



Title	Drug retention of sarilumab, baricitinib, and tofacitinib in patients with rheumatoid arthritis: the ANSWER cohort study
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1 **Original Article**

2

3 **Title:**4 Drug retention of sarilumab, baricitinib, and tofacitinib in patients with rheumatoid arthritis: The
5 ANSWER cohort study

6

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56 **Abstract**

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

59 Methods: Patients treated with either SAR (n = 62), BAR (n = 166), or TOF (n = 185) (females,
60 80.9%; age, 61.0 years; disease duration, 11.1 years; rheumatoid factor positivity, 84.4%; Disease
61 Activity Score in 28 joints using erythrocyte sedimentation rate, 4.3; concomitant prednisolone dose,
62 5.3 mg/day [47.0%] and methotrexate dose, 8.8 mg/week [58.4%]; biologics- or Janus kinase
63 inhibitors-switched cases 78.4%) were included. The reasons for drug discontinuation were classified
64 into 4 major categories (lack of effectiveness, toxic adverse events, non-toxic reasons, and remission)
65 by each attending physician. The drug retention rate was estimated at 18 months using the Kaplan–
66 Meier method and adjusted for potential confounders by Cox proportional hazards modeling.

67 Results: The discontinuation rates of SAR, BAR, and TOF for the corresponding reasons were as
68 follows, respectively: lack of effectiveness (15.7%, 15.6%, and 21.5%; P = 0.84), toxic adverse events
69 (15.8%, 12.1%, and 12.3%; P = 0.35), non-toxic reasons (10.9%, 7.7%, and 6.8%; P = 0.35), and
70 remission (0.0%, 2.8%, and 0.0%; P = 1.0). The overall retention rates excluding non-toxic reasons
71 and remission were as follows: 68.8% for SAR, 72.5% for BAR, and 66.7% for TOF (P = 0.54).

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

74

75 **Keywords**

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

77

78 **Key Points**

79 This is the first retrospective multicenter study that aimed to clarify the retention rates and reasons for

80 discontinuation of SAR, BAR, and TOF in patients with RA.

81

82 **Abbreviations**

83 Abbreviations are listed in supplementary table 1.

84

85 **Introduction**

86 The recommendations of the 2019 European League Against Rheumatism (EULAR) stated that the
87 efficacies of anti-interleukin (IL)-6 receptor antibody (IL-6R; tocilizumab [TCZ] and sarilumab
88 [SAR]), CTLA4-Ig (abatacept), and Janus kinase inhibitors (JAKi) such as baricitinib (BAR; JAK1
89 and JAK2 inhibitor) and tofacitinib (TOF; JAK1 and JAK3 inhibitor) are considered equivalent to
90 those of tumor necrosis factor inhibitors (TNFi) in both the phase II and III treatments of rheumatoid
91 arthritis (RA) [1]. The findings of this report also showed no significant differences in outcomes
92 among the biological disease-modifying antirheumatic drugs (bDMARDs) and JAKi, irrespective of
93 their targets. However, cohort-based studies revealed that in patients who showed inadequate response
94 to TNFi, switching to a non-TNFi agent (such as ABT, rituximab, or TCZ) showed significantly
95 higher drug retention rates compared with switching to another TNFi [2,3]. In addition, we recently
96 reported that among bDMARDs-switched patients, those who were taking TCZ and TOF showed
97 lower discontinuation rates due to lack of effectiveness than those who were receiving TNFi,
98 suggesting that anti-IL-6R and JAKi had better retention than TNFi in real-world settings [4].
99 The use of TOF (2013), SAR (2017), and BAR (2017) was recently approved in Japan, and reliable
100 evidence of direct comparison between these agents is still lacking. SAR is a human IgG1 monoclonal
101 antibody that binds to soluble and membrane-bound IL-6 receptors, and a recent report demonstrated
102 similar safety and laboratory changes between patients treated with SAR and TCZ [5]. JAKi inhibits

103 the JAK-signal transducer and activator of transcription pathways, which leads to the inhibition of
104 IL-6 and other various cytokines [6]. A recent meta-analysis revealed that in patients with inadequate
105 response (IR) to bDMARDs (bDMARDs-IR), both TOF 10 mg (standard dose in Japan) and BAR 4
106 mg (standard dose in Japan) with methotrexate (MTX) were efficacious to similar extents [7],
107 although no detailed comparison using data from the same registry has been reported. In a comparison
108 between anti-IL-6R and JAKi in patients with TNFi-IR, TOF showed a lower discontinuation rate due
109 to lack of effectiveness than TCZ [8]. However, we recently reported that in bDMARDs-switched
110 patients, TCZ showed similar good retention due to lack of effectiveness compared to TOF [4]. Taken
111 together, comparison between the effectiveness of anti-IL-6R and JAKi still remains unclear.
112 Moreover, SAR, BAR, and TOF tended to be introduced in patient with multiple bDMARDs failure or
113 intolerance to MTX due to comorbidities in real-world settings, which is quite different from those
114 recruited in randomized controlled trials. Therefore, investigating the effectiveness and safety of these
115 agents in “difficult-to-treat” RA patients are of great interest.
116 Recently, cohort-based observational studies have increasingly been conducted to investigate the
117 performance of bDMARDs [9,10]. In these studies, drug retention is considered a major index of both
118 treatment safety and effectiveness [11,12]. On the basis of our findings from our cohort, we have
119 recently reported the drug retention rates of bDMARDs [4,13,14,15] (summaries of these studies are
120 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

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

143 In Japan, the national health insurance covers 70%–90% of the medical expense, and bDMARDs or
144 JAKi can be administered at the discretion of attending rheumatologists in accordance with the Japan
145 College of Rheumatology guidelines (generally in patients who showed inadequate response to
146 csDMARDs or with high risk of progressive joint destruction) [20,21,22]. The dose of each agent is
147 determined in accordance with the manufacturer's recommendation. Drug retention was
148 retrospectively evaluated as the duration until definitive treatment interruption. The reasons for
149 discontinuation were analyzed and classified into four major categories as follows: 1) lack of
150 effectiveness (including primary and secondary); 2) toxic adverse events (infection, skin or systemic
151 reaction, and other toxic events, including hematologic, pulmonary, renal, cardiovascular
152 complications, and malignancies); 3) non-toxic reasons (patient preference, change in hospital, desire
153 for pregnancy, etc.); and 4) disease remission [4,13,14,15,19]. Physicians were allowed to cite only
154 one reason for discontinuation.

155

156 **Statistical analyses**

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

168

169 **Results**

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

175 JAKi, suggesting “difficult-to-treat” backgrounds. We found significant differences in sex ratio (P =
176 0.02), disease duration (P = 0.02), MTX use (P = 0.03), SASP use (P = 0.01), and prior use of JAKi (P
177 < 0.001) between the groups. SAR (25.8%) and BAR (20.5%) showed higher rate of prior use of JAKi
178 compared to TOF (6.5%).

179 The adjusted drug discontinuation rates of SAR, BAR, and TOF for the corresponding reasons were as
180 follows, respectively: lack of effectiveness (15.7%, 15.6%, and 21.5%; P = 0.84 between the groups;
181 Fig. 1a), toxic adverse events (15.8%, 12.1%, and 12.3%; P = 0.35 between the groups; Fig. 1b),
182 non-toxic reasons (10.9%, 7.7%, and 6.8%; P = 0.35 between the groups; Fig. 2a), and remission
183 (0.0%, 2.8%, and 0.0%; P = 1.0 between the groups). The overall retention rates excluding non-toxic
184 reasons and remission were as follows: 68.8% for SAR, 72.5% for BAR, and 66.7% for TOF (P = 0.54
185 between the groups; Fig. 2b).

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

192

193 **Discussion**

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

202 Concerning JAKi, only a few meta-analyses have compared the effectiveness and safety of BAR and
203 TOF. Recent reports demonstrated that in patients with MTX-IR [26] or bDMARDs-IR [27], BAR 4
204 mg (standard dose in Japan) with MTX showed a higher American College of Rheumatology 20%
205 (ACR20) or ACR50 response rate than TOF 5 mg (10mg is standard dose in Japan) with MTX.
206 However, another meta-analysis revealed that in patients with csDMARDs-IR or bDMARDs-IR, BAR
207 4 mg and TOF 10 mg with MTX were both efficacious to similar extents [7]. Taken together, TOF 5
208 mg may be inferior, although TOF 10 mg may be equivalent to BAR 4 mg, which is in accordance
209 with the results of the present study.

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

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

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

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

244 of this study is that as far as we know, this is the first study to directly compare the drug retention rates

245 and reasons for discontinuation of SAR, BAR, and TOF in the same multicenter cohort.

246 After adjustment for the potent confounders, SAR, BAR, and TOF showed similar discontinuation

247 rates due to lack of effectiveness and toxic adverse events, and total drug retention rates. These

248 findings may provide new insight into the decision to use these agents in clinical practice.

249

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252 providing the data.

253

254 **Declarations**

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259 (CAC). This study was conducted as an investigator-initiated study. These companies had no roles in
260 the study design, data collection, data analysis, data interpretation, or writing of the report.

261

262 **Conflict of interest**

263 KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University,
264 Graduate School of Medicine, which is supported by Taisho. KE has received research grants from
265 Abbie, Asahi-Kasei, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Ono Pharmaceutical, Teijin Pharma,
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288 concerning this manuscript. These companies had no role in the study design, data collection, data
289 analysis, data interpretation, and preparation of the manuscript.

290

291 **Ethical approval**

292 The representative facility of this registry was Kyoto University, and this observational study was
293 conducted in accordance with the Declaration of Helsinki, with the approval of the ethics committees
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295 University (2015-11-04/approval No. 15300), Osaka Medical College (2014-07-14/approval No.
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299 Ethics Committee waived the requirement for patient informed consent because of the anonymous
300 nature of the data. Written informed consent was obtained from the participants in other institutes.

301

302 **Consent for participation and publication**

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

304 the hospitals' home page.

305

306 **Availability of data and materials**

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

308 reasonable request.

309

310 **Authors' contributions**

311 KE was responsible for conception and design. KE, TH, YM, YO, MH, KM, AO, SJ, RH, TT, AY, YS,

312 HA, and MK contributed to data extraction and interpretation. KE, WY, and KY contributed to the

313 design and conduction of statistical analysis. KE and MH prepared the manuscript. AK, MH, and KN

314 supervised the manuscript. All the authors read and approved the final manuscript.

315

316

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318

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Figure Legends

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

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

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

435

436 **Figure 2. Adjusted drug retention due to non-toxic reasons (a) and total drug retention**

437 excluding non-toxic reasons and remission (b).

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

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

1 **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

2 Values are presented as mean ± standard deviation or percentage.

3 N.A., not applicable; SAR, sarilumab; BAR, baricitinib; TOF, tofacitinib; RF, rheumatoid factor; ACPA, 4 anticyclic citrullinated peptide antibody; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte 5 sedimentation rate; CDAI, clinical disease activity index; HAQ-DI, Health Assessment Questionnaire disability

6 index; PSL, prednisolone; MTX, methotrexate; SASP, salazosulfapyridine; BUC, bucillamine; IGU, iguratimod;
7 TAC, tacrolimus; LEF, leflunomide; bDMARDs, biological disease-modifying antirheumatic drugs; JAKi, Janus
8 kinase inhibitor: **TNF α** , tumor necrosis factor inhibitors; **IL-6R**, interleukin-6 receptor; **CTLA4-Ig**, cytotoxic T
9 lymphocyte-associated antigen-4-Ig.

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

11

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)

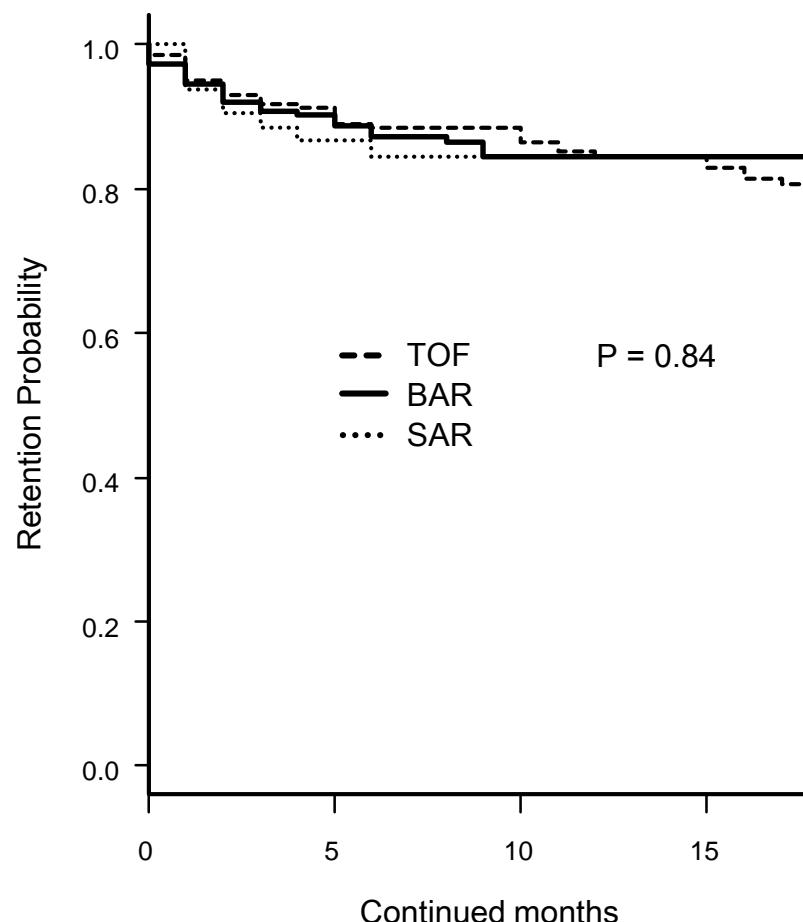
	Reference	HR (95% CI)		P value
Variable	SAR (n = 62)	BAR (n = 166)	TOF (n = 185)	
Lack of effectiveness	1	0.87 (0.40–1.90)	1.02 (0.49–2.15)	0.84
Toxic adverse events	1	0.58 (0.25–1.32)	0.57 (0.26–1.29)	0.35
Non-toxic events	1	0.58 (0.22–1.53)	0.50 (0.20–1.29)	0.35
Total discontinuation (excluding non-toxic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

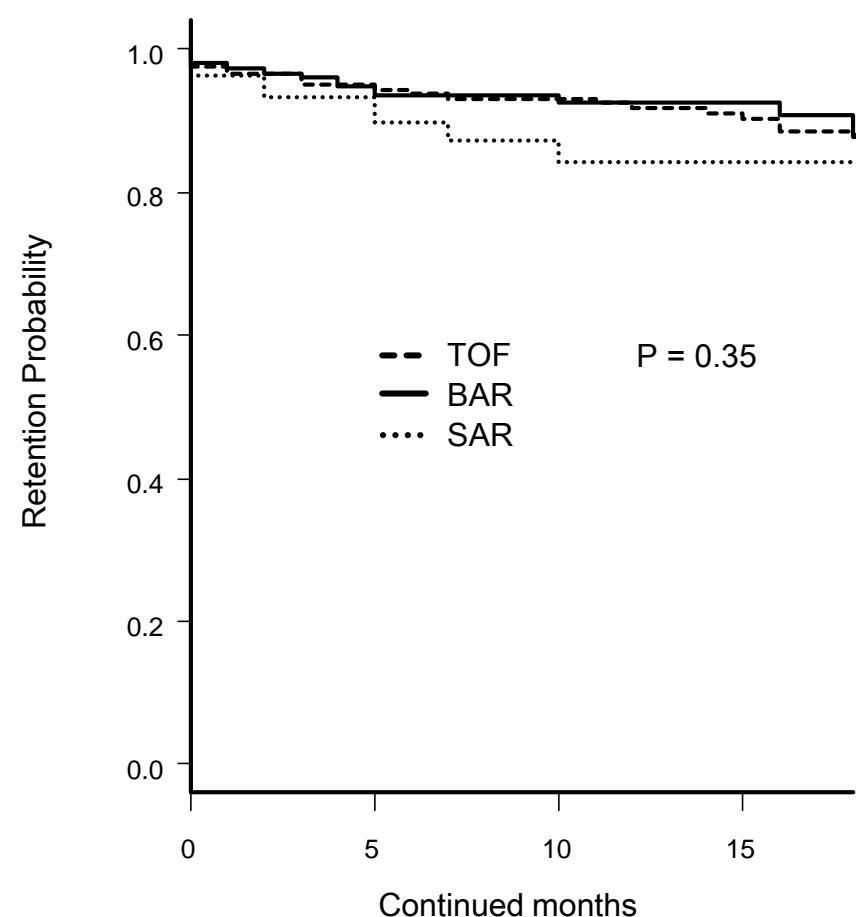
a Drug retention due to lack of effectiveness



Number at risk

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

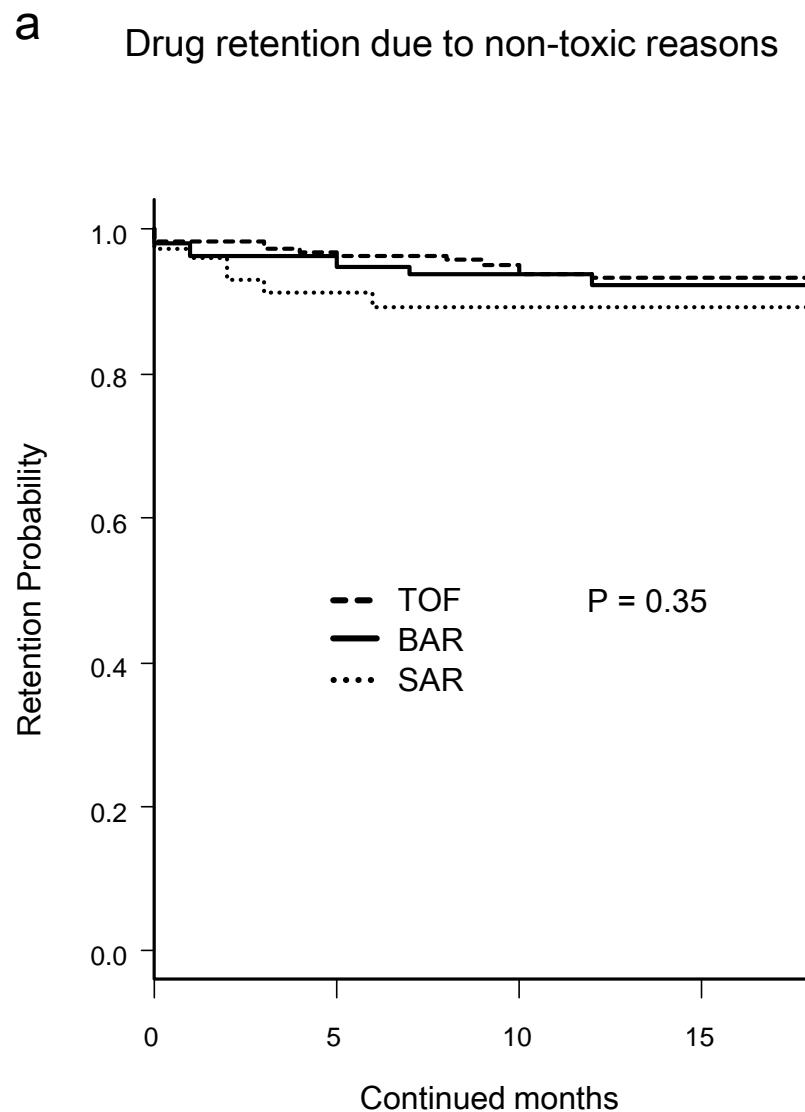
b Drug retention due to toxic adverse events



Number at risk

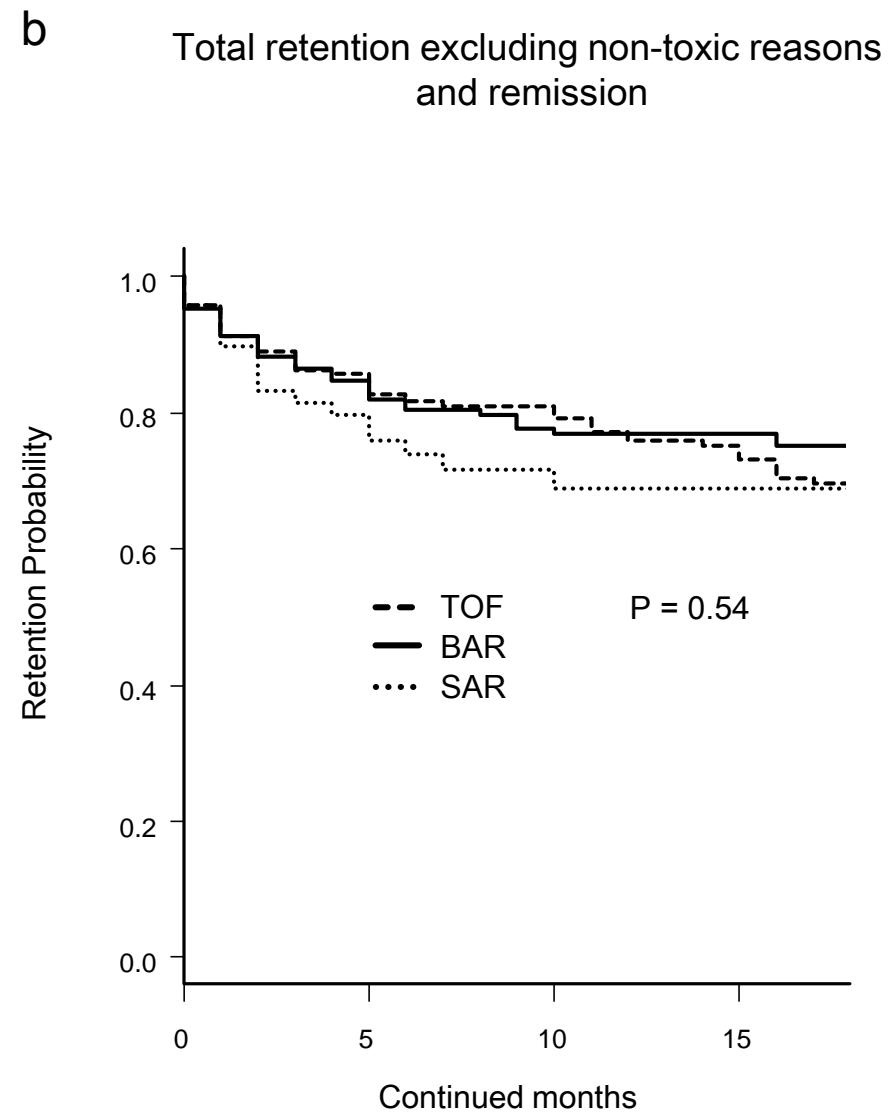
	BAR	SAR	TOF
166	116	72	42
62	40	25	9
185	142	127	105

Figure2



Number at risk

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



Number at risk

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

1 Supplementary table 1. List of abbreviations

2

3 ACPA; anticyclic citrullinated peptide antibody

4 ANSWER; The Kansai Consortium for Well-being of Rheumatic Disease Patients

5 BAR; baricitinib

6 bDMARDs; biological disease-modifying antirheumatic drugs

7 BUC; bucillamine

8 CDAI; clinical disease activity index

9 csDMARDs; conventional disease-modifying antirheumatic drugs

10 CTLA4-Ig; cytotoxic T lymphocyte-associated antigen-4-Ig

11 DAS28-ESR; Disease Activity Score in 28 joints using erythrocyte sedimentation rate

12 HAQ-DI; Health Assessment Questionnaire disability index

13 HR; hazard ratio

14 IgU; iguratimod

15 IL-6R; interleukin-6 receptor

16 IR; inadequate response

17 JAKi; Janus kinase inhibitor

18 LEF; leflunomide

19 MTX; methotrexate

20 PSL; prednisolone

21 RA; rheumatoid arthritis

22 RF; rheumatoid factor

23 SAR; sarilumab

24 SASP; salazosulfapyridine

25 TAC; tacrolimus

26 TCZ; tocilizumab

27 TNFi; tumor necrosis factor inhibitors

28 TOF; tofacitinib

29

1 **Supplementary table 2. Summary of drug retention in ANSWER cohort**2 **Ebina K et al. PLOS ONE 2018 [1]**

- 4 ● 1,037 treatment courses of 750 RA patients.
- 5 ● Treatment courses included abatacept (ABT; n = 221), adalimumab (ADA; n = 115),
6 certolizumab pegol (CZP; n = 82), etanercept (ETN; n = 141), golimumab (GLM; n = 175),
7 infliximab (IFX; n = 88), and tocilizumab (TCZ; n = 215).
- 8 ● Drug retention at 36 months were estimated using the Kaplan-Meier method and adjusted by
9 potent confounders using Cox proportional hazards modeling.
- 10 ● ABT and TCZ showed higher overall retention, and TCZ showed lower inefficacy compared to
11 IFX, while IFX showed higher discontinuation due to remission compared to ABT, ETN, GLM,
12 and TCZ in adjusted modeling.

13 **Ebina K et al. PLOS ONE 2019 [2]**

- 15 ● 1,098 treatment courses of 661 elderly RA patients (65 years of age or older).
- 16 ● Treatment courses included abatacept (ABT; n = 272), tocilizumab (TCZ; n = 234), etanercept
17 (ETN; n = 184), golimumab (GLM; n = 159), infliximab (IFX; n = 101), adalimumab (ADA; n =
18 97), and certolizumab pegol (CZP; n = 51).
- 19 ● Drug retention rates were estimated at 36 months using the Kaplan-Meier method and adjusted
20 for potential clinical confounders (age, sex, disease duration, concomitant PSL and MTX, starting
21 date and switched number of bDMARDs).
- 22 ● Drug retention rates for each discontinuation reason were as follows; lack of effectiveness [from
23 55.4% (ETN) to 81.6% (ABT); with significant differences between groups (Cox P<0.001)], toxic
24 adverse events [from 79.3% (IFX) to 95.4% (ABT), Cox P = 0.043], and remission [from 94.2%
25 (TCZ) to 100.0% (CZP), Cox P = 0.58]. Finally, overall retention rates excluding non-toxic
26 reasons and remission for discontinuation ranged from 50.0% (ETN) to 78.1% (ABT) (Cox
27 P<0.001).

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

- 30 ● 4,466 treatment courses of 2,494 RA patients.
- 31 ● Treatment courses included tocilizumab (TCZ; n = 895), etanercept (ETN; n = 891), infliximab
32 (IFX; n = 748), abatacept (ABT; n = 681), adalimumab (ADA; n = 558), golimumab (GLM; n =
33 464), and certolizumab pegol (CZP; n = 229).
- 34 ● Drug retention rates were estimated at 36 months using the Kaplan-Meier method and adjusted
35 for potential confounders (age, sex, disease duration, concomitant PSL and MTX, and switched
36 number of bDMARDs) using Cox proportional hazards modeling.

37 ● Drug retention rates for each discontinuation reason were as follows: lack of effectiveness [from
38 65.5% (IFX) to 81.7% (TCZ); with significant differences between groups (Cox $P < 0.001$)], toxic
39 adverse events [from 81.8% (IFX) to 94.0% (ABT), Cox $P < 0.001$], and remission [from 92.4%
40 (ADA and IFX) to 97.7% (ETN), Cox $P < 0.001$]. Finally, overall retention rates excluding
41 non-toxic reasons and remission for discontinuation ranged from 53.4% (IFX) to 75.5% (ABT)
42 (Cox $P < 0.001$).
43

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

45 ● 4,415 treatment courses of 3,897 RA patients (2,737 bDMARDs-naïve courses and 1,678
46 bDMARDs-switched courses).
47 ● Treatment courses included abatacept (ABT; $n = 663$), adalimumab (ADA; $n = 536$),
48 certolizumab pegol (CZP; $n = 226$), etanercept (ETN; $n = 856$), golimumab (GLM; $n = 458$),
49 infliximab (IFX; $n = 724$), tocilizumab (TCZ; $n = 851$), and tofacitinib (TOF; $n = 101$).
50 ● Drug discontinuation reasons (categorized into lack of effectiveness, toxic adverse events,
51 non-toxic reasons, or remission) and rates were estimated at 36 months using Gray's test and
52 statistically evaluated after adjusted by potential clinical confounders (age, sex, disease duration,
53 concomitant PSL and MTX usage, starting date, and number of switched bDMARDs) using the
54 Fine-Gray model.
55 ● Cumulative incidence of drug discontinuation for each reason was as follows: lack of
56 effectiveness in the bDMARDs-naïve group (from 13.7% [ABT] to 26.9% [CZP]; $P < 0.001$
57 between agents) and the bDMARDs-switched group (from 18.9% [TCZ] to 46.1% [CZP]; $P <$
58 0.001 between agents); toxic adverse events in the bDMARDs-naïve group (from 4.6% [ABT] to
59 11.2% [ETN]; $P < 0.001$ between agents) and the bDMARDs-switched group (from 5.0% [ETN]
60 to 15.7% [TOF]; $P = 0.004$ between agents); and remission in the bDMARDs-naïve group (from
61 2.9% [ETN] to 10.0% [IFX]; $P < 0.001$ between agents) and the bDMARDs-switched group
62 (from 1.1% [CZP] to 3.3% [GLM]; $P = 0.9$ between agents).
63

64 **Abbreviations**

65
66 bDMARDs = biological disease-modifying antirheumatic drugs, ABT = abatacept, ADA =
67 adalimumab, CZP = certolizumab pegol, ETN = etanercept, GLM = golimumab, IFX = infliximab,
68 TCZ = tocilizumab, TOF = tofacitinib, PSL = prednisolone, MTX = methotrexate.
69

70 **References**

71
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