80.9%; age, 61.0 years; disease duration, 11.1 years; rheumatoid factor positivity, 84.4%; Disease Activity Score in 28 joints using erythrocyte sedimentation rate, 4.3; concomitant prednisolone dose, 5.3 mg/day [47.0%] and methotrexate dose, 8.8 mg/week [58.4%]; biologics- or Janus kinase inhibitors-switched cases 78.4%) were included. The reasons for drug discontinuation were classified into 4 major categories (lack of effectiveness, toxic adverse events, non-toxic reasons, and remission) by each attending physician. The drug retention rate was estimated at 18 months using the Kaplan–Meier method and adjusted for potential confounders by Cox proportional hazards modeling.

Results: The discontinuation rates of SAR, BAR, and TOF for the corresponding reasons were as follows, respectively: lack of effectiveness (15.7%, 15.6%, and 21.5%; P = 0.84), toxic adverse events (15.8%, 12.1%, and 12.3%; P = 0.35), non-toxic reasons (10.9%, 7.7%, and 6.8%; P = 0.35), and remission (0.0%, 2.8%, and 0.0%; P = 1.0). The overall retention rates excluding non-toxic reasons and remission were as follows: 68.8% for SAR, 72.5% for BAR, and 66.7% for TOF (P = 0.54).

Conclusions: After adjustment by potent confounders, SAR, BAR, and TOF showed similar discontinuation rates due to lack of effectiveness and toxic adverse events.

Keywords

ANSWER cohort, Baricitinib, Drug retention, Rheumatoid arthritis, Sarilumab, and Tofacitinib

Key Points

This is the first retrospective multicenter study that aimed to clarify the retention rates and reasons for discontinuation of SAR, BAR, and TOF in patients with RA.

Abbreviations

Abbreviations are listed in supplementary table 1.

Introduction

The recommendations of the 2019 European League Against Rheumatism (EULAR) stated that the efficacies of anti-interleukin (IL)-6 receptor antibody (IL-6R; tocilizumab [TCZ] and sarilumab [SAR]), CTLA4-Ig (abatacept), and Janus kinase inhibitors (JAKi) such as baricitinib (BAR; JAK1 and JAK2 inhibitor) and tofacitinib (TOF; JAK1 and JAK3 inhibitor) are considered equivalent to those of tumor necrosis factor inhibitors (TNFi) in both the phase II and III treatments of rheumatoid arthritis (RA) [1]. The findings of this report also showed no significant differences in outcomes among the biological disease-modifying antirheumatic drugs (bDMARDs) and JAKi, irrespective of their targets. 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 [2,3]. In addition, we recently reported that among bDMARDs-switched patients, those who were taking TCZ and TOF showed lower discontinuation rates due to lack of effectiveness than those who were receiving TNFi, suggesting that anti-IL-6R and JAKi had better retention than TNFi in real-world settings [4].

The use of TOF (2013), SAR (2017), and BAR (2017) was recently approved in Japan, and reliable evidence of direct comparison between these agents is still lacking. SAR is a human IgG1 monoclonal antibody that binds to soluble and membrane-bound IL-6 receptors, and a recent report demonstrated similar safety and laboratory changes between patients treated with SAR and TCZ [5]. JAKi inhibits

the JAK-signal transducer and activator of transcription pathways, which leads to the inhibition of IL-6 and other various cytokines [6]. A recent meta-analysis revealed that in patients with inadequate response (IR) to bDMARDs (bDMARDs-IR), both TOF 10 mg (standard dose in Japan) and BAR 4 mg (standard dose in Japan) with methotrexate (MTX) were efficacious to similar extents [7], although no detailed comparison using data from the same registry has been reported. In a comparison between anti-IL-6R and JAKi in patients with TNFi-IR, TOF showed a lower discontinuation rate due to lack of effectiveness than TCZ [8]. However, we recently reported that in bDMARDs-switched patients, TCZ showed similar good retention due to lack of effectiveness compared to TOF [4]. Taken together, comparison between the effectiveness of anti-IL-6R and JAKi still remains unclear. Moreover, SAR, BAR, and TOF tended to be introduced in patient with multiple bDMARDs failure or intolerance to MTX due to comorbidities in real-world settings, which is quite different from those recruited in randomized controlled trials. Therefore, investigating the effectiveness and safety of these agents in “difficult-to-treat” RA patients are of great interest.

Recently, cohort-based observational studies have increasingly been conducted to investigate the performance of bDMARDs [9,10]. In these studies, drug retention is considered a major index of both treatment safety and effectiveness [11,12]. On the basis of our findings from our cohort, we have recently reported the drug retention rates of bDMARDs [4,13,14,15] (summaries of these studies are listed in supplementary table 2) and factors associated with the achievement of bDMARDs-free

121 remission [16]. The aim of the present multicenter retrospective study was to clarify the retention rates
122 and reasons for discontinuation of SAR, BAR, and TOF in real-world settings.
123
124 **Materials and Methods**
125 **Patients**
126 The Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort is an
127 observational multicenter registry of patients with RA in the Kansai district of Japan. Data were
128 retrospectively collected from patients who were examined at 7 major university-related hospitals
129 (Kyoto University, Osaka University, Osaka Medical College, Kansai Medical University, Kobe
130 University, Nara Medial University, and Osaka Red Cross Hospital). RA was diagnosed on the basis
131 of either the 1987 RA classification criteria of the American College of Rheumatology (ACR) [17] or
132 the 2010 ACR/EULAR RA classification criteria [18].
133 Patients who were treated by senior rheumatologists with either SAR, BAR, or TOF between 2013 and
134 2020 with complete data on the start and discontinuation dates and the reasons for discontinuation
135 were included in this study. In addition, their baseline demographic data such as age; sex; disease
136 duration; disease activity (Disease Activity Score in 28 joints using erythrocyte sedimentation rate
137 [DAS28-ESR]); Clinical Disease Activity Index score; concomitant doses (calculated as a blank when
138 not combined) and ratios of methotrexate (MTX) and prednisolone (PSL); concomitant ratio of other

conventional disease-modifying antirheumatic drugs (csDMARDs) such as salazosulfapyridine (SASP), bucillamine, iguratimod, tacrolimus, and leflunomide; rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody positivity; and Health Assessment Questionnaire Disability Index score were also collected [4,13,14,19].

In Japan, the national health insurance covers 70%–90% of the medical expense, and bDMARDs or JAKi can be administered at the discretion of attending rheumatologists in accordance with the Japan College of Rheumatology guidelines (generally in patients who showed inadequate response to csDMARDs or with high risk of progressive joint destruction) [20,21,22]. The dose of each agent is determined in accordance with the manufacturer's recommendation. Drug retention was retrospectively evaluated as the duration until definitive treatment interruption. The reasons for discontinuation were analyzed and classified into four major categories as follows: 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); 3) non-toxic reasons (patient preference, change in hospital, desire for pregnancy, etc.); and 4) disease remission [4,13,14,15,19]. Physicians were allowed to cite only one reason for discontinuation.

Statistical analyses

The differences in baseline clinical characteristics between the groups were assessed using an analysis of variance for continuous variables and the Fisher exact test for categorical variables. The Kaplan–Meier method was used to examine the survival curves for the agents as determined by the specific causes. The hazard ratio (HR) for treatment discontinuation at 18 months was analyzed and statistically compared using multivariate Cox proportional hazards modeling [9,13,14,19]. The analysis was adjusted for the potential confounders that could influence drug retention as previously described (age; sex; disease duration; concomitant PSL, MTX, and SASP use; and number of switched bDMARDs or JAKi) [9,13,14,15,19]. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software (The R Foundation for Statistical Computing, Vienna, Austria) [23]. A P value < 0.05 was considered statistically significant.

Results

Table 1 presents the baseline clinical characteristics of the patients at treatment initiation with each agent (female, 80.9%; age, 61.0 years; disease duration, 11.1 years; RF positivity, 84.4%; DAS28-ESR, 4.3; concomitant PSL dose, 5.3 mg/day and ratio, 47.0%; MTX dose, 8.8 mg/week and ratio, 58.4%; and bDMARDs or JAKi switched cases, 78.4%). Overall, patients were treated by high dose and ratio of PSL, low dose and ratio of MTX, and mostly switched from other bDMARDs or

JAKi, suggesting “difficult-to-treat” backgrounds. We found significant differences in sex ratio (P = 0.02), disease duration (P = 0.02), MTX use (P = 0.03), SASP use (P = 0.01), and prior use of JAKi (P < 0.001) between the groups. SAR (25.8%) and BAR (20.5%) showed higher rate of prior use of JAKi compared to TOF (6.5%).

The adjusted drug discontinuation rates of SAR, BAR, and TOF for the corresponding reasons were as follows, respectively: lack of effectiveness (15.7%, 15.6%, and 21.5%; P = 0.84 between the groups; Fig. 1a), toxic adverse events (15.8%, 12.1%, and 12.3%; P = 0.35 between the groups; Fig. 1b), non-toxic reasons (10.9%, 7.7%, and 6.8%; P = 0.35 between the groups; Fig. 2a), and remission (0.0%, 2.8%, and 0.0%; P = 1.0 between the groups). The overall retention rates excluding non-toxic reasons and remission were as follows: 68.8% for SAR, 72.5% for BAR, and 66.7% for TOF (P = 0.54 between the groups; Fig. 2b).

Table 2 shows the adjusted HRs for the reasons of discontinuation. The HR due to lack of effectiveness was similar between the groups (P = 0.84). The HR due to toxic adverse events tended to be lower for BAR (0.58) and TOF (0.57) than for SAR. The HR due to non-toxic events also tended to be lower for BAR (0.58) and TOF (0.50) than for SAR, although no significant difference was observed (P = 0.35 between the groups). Finally, we found no significant difference in the HR for total discontinuation (excluding non-toxic reasons and remission) between the groups (P = 0.54).

Discussion

To the best of our knowledge, this is the first study to directly compare the reasons of discontinuation and retention rates of SAR, BAR, and TOF in the same multicenter cohort. Concerning the differences of SAR and TCZ, a previous report demonstrated that SAR showed higher affinities to recombinant human and monkey IL-6R with a 10- to 40-fold greater dissociation constant (Kd) value than TCZ in vitro [24]. However, a recent report demonstrated no clinically meaningful differences in both safety and laboratory changes between the patients treated with SAR and TCZ [5]. In addition, switching intravenous TCZ to SAR sustained both clinical efficacy and safety [25]. Taken together, as far as we know, SAR may exhibit similar clinical effectiveness and safety as TCZ.

Concerning JAKi, only a few meta-analyses have compared the effectiveness and safety of BAR and TOF. Recent reports demonstrated that in patients with MTX-IR [26] or bDMARDs-IR [27], BAR 4 mg (standard dose in Japan) with MTX showed a higher American College of Rheumatology 20% (ACR20) or ACR50 response rate than TOF 5 mg (10mg is standard dose in Japan) with MTX. However, another meta-analysis revealed that in patients with csDMARDs-IR or bDMARDs-IR, BAR 4 mg and TOF 10 mg with MTX were both efficacious to similar extents [7]. Taken together, TOF 5 mg may be inferior, although TOF 10 mg may be equivalent to BAR 4 mg, which is in accordance with the results of the present study.

In a comparison of anti-IL-6R and JAKi in patients with TNFi-IR, TOF showed a lower discontinuation rate due to lack of effectiveness than TCZ [8]. However, we recently reported that in bDMARDs-switched patients, TOF and TCZ showed similar better retention due to lack of effectiveness compared to TNFi [4]. Comparing SAR and TOF, a systematic review and network meta-analysis demonstrated that in patients with csDMARDs-IR, SAR 200 mg (standard dose in Japan) monotherapy showed a similar effectiveness and safety compared to TOF [28]. On the other hand, another systematic review showed that in csDMARDs-IR and TNFi-IR patients, SAR 200 mg with csDMARDs showed superiority to BAR 2 mg in terms of ACR50 and DAS28<2.6 achievement, and to BAR 2 mg and TOF (dose not mentioned) in terms of the 24-week modified total Sharp score progression [29]. In addition, SAR 150 mg showed superiority to BAR 2 mg, and similarity to other JAKi in terms of DAS28<2.6 achievement [29]. Taken together, SAR may exhibit at least similar effectiveness and safety to BAR and TOF, which is in accordance with the results of our present study. Considering the underlying mechanisms, a recent report demonstrated that IL-6 is one of the most dominant cytokines in both seropositive and seronegative RA patients [30]. In addition, anti-IL-6R therapy is associated with relatively low incidence of antidrug antibody production regardless of csDMARDs combination, as IL-6 itself promotes antibody production [31]. BAR inhibits JAK1 and JAK2, and TOF inhibits JAK1 and JAK3 signaling, which are both involved in IL-6 production [6].

Although difficult to compare the degree, substantial inhibition of IL-6 by SAR, BAR, and TOF may lead to similar clinical effectiveness and safety in a certain patients' population.

The effectiveness of low-dose MTX in Japanese populations should be considered. Intra-erythrocyte MTX-polyglutamate (MTX-PG) concentration, which is considered a useful biomarker of MTX efficacy, was 65 nmol/L with 13.4-mg/week dose of MTX in the United States patients, although reached 94 nmol/L with 10.3-mg/week dose of MTX in Japanese patients [32]. Thus, a relatively low MTX dose may exhibit positive effects in Japanese populations.

The limitations of the present study were as follows: First, the number of patients in the study was small (especially that of patients who received SAR), and in spite of the adjustment, the difference of patients' background (including combined medications such as MTX and SASP, and prior medications of bDMARDs and JAKi) between the groups may have affected the results. Second, the judgment and reasons for discontinuation (e.g., lack of effectiveness or remission) depended on the decisions of each physician, without standardized criteria. Third, as the initial dose of each agent was determined according to the manufacturer's recommendations, minor dose changes of each agent during the period could not be monitored. Fourth, comorbidities, which can potentially affect drug retention, could not be evaluated. Fifth, the data is limited to Japanese and may differ from that of western populations, and future studies with longer follow-up may be required. However, the strength

of this study is that as far as we know, this is the first study to directly compare the drug retention rates and reasons for discontinuation of SAR, BAR, and TOF in the same multicenter cohort.

After adjustment for the potent confounders, SAR, BAR, and TOF showed similar discontinuation rates due to lack of effectiveness and toxic adverse events, and total drug retention rates. These findings may provide new insight into the decision to use these agents in clinical practice.

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Declarations

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Conflict of interest

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, Mitsubishi-Tanabe, Ono Pharmaceutical, Teijin Pharma, 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,

Pfizer, Sanofi, and UCB Japan. TH received a research grant and/or speaker fee from Astellas, Chugai, GlaxoSmithKline, Nippon Shinyaku, and Eisai. 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 (Asahi-Kasei, Mitsubishi-Tanabe, Chugai, Ayumi, and UCB Japan) and the city government (Nagahama City). MHashimoto received a research grant and/or speaker fee from Mitsubishi-Tanabe, Eisai, Eli Lilly, and Bristol-Myers Squibb. KM received a speaker 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, cover letter 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. SJ has received speaking fees from AbbVie, Asahi-Kasei, Bristol-Myers Squib, Chugai, Eisai, Eli Lilly, Janssen Pharmaceutical, Mitsubishi-Tanabe, and Ono Pharmaceutical. RH received a speaker fee from AbbVie. MHirao 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. KN has received a research grant from Astellas, and supervises the Department of Musculoskeletal

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Ethical approval

The representative facility of this registry was Kyoto University, and this observational study was conducted in accordance with the Declaration of Helsinki, with the approval of the ethics committees of the following seven institutes: Kyoto University (2016-03-24/approval No. R053), Osaka University (2015-11-04/approval No. 15300), Osaka Medical College (2014-07-14/approval No. 1529), Kansai Medical University (2017-11-21/approval No. 2014625), Kobe University (2015-03-20/approval No. 1738), Nara Medial University (2018-01-23/approval No. 1692), and Osaka Red Cross Hospital (2015-09-01/approval No. 644). The board of the Osaka University Hospital Ethics Committee waived the requirement for patient informed consent because of the anonymous nature of the data. Written informed consent was obtained from the participants in other institutes.

Consent for participation and publication

The board waived the requirement for patient informed consent by posting the opt-out information in

the hospitals' home page.

Availability of data and materials

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

Authors' contributions

KE was responsible for conception and design. KE, TH, YM, YO, MH, KM, AO, SJ, RH, TT, AY, YS, HA, 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, MH, and KN supervised the manuscript. All the authors read and approved the final manuscript.

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Figure Legends

Figure 1. Adjusted drug retention due to lack of effectiveness (a) and toxic adverse events (b).

Adjusted confounders included age, sex, disease duration, concomitant prednisolone, methotrexate, and salazosulfapyridine, and number of switched biologics bDMARDs or JAKi.

TOF = Tofacitinib, BAR = Baricitinib, SAR = Sarilumab, bDMARDs = biological disease-modifying antirheumatic drugs, JAKi = Janus kinase inhibitors.

Figure 2. Adjusted drug retention due to non-toxic reasons (a) and total drug retention excluding non-toxic reasons and remission (b).

Adjusted confounders included age, sex, disease duration, concomitant prednisolone, methotrexate, and salazosulfapyridine, and number of switched biologics bDMARDs or JAKi.

TOF = Tofacitinib, BAR = Baricitinib, SAR = Sarilumab, bDMARDs = biological disease-modifying antirheumatic drugs, JAKi = Janus kinase inhibitors.

Table 1. Patients' clinical characteristics at treatment initiation with each agent

Variable	SAR (n = 62)	BAR (n = 166)	TOF (n = 185)	P value
Age (years)	63.8 ± 11.8	60.2 ± 13.5	60.7 ± 13.1	0.17
Female sex (%)	82.3	86.7	75.1	0.02
Disease duration (years)	11.4 ± 10.7	12.6 ± 10.6	9.7 ± 8.3	0.02
RF positivity (%)	86.8	86.1	81.6	0.64
ACPA positivity (%)	75.0	82.0	83.1	0.44
DAS28-ESR	4.1 ± 1.4	4.3 ± 1.3	4.3 ± 1.3	0.50
CDAI	15.6 ± 8.7	17.2 ± 11.0	18.8 ± 11.1	0.18
HAQ-DI	1.1 ± 0.8	0.9 ± 0.7	0.9 ± 0.8	0.62
PSL use (%)	48.4	42.8	50.3	0.36
PSL dose (mg/day)	5.2 ± 3.0	4.7 ± 3.2	5.7 ± 3.3	0.11
MTX use (%)	45.2	64.5	57.3	0.03
MTX dose (mg/week)	7.9 ± 4.1	8.7 ± 3.1	9.2 ± 3.3	0.15
SASP use (%)	16.1	11.4	23.8	0.01
BUC use (%)	9.7	7.8	8.6	0.86
IGU use (%)	24.2	13.3	17.8	0.13
TAC use (%)	14.5	15.7	9.7	0.21
LEF use (%)	0.0	0.0	0.0	N.A.
bDMARDs or JAKi naive (%)	11.3	22.3	24.3	0.08
2nd bDMARDs or JAKi (%)	25.8	23.5	24.3	0.93
≥3rd bDMARDs or JAKi (%)	62.9	54.2	51.4	0.29
Prior TNFi use (%)	64.5	57.8	65.9	0.28
Prior anti-IL-6R use (%)	51.6	36.1	40.5	0.11
Prior CTLA4-Ig (abatacept) use (%)	32.3	31.9	25.4	0.34
Prior JAKi use (%)	25.8	20.5	6.5	< 0.001

Values are presented as mean ± standard deviation or percentage.

N.A., not applicable; SAR, sarilumab; BAR, baricitinib; TOF, tofacitinib; RF, rheumatoid factor; ACPA, anticyclic 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; SASP, salazosulfapyridine; BUC, bucillamine; IGU, iguratimod; TAC, tacrolimus; LEF, leflunomide; bDMARDs, biological disease-modifying antirheumatic drugs; JAKi, Janus kinase inhibitor: TNFi, tumor necrosis factor inhibitors; IL-6R, interleukin-6 receptor; CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4-Ig.

Differences between the groups were assessed using an analysis of variance or the Fisher exact test.

Table2

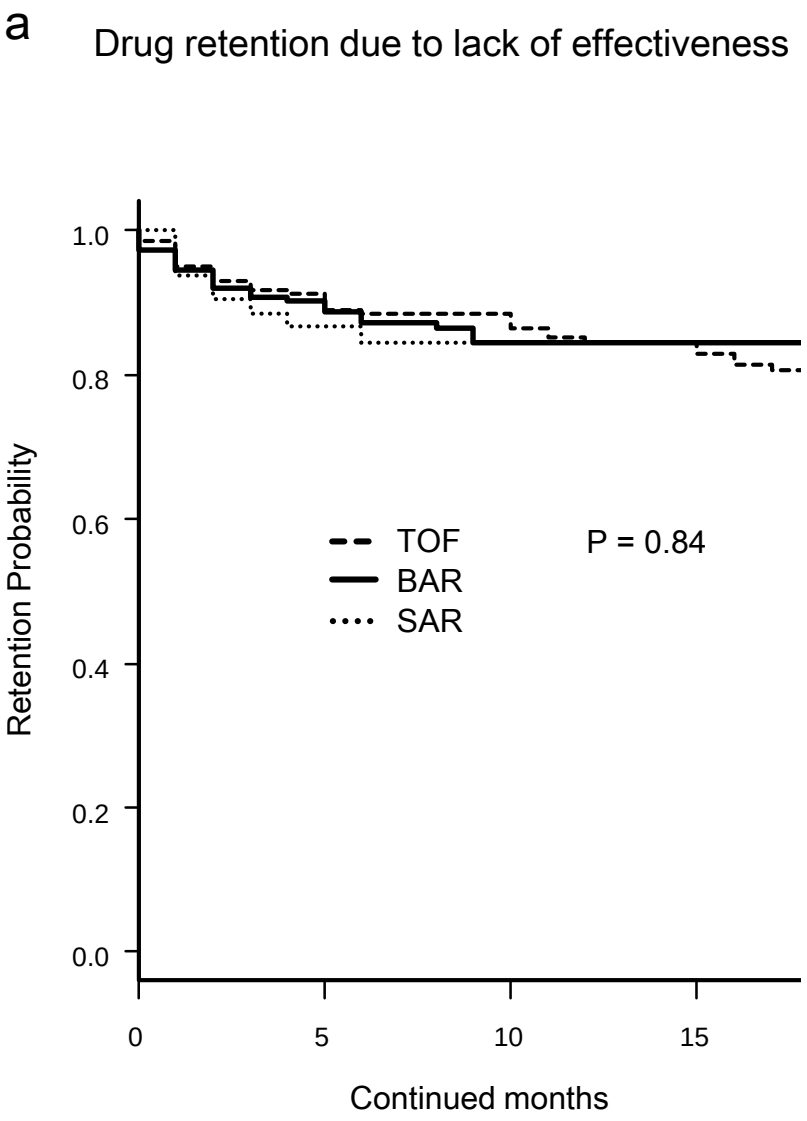
Table 2. Hazard ratios for treatment discontinuation in the cases (Cox proportional hazards model: adjusted for baseline age; sex; disease duration; concomitant PSL, SASP, and MTX use; and number of bDMARDs- or JAKi-switched cases)

	Reference	HR (95% CI)		P value
Variable	SAR (n = 62)	BAR (n = 166)	TOF (n = 185)	
Lack of effectiveness	1	0.87 (0.40–1.90)	1.02 (0.49–2.15)	0.84
Toxic adverse events	1	0.58 (0.25–1.32)	0.57 (0.26–1.29)	0.35
Non-toxic events	1	0.58 (0.22–1.53)	0.50 (0.20–1.29)	0.35
Total discontinuation (excluding non-toxic reasons and remission)	1	0.73 (0.41–1.28)	0.81 (0.47–1.38)	0.54

PSL, prednisolone; SASP, salazosulfapyridine; MTX, methotrexate; bDMARDs, biological disease-modifying antirheumatic drugs; JAKi, Janus kinase inhibitors; HR, hazard ratio; 95% CI, 95% confidence interval; SAR, sarilumab; BAR, baricitinib; TOF, tofacitinib.

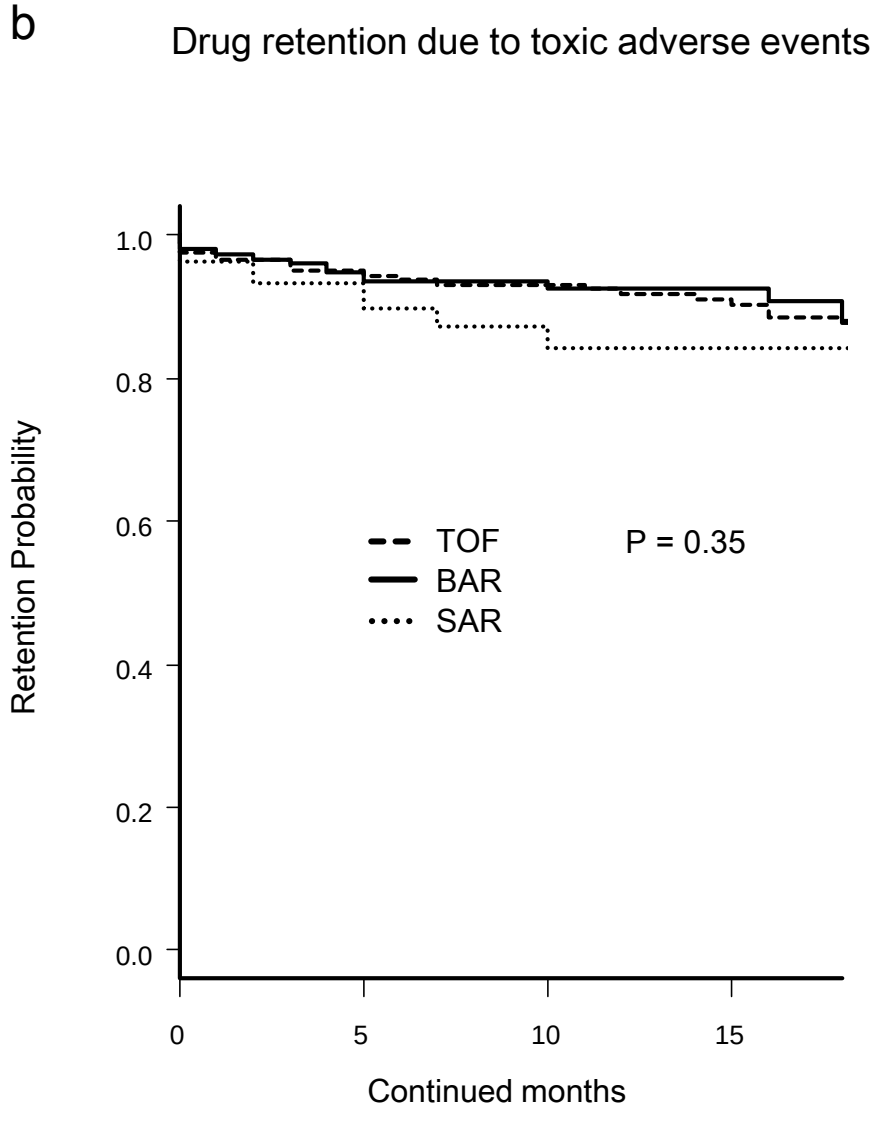
Differences between the groups were assessed using the Cox P value.

Figure1



Number at risk

BAR	166	116	72	42
SAR	62	40	25	9
TOF	185	142	127	105



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BAR	166	116	72	42
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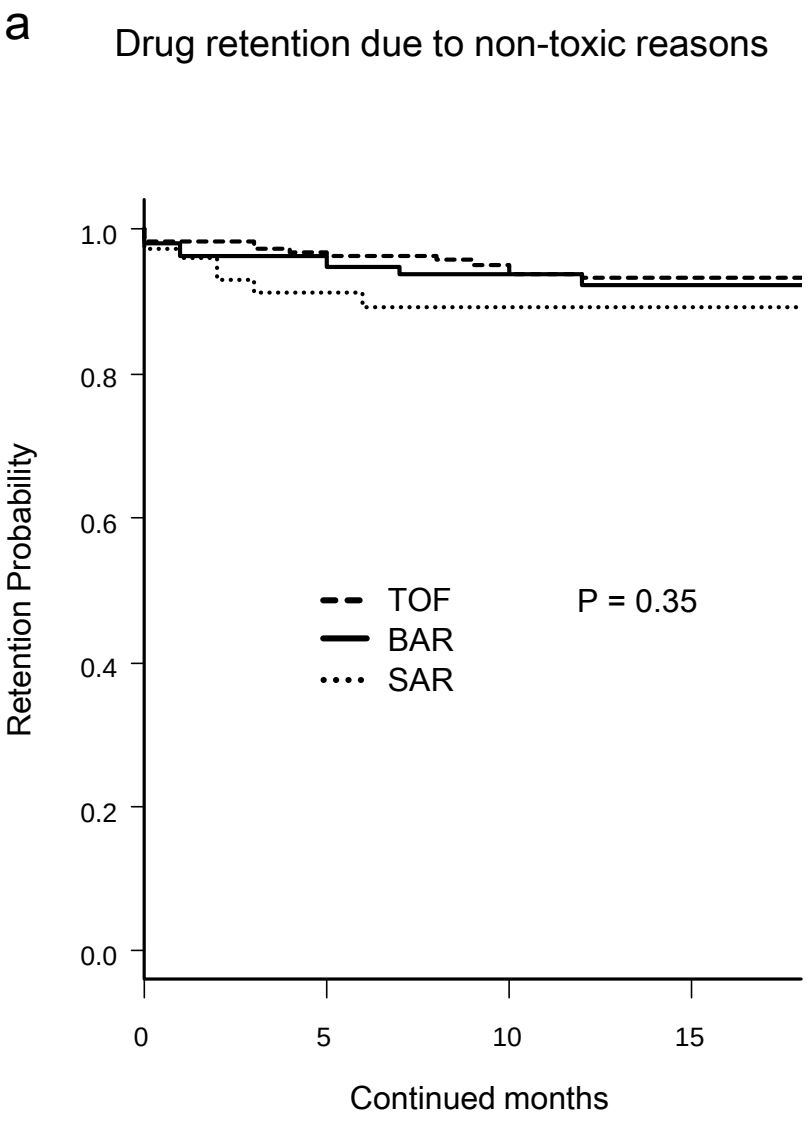
Figure2



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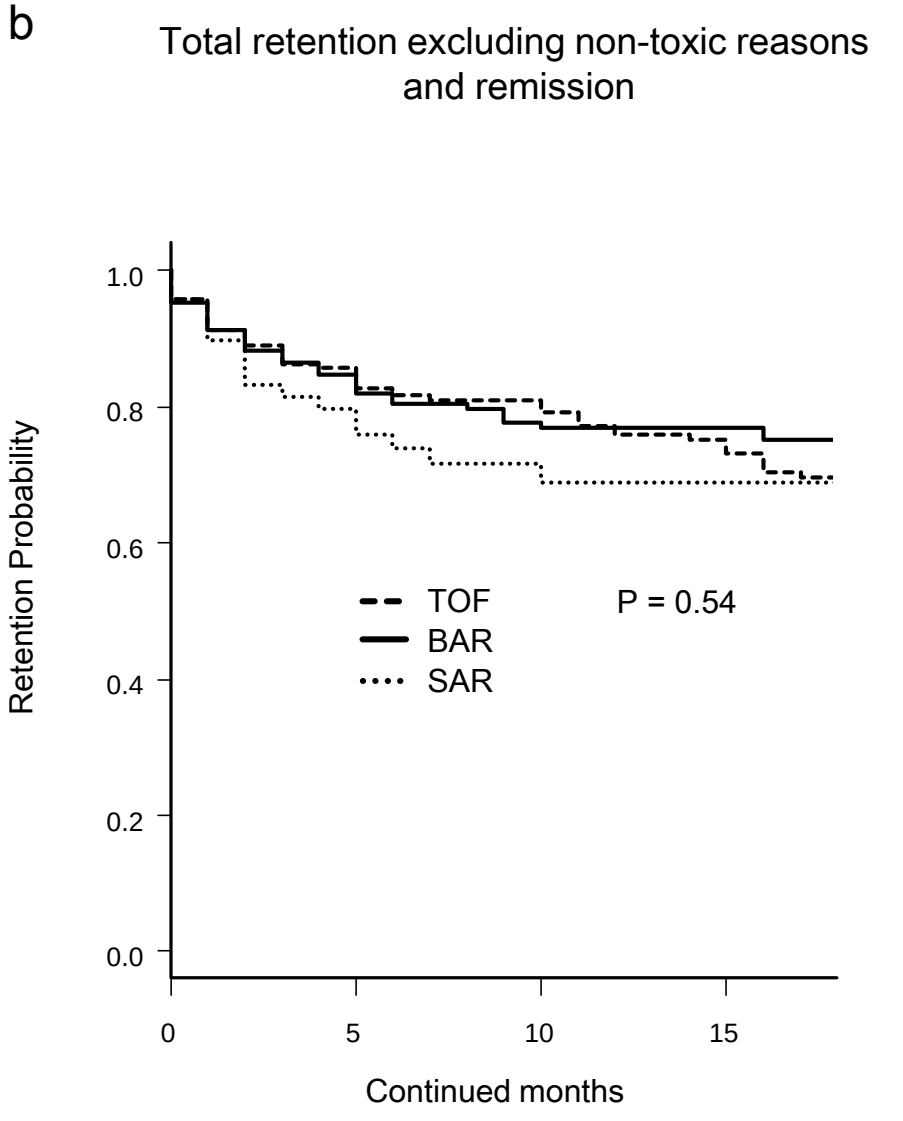

Number at risk

BAR	166	116	72	42
SAR	62	40	25	9
TOF	185	142	127	105

Supplementary table 1. List of abbreviations

ACPA; anticyclic citrullinated peptide antibody
ANSWER; The Kansai Consortium for Well-being of Rheumatic Disease Patients
BAR; baricitinib
bDMARDs; biological disease-modifying antirheumatic drugs
BUC; bucillamine
CDAI; clinical disease activity index
csDMARDs; conventional disease-modifying antirheumatic drugs
CTLA4-Ig; cytotoxic T lymphocyte-associated antigen-4-Ig
DAS28-ESR; Disease Activity Score in 28 joints using erythrocyte sedimentation rate
HAQ-DI; Health Assessment Questionnaire disability index
HR; hazard ratio
IGU; iguratimod
IL-6R; interleukin-6 receptor
IR; inadequate response
JAKi; Janus kinase inhibitor
LEF; leflunomide
MTX; methotrexate
PSL; prednisolone
RA; rheumatoid arthritis
RF; rheumatoid factor
SAR; sarilumab
SASP; salazosulfapyridine
TAC; tacrolimus
TCZ; tocilizumab
TNFi; tumor necrosis factor inhibitors
TOF; tofacitinib

Supplementary table 2. Summary of drug retention in ANSWER cohort

Ebina K et al. PLOSONE 2018 [1]

- 1,037 treatment courses of 750 RA patients.
- Treatment courses included abatacept (ABT; n = 221), adalimumab (ADA; n = 115), certolizumab pegol (CZP; n = 82), etanercept (ETN; n = 141), golimumab (GLM; n = 175), infliximab (IFX; n = 88), and tocilizumab (TCZ; n = 215).
- Drug retention at 36 months were estimated using the Kaplan-Meier method and adjusted by potent confounders using Cox proportional hazards modeling.
- ABT and TCZ showed higher overall retention, and TCZ showed lower inefficacy compared to IFX, while IFX showed higher discontinuation due to remission compared to ABT, ETN, GLM, and TCZ in adjusted modeling.

Ebina K et al. PLOSONE 2019 [2]

- 1,098 treatment courses of 661 elderly RA patients (65 years of age or older).
- Treatment courses included abatacept (ABT; n = 272), tocilizumab (TCZ; n = 234), etanercept (ETN; n = 184), golimumab (GLM; n = 159), infliximab (IFX; n = 101), adalimumab (ADA; n = 97), and certolizumab pegol (CZP; n = 51).
- Drug retention rates were estimated at 36 months using the Kaplan-Meier method and adjusted for potential clinical confounders (age, sex, disease duration, concomitant PSL and MTX, starting date and switched number of bDMARDs).
- Drug retention rates for each discontinuation reason were as follows; lack of effectiveness [from 55.4% (ETN) to 81.6% (ABT); with significant differences between groups (Cox P<0.001)], toxic adverse events [from 79.3% (IFX) to 95.4% (ABT), Cox P = 0.043], and remission [from 94.2% (TCZ) to 100.0% (CZP), Cox P = 0.58]. Finally, overall retention rates excluding non-toxic reasons and remission for discontinuation ranged from 50.0% (ETN) to 78.1% (ABT) (Cox P<0.001).

Ebina K et al. Arthritis Research & Therapy 2019 [3]

- 4,466 treatment courses of 2,494 RA patients.
- Treatment courses included tocilizumab (TCZ; n = 895), etanercept (ETN; n = 891), infliximab (IFX; n = 748), abatacept (ABT; n = 681), adalimumab (ADA; n = 558), golimumab (GLM; n = 464), and certolizumab pegol (CZP; n = 229).
- Drug retention rates were estimated at 36 months using the Kaplan-Meier method and adjusted for potential confounders (age, sex, disease duration, concomitant PSL and MTX, and switched number of bDMARDs) using Cox proportional hazards modeling.

- Drug retention rates for each discontinuation reason were as follows: lack of effectiveness [from 65.5% (IFX) to 81.7% (TCZ); with significant differences between groups (Cox P < 0.001)], toxic adverse events [from 81.8% (IFX) to 94.0% (ABT), Cox P < 0.001], and remission [from 92.4% (ADA and IFX) to 97.7% (ETN), Cox P < 0.001]. Finally, overall retention rates excluding non-toxic reasons and remission for discontinuation ranged from 53.4% (IFX) to 75.5% (ABT) (Cox P < 0.001).

Ebina K et al. Arthritis Research & Therapy 2020 [4]

- 4,415 treatment courses of 3,897 RA patients (2,737 bDMARDs-naïve courses and 1,678 bDMARDs-switched courses).
- 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 tofacitinib (TOF; n = 101).
- Drug discontinuation reasons (categorized into lack of effectiveness, toxic adverse events, non-toxic reasons, or remission) and rates were estimated at 36 months using 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.
- 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); and 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).

Abbreviations

bDMARDs = biological disease-modifying antirheumatic drugs, ABT = abatacept, ADA = adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab, TCZ = tocilizumab, TOF = tofacitinib, PSL = prednisolone, MTX = methotrexate.

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