

Title	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-
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Osaka University

1 **Original Article**

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3 **Title:**

4 **Drug retention of secondary biologics or JAK inhibitors after tocilizumab or abatacept failure as first**  
5 **biologics in patients with rheumatoid arthritis -The ANSWER cohort study-**

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31

32 **Keywords**

33 Abatacept, biologics, drug retention, Janus kinase inhibitors, rheumatoid arthritis, tocilizumab

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61 analysis, data interpretation, and preparation of the manuscript.

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70 **Abstract**

71 Objectives: The aim of this multicenter, retrospective study was to clarify the retention of secondary  
72 biological disease-modifying antirheumatic drugs (bDMARDs) or Janus kinase inhibitors (JAKi) in  
73 patients with rheumatoid arthritis (RA) who were primarily treated by tocilizumab (TCZ) or abatacept  
74 (ABT) as first bDMARDs.

75 Method: Patients who were treated by either TCZ (n=145) or ABT (n=76) and then switched to either  
76 tumor necrosis factor inhibitors (TNFi), TCZ, ABT, or JAKi (including only cases switched from  
77 TCZ) from 2001 to 2019 [female 81.0%, age 59.5 years, disease duration 8.8 years; rheumatoid factor  
78 positivity 75.4%; Disease Activity Score in 28 joints using C-reactive protein 3.7; concomitant  
79 prednisolone (PSL) dose 6.0 mg/day (51.8%) and methotrexate (MTX) dose 8.0 mg/week (56.1%);  
80 81.9% discontinued first bDMARDs due to lack of effectiveness] were included. Drug retention and  
81 discontinuation reasons were estimated at 24 months using the Kaplan-Meier method and adjusted for  
82 potential confounders by Cox proportional hazards modeling.

83 Results: Drug retentions for each of the reasons for discontinuation were as follows; lack of  
84 effectiveness in TCZ-switched group [TNFi (59.5%), ABT (82.2%), and JAKi (84.3%); TNFi vs.  
85 ABT; P=0.009] and ABT-switched group [TNFi (79.6%) and TCZ (92.6%); P=0.053]. Overall  
86 retention excluding non-toxic reasons and remission for discontinuation were TNFi (49.9%), ABT

87 (72.7%), and JAKi (72.6%) (TNFi vs. ABT; P=0.017) in the TCZ-switched group and TNFi (69.6%)

88 and TCZ (72.4%) (P=0.44) in the ABT-switched group.

89 Conclusions: Switching to ABT in TCZ-treated patients led to higher retention as compared to TNFi.

90 Switching to TCZ in ABT-treated patients tended to led to higher retention due to effectiveness,

91 although total retention was similar as compared to TNFi.

92

### 93 **Key-points**

94 This is the first retrospective, multi-center study aimed to clarify the retention rates of secondary

95 bDMARDs or JAKi in patients with RA who were primarily being treated by TCZ or ABT as the first

96 bDMARDs.

97

### 98 **Introduction**

99 The recommendations of the 2016 European League Against Rheumatism (EULAR) stated that

100 CTLA4-Ig [abatacept (ABT)], anti-interleukin (IL)-6 receptor antibody [tocilizumab (TCZ)], and

101 Janus kinase inhibitors (JAKi) were considered to be equivalent to tumor necrosis factor inhibitors

102 (TNFi) for both the phase II and phase III treatment of rheumatoid arthritis (RA) [1]. The findings of

103 this report also stated that there was no difference in the outcomes among these biological

104 disease-modifying antirheumatic drugs (bDMARDs) and JAKi, irrespective of their target. Moreover,

105 Smolen et al. reported that these agents also have a similar efficacy in previously TNFi-experienced  
106 patients, although this efficacy may be decreased as compared to the bDMARDs-naïve patients [2]. In  
107 our country, national health insurance covers 70-90% of the medical expense, and bDMARDs or JAKi  
108 can be selected by attending physicians' discretion according to the Japan College of Rheumatology  
109 guideline.

110 However, other cohort-based studies revealed that for the second-line bDMARDs, ABT [3] and TCZ  
111 [4] exhibited a better retention as compared to TNFi. Moreover, both ABT and TCZ administrations  
112 were reported to lead to substantial improvement of the disease activity in patients who discontinued  
113 TNFi [5]. In addition, we previously reported that ABT and TCZ had a higher retention as compared  
114 to TNFi, even when adjusted in accordance with the clinical backgrounds [6,7]. Concerning JAKi, as  
115 far as we know, there have been no previous reports that have compared treatment retention with TNFi,  
116 ABT, or TCZ. However, in patients who exhibited an inadequate response to TNFi, there was a higher  
117 retention for tofacitinib (TOF), which was reported to be due to a lack of efficacy compared to ABT,  
118 golimumab (GLM), and TCZ [8]. Thus, when taken together, this suggests that switching to non-TNFi  
119 (such as ABT or TCZ) or JAKi in TNFi-experienced patients may lead to better drug retention.

120 Recent studies have reported that non-TNFi tended to be selected as the first bDMARDs due to  
121 advanced age, comorbidities, and a high ACPA titer (ABT) or monotherapy (TCZ) [9,10]. However,  
122 when choosing ABT or TCZ as the first bDMARDs, there has been a concern about the effectiveness



123 of using a second bDMARDs or JAKi, especially in patients who originally exhibited an inadequate  
124 response to ABT or TCZ. As far as we know, there have yet to be any reports showing drug retention  
125 of secondary bDMARDs or JAKi in patients who were primarily treated by ABT or TCZ as first  
126 bDMARDs. At the present time, reliable evidence is still lacking in these types of cases.  
127 Randomized controlled trials (RCTs) often recruits patients with fewer comorbidities than that often  
128 seen in real-world settings [11]. Moreover, cohort-based observational studies have increasingly been  
129 used to investigate the performance of bDMARDs [12,13,14,15,16]. In these studies, drug retention is  
130 considered to be a major index of both the safety and effectiveness [17,18,19].  
131 Based on the findings of our cohort, we have recently reported on the drug retention found among  
132 bDMARDs [6,7,20,21], factors associated with the achievement of bDMARDs-free remission [22],  
133 and the influence of family history on treatment response [23]. The aim of current multicenter,  
134 retrospective study was to clarify within a real-world setting the retention of secondary bDMARDs or  
135 JAKi in patients who were primarily treated by ABT or TCZ as the first bDMARDs.

136

## 137 **Materials and methods**

### 138 **Patients**

139 The Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort is an  
140 observational multicenter registry of patients with RA living in the Kansai district of Japan. Data were

141 collected from patients who were examined at 7 major university-related hospitals (Kyoto University,  
142 Osaka University, Osaka Medical College, Kansai Medical University, Kobe University, Nara Medical  
143 University, and Osaka Red Cross Hospital). RA was diagnosed using the 1987 RA classification  
144 criteria of the American College of Rheumatology (ACR) [24] or the 2010 ACR / EULAR RA  
145 classification criteria [25]. From 2001 to 2019, data of patients who were primarily treated by ABT or  
146 TCZ as first bDMARDs, and then switched to either TNFi [infliximab (IFX), etanercept (ETN),  
147 adalimumab (ADA), certolizumab pegol (CZP), and GLM; and which excluded bio-similar agents],  
148 ABT, TCZ (including both intravenous and subcutaneous agents), or JAKi [tofacitinib (TOF) or  
149 baricitinib (BAR)] were retrospectively collected.

150 To be included in this study, patients were required to have data on the start and discontinuation dates  
151 for bDMARDs or JAKi, and the reasons for discontinuation. In addition, we also collected baseline  
152 demographic data such as age, sex, duration of disease, disease activity (Disease Activity Score in 28  
153 joints using C-reactive protein [DAS28-CRP]), Clinical Disease Activity Index (CDAI), concomitant  
154 doses and ratio of methotrexate (MTX) and prednisolone (PSL) (dose was calculated as a blank when  
155 not combined), **concomitant ratio of other conventional disease-modifying antirheumatic drugs**  
156 **(csDMARDs) such as salazosulfapyridine (SASP), leflunomide (LEF), bucillamine (BUC), tacrolimus**  
157 **(TAC), and iguratimod (IGU),** rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody  
158 (ACPA) positivity, and Health Assessment Questionnaire [HAQ] Disability Index [DI] score [6,7,21].

159 Treatments were administered by the attending rheumatologists in accordance with guidelines of the  
160 Japan College of Rheumatology [26,27,28]. Drug retention was retrospectively evaluated as the  
161 duration until definitive treatment interruption. Reasons for discontinuation were analyzed and  
162 classified into four major categories: 1) lack of effectiveness (including primary and secondary); 2)  
163 toxic adverse events (infection, skin or systemic reaction, and other toxic events, including  
164 hematologic, pulmonary, renal, cardiovascular complications, and malignancies, etc.); 3) non-toxic  
165 reasons (patient preference, change in hospital, desire for pregnancy, etc.); and 4) disease remission  
166 [6,7,21]. Physicians were allowed to cite only one reason for discontinuation.

167

#### 168 **Statistical analysis**

169 The differences in the baseline clinical characteristics between the groups were assessed using the  
170 Mann-Whitney U test (for 2 groups) or by an analysis of variance (for 3 groups) for continuous  
171 variables, and the Pearson's chi-squared test (for 2 groups) or the Fisher's exact test (for 3 groups) for  
172 categorical variables. The Kaplan-Meier method was used to examine the survival curves for each of  
173 the agents as determined by the specific causes. The hazard ratio (HR) for the treatment  
174 discontinuation at 24 months was analyzed and statistically compared using multivariate Cox  
175 proportional hazards modeling [6,7,12,21]. This analysis was adjusted for the potential confounders  
176 that could have influenced drug retention as previously described (age, sex, disease duration,

177 concomitant PSL and MTX, treatment duration of primary ABT or TCZ, and reasons of ABT or TCZ  
178 discontinuation) [12,14,16,29,30]. Statistical analyses were performed using EZR (Saitama Medical  
179 Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R  
180 Foundation for Statistical Computing, Vienna, Austria) [31].  $P < 0.05$  was considered statistically  
181 significant.

182

### 183 **Results**

184 Table 1 presents the baseline clinical characteristics of the patients initially treated by TCZ and then  
185 changed to another agent. The agents switched to in the TNFi group included GLM (n=27), ETN  
186 (n=17), IFX (n=14), ADA (n=11), and CZP (n=7), while in the JAKi group, patients were switched to  
187 TOF (n=13) and BAR (n=11). The primary reason for discontinuation of TCZ in all groups was the  
188 lack of effectiveness (from 70.8% to 80.0%;  $P = 0.13$  between the groups). Significant differences in  
189 the age ( $P = 0.011$ ), concomitant PSL dose ( $P < 0.001$ ), **SASP usage (%) ( $P = 0.04$ ), and IGU usage (%)**  
190 **( $P = 0.002$ )** were noted between the groups.

191 The adjusted drug retention rates due to lack of effectiveness in the TCZ-switched group were as  
192 follows: 59.5% (TNFi), 82.2% (ABT), and 84.3 (JAKi) [ $P = 0.017$  between the groups] (Fig. 1a). After  
193 excluding non-toxic reasons and remission for discontinuation, the overall retention rates were 49.9%  
194 (TNFi), 72.7% (ABT), and 72.6% (JAKi) [ $P = 0.023$  between the groups] (Fig. 1b).

195 Table 2 shows the adjusted HR for each of the discontinuation reasons. The HRs due to lack of  
196 effectiveness were significantly lower in ABT (HR=0.3, P=0.009), and additionally tended to be lower  
197 in the JAKi (HR=0.5, P=0.10) group as compared to TNFi (P=0.017 between the groups). There was  
198 no significant difference in the HR due to toxic adverse events between the groups (P=0.86). The HR  
199 for total discontinuation (excluding non-toxic reasons and remission) was significantly lower for the  
200 ABT (HR=0.5, P=0.017), and additionally tended to be lower in the JAKi (HR=0.5, P=0.072) group as  
201 compared to TNFi (P=0.023 between the groups). Comparing non-TNFi (ABT and JAKi) and TNFi,  
202 the HRs due to lack of effectiveness were significantly lower in non-TNFi (HR=0.4, 95% CI=0.2-0.7,  
203 P=0.005), and also HRs for total discontinuation (excluding non-toxic reasons and remission) were  
204 significantly lower in non-TNFi (HR=0.5, 95% CI=0.3-0.8, P=0.006) as compared to TNFi.

205 Table 3 shows the baseline clinical characteristics of the patients initially treated by ABT and then  
206 changed to another agent. The agents switched to in the TNFi group included GLM (n=17), ETN  
207 (n=11), ADA (n=9), IFX (n=4), and CZP (n=1). There was a significantly higher ratio (P=0.010) and  
208 dose (P=0.010) for the PSL treatment in the TCZ group, while there was also a lower ratio of MTX  
209 (P=0.029) as compared to the TNFi group.

210 The adjusted drug retention rates due to lack of effectiveness in the ABT-switched group were as  
211 follows: 79.6% (TNFi) and 92.6% (TCZ) [P=0.053 between the groups] (Fig. 2a). After excluding  
212 non-toxic reasons and remission for discontinuation, the overall retention rates were 69.6% (TNFi)

213 and 72.4% (TCZ) (P=0.44) (Fig. 2b).

214 Table 4 shows the adjusted HR for each of the discontinuation reasons. The HR due to a lack of

215 effectiveness tended to be lower in the TCZ (HR=0.3, P=0.053) versus the TNFi group. In contrast,

216 the HR due to toxic adverse events tended to be higher in the TCZ (HR=2.8, P=0.19) versus the TNFi

217 group, while the HRs for total discontinuation (excluding non-toxic reasons and remission) were

218 similar between the TCZ and TNFi group (HR=0.7, P=0.44).

219

## 220 **Discussion**

221 To the best of our knowledge, this is the first time that the retention rates of secondary bDMARDs or

222 JAKi have been documented in patients with RA who were primarily being treated by TCZ or ABT as

223 the first bDMARDs.

224 Previously, there have only been a few reports that have examined these types of issues with the

225 administration of these drugs. Akiyama et al. examined patients with an insufficient response to TCZ

226 and reported that the drug retention was comparable for both TNFi and ABT after switching [32].

227 However, only 41.3% of the patients were treated by TCZ as first bDMARDs, with 55.6% of the

228 patients found to have a TNFi failure history, which could have affected these results.

229 At the present time, precise mechanisms still remain unknown with regard to TCZ failure (especially

230 loss of effectiveness). Previous studies have reported that TCZ showed a similar retention in both

231 monotherapy and in combination with MTX [33]. Burmester et al. reported finding that anti-TCZ  
232 antibodies developed in a very small portion of patients (0.7-2.0%), regardless of the combination with  
233 csDMARDs during both subcutaneous and intravenous TCZ treatments, which was not correlated with  
234 its effectiveness [34]. Furthermore, these authors also suggested that one possible mechanism for the  
235 low immunogenicity in TCZ treatment was that there could have been downregulation of the B cell  
236 activity due to blocking of the IL-6 signaling [34]. The lack of a sufficient dose has also been  
237 suggested, as some patients who initially showed an inadequate response to subcutaneous TCZ when it  
238 was given every other week (q2w), exhibited a significantly improved efficacy after shortening the  
239 dose interval to every week (qw) [35].

240 As for ABT, a recent report stated that RF and ACPA positivity was a positive predictor of ABT  
241 retention in both bDMARDs-naïve and bDMARDs-failure patients [36]. Although the main reason for  
242 discontinuation was the lack of effectiveness [3,36], immunogenicity was not found to be associated  
243 with the loss of effectiveness [37].

244 Taken together, the lack or loss of effectiveness in ABT or TCZ treatments when used as first  
245 bDMARDs irrespective of the dosing escalation may actually be due to an incorrect treatment target or  
246 a change of the immunological backgrounds during the treatment. Thus, in these types of cases,  
247 switching the treatment mode of action should perhaps be considered.

248 Although TNF is a common cytokine that plays a central role in the pathology of several autoimmune  
249 diseases, IL-6 has been reported to be more dominant in the RA pathology [38]. However, TNF and  
250 IL-6 are downstream cytokines of the RA pathology, with ABT or JAKi potentially regulating more  
251 upstream inflammatory processes, including T-cells [39]. These speculations suggest that targeting the  
252 upstream process by ABT or JAKi in TCZ failure patients could potentially be more effective than  
253 targeting another downstream cytokine such as TNFi. However, elucidation of the mechanisms  
254 associated with ABT failure patients has proven to be quite difficult (80.3% were ACPA positive in  
255 this study). Thus, in such cases, targeting relatively RA-dominant cytokines such as IL-6 may be more  
256 promising as opposed to the targeting of broad cytokines such as TNF. The effect of switching from  
257 ABT to JAKi will need to be evaluated in future studies.

258 It is also necessary to point out the differences that have been found for the effectiveness of low-dose  
259 MTX in Japanese versus Western populations. We previously reported that intraerythrocyte  
260 MTX-polyglutamate (MTX-PG) concentrations, which are considered to be a useful biomarker of  
261 MTX efficacy, were 65 nmol/L when a 13.4 mg/week dose of MTX was administered to patients in  
262 the United States, whereas concentrations reached 94 nmol/L when a 10.3 mg/week dose of MTX was  
263 administered in Japanese patients [40]. Thus, a relatively low dose of MTX may exhibit positive  
264 effects on bDMARD retention in Japanese populations, **although may have stronger influence on the**  
265 **retention of TNFi compared to that of non-TNFi.**



266 The limitations of the current study were as follows. First, since relatively special conditions were  
267 followed during the recruitment of subjects, the number of patients in the study was small, which may  
268 have affected the results. Second, the judgment and reasons for discontinuation (such as lack of  
269 effectiveness or remission) depended on the decisions of each physician, without standardized criteria.  
270 Third, the difference between the intravenous and subcutaneous bDMARDs, the presence of other  
271 csDMARDs, and the minor dose changes that occurred for the bDMARDs, MTX, and PSL, and prior  
272 treatment before TCZ or ABT introduction could not be monitored. Fourth, comorbidities, which can  
273 potentially affect the drug retention, could not be evaluated. Fifth, the differences of treatment  
274 intervals between 1st and 2nd agents (although no significant differences were observed between the  
275 groups) may have affected the results.

276

## 277 **Conclusions**

278 Optimal strategy from these data is when choosing secondary agents after TCZ or ABT failure,  
279 switching TCZ to ABT may exhibit higher total retention, and switching TCZ to JAKi or switching  
280 ABT to TCZ tend to show higher retention due to the effectiveness compared to switching these  
281 non-TNFi agents to TNFi in certain conditions.

282

## 283 **Figure Legends**

284 **Figure 1. Adjusted drug retention due to lack of effectiveness (a) and total drug retention**

285 **excluding non-toxic reasons and remission (b) in TCZ-switched cases.**

286 Adjusted confounders included age, sex, disease duration, concomitant prednisolone and methotrexate,

287 treatment duration and discontinuation reasons of the TCZ.

288 TCZ = tocilizumab, ABT = abatacept, JAKi = Janus kinase inhibitors, TNFi = tumor necrosis factor

289 inhibitors.

290

291 **Figure 2. Adjusted drug retention due to lack of effectiveness (a) and total drug retention**

292 **excluding non-toxic reasons and remission (b) in ABT-switched cases.**

293 Adjusted confounders included age, sex, disease duration, concomitant prednisolone and methotrexate,

294 treatment duration and discontinuation reasons of the ABT.

295 ABT = abatacept, TCZ = tocilizumab, TNFi = tumor necrosis factor inhibitors.

296

297 **Availability of data and materials**

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

299 reasonable request.

300

301 **Authors' contributions**

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

306

307 **Compliance with ethical standards**

308 **Conflict of interest**

309 KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University,  
310 Graduate School of Medicine, which is supported by Taisho. KE has received research grants from  
311 Abbie, Asahi-Kasei, Astellas, Chugai, Eisai, Ono Pharmaceutical, and UCB Japan. KE has received  
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331 preparation of the manuscript.

332

### 333 **Ethical approval**

334 The representative facility of this registry was Kyoto University, and this observational study was  
335 conducted in accordance with the Declaration of Helsinki, with approval by each of the ethics  
336 committees of the seven institutes: Kyoto University (2016-03-24/ approved number R053), Osaka  
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341 Hospital Ethical Committee waived the requirement for patients' informed consent because of the  
342 anonymous nature of the data. Written informed consent was obtained from the participants in other  
343 institutes.

344

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**Table 1. Baseline clinical characteristics of patients initially treated by TCZ and then changed to another agent**

Variable	TCZ→TNFi (n=76)	TCZ→ABT (n=45)	TCZ→JAKi (n=24)	P-value
Agents used for follow-up	GLM (n=27), ETN (n=17), IFX (n=14), ADA (n=11), CZP (n=7)		TOF (n=13), BAR (n=11)	NA
Months TCZ continued	16.4±21.6	26.7±37.8	18.8±22.0	0.26
Reasons for discontinuing TCZ	Ineffectiveness (76.3%), toxic reasons (9.2%), non-toxic reasons (14.5%)	Ineffectiveness (80.0%), toxic reasons (17.8%), non-toxic reasons (2.2%)	Ineffectiveness (70.8%), toxic reasons (16.7%), non-toxic reasons (12.5%)	0.13
Treatment interval (months)	2.8±6.2	5.8±12.0	9.8±14.2	0.053
Age (years)	54.2±16.2	62.2±11.9	57.7±13.1	0.011
Disease duration (years)	7.8±8.2	11.6±9.6	8.8±6.5	0.096
RF positivity (%)	63.1	80.6	78.6	0.32
ACPA positivity (%)	73.2	87.1	75.0	0.53
DAS28-CRP	3.2±1.3	3.9±1.4	3.7±1.6	0.17
CDAI	16.6±10.5	17.5±10.2	20.3±12.9	0.56
HAQ-DI	0.9±0.7	0.9±0.5	1.2±0.8	0.61
PSL usage (%)	60.5	48.9	66.7	0.44
PSL dose (mg/day)	6.7±5.0	6.7±3.8	3.4±2.3	<0.001
MTX usage (%)	45.8	40.0	45.8	0.073
MTX dose (mg/week)	7.8±3.2	7.1±3.7	9.1±3.3	0.34
SASP usage (%)	6.6	6.7	25.0	0.04
LEF usage (%)	0.0	0.0	0.0	1.0
BUC usage (%)	3.9	4.4	0.0	0.85
TAC usage (%)	5.3	8.9	12.5	0.39
IGU usage (%)	1.3	2.2	20.8	0.002

Values represent mean ± standard deviation. NA = not applicable.

TCZ = tocilizumab, TNFi = tumor necrosis factor inhibitors, ABT = abatacept, JAKi = Janus kinase

inhibitors, GLM = golimumab, ETN = etanercept, IFX = infliximab, ADA = adalimumab, CZP = certolizumab pegol, TOF = tofacitinib, BAR = baricitinib, RF = rheumatoid factor, ACPA = anti-cyclic citrullinated peptide antibody, DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein, CDAI = Clinical Disease Activity Index, HAQ-DI = Health Assessment Questionnaire Disability Index, PSL = prednisolone, MTX = methotrexate, **SASP = salazosulfapyridine, LEF = leflunomide, BUC = bucillamine, TAC = tacrolimus, IGU = iguratimod.**

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

**Table 2. Hazard ratio for treatment discontinuation in TCZ-switched cases (Cox proportional hazards model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX, treatment of TCZ, and reasons of TCZ discontinuation)**

Variable	Reference	HR (95% CI)		P-value
	TCZ→TNFi (n=76)	TCZ→ABT (n=45)	TCZ→JAKi (n=24)	
Lack of effectiveness	1	0.3 (0.2-0.8)**	0.5 (0.2-1.2)	0.017
All toxic adverse events	1	0.9 (0.3-2.9)	0.7 (0.1-3.1)	0.86
Non-toxic events	1	3.9 (1.0-15.0)*	1.4 (0.1-13.5)	0.13
Total discontinuation (excluding non-toxic reasons and remission)	1	0.5 (0.2-0.9)*	0.5 (0.2-1.1)	0.023

TCZ = tocilizumab, PSL = prednisolone, MTX = methotrexate, HR = hazard ratio, 95% CI = 95% confidence interval, TNFi = tumor necrosis factor inhibitors, ABT = abatacept, JAKi = Janus kinase inhibitors.

Differences between the groups were assessed using the Cox P-value. \* P<0.05, \*\*P<0.01.

**Table 3. Baseline clinical characteristics of patients initially treated by ABT and then changed to other agents**

Variable	ABT→TNFi (n=42)	ABT→TCZ (n=34)	P-value
Agents used for follow-up	GLM (n=17), ETN (n=11), ADA (n=9), IFX (n=4), CZP (n=1)		NA
Months ABT continued	11.0±14.0	10.9±14.2	0.97
Reasons for discontinuing ABT	Ineffectiveness (90.5%), non-toxic reasons (9.5%)	Ineffectiveness (94.2%), toxic reasons (2.9%), non-toxic reasons (2.9%)	0.26
<b>Treatment interval (months)</b>	<b>2.2±4.0</b>	<b>1.9±4.8</b>	<b>0.78</b>
Age (years)	66.0±13.6	60.8±11.1	0.070
Disease duration (years)	6.6±8.0	9.8±8.7	0.10
RF positivity (%)	82.9	81.5	1.0
ACPA positivity (%)	77.8	84.0	0.75
DAS28-CRP	4.0±1.1	3.8±1.3	0.64
CDAI	16.8±9.9	16.6±9.4	0.94
HAQ-DI	0.8±0.6	1.3±0.8	0.15
PSL usage (%)	26.2	55.9	0.010
PSL dose (mg/day)	3.8±2.6	6.8±3.4	0.010
MTX usage (%)	76.2	50.0	0.029
MTX dose (mg/week)	8.7±2.9	7.3±2.3	0.076
<b>SASP usage (%)</b>	<b>21.4</b>	<b>17.6</b>	<b>0.78</b>
<b>LEF usage (%)</b>	<b>0.0</b>	<b>0.0</b>	<b>1.0</b>
<b>BUC usage (%)</b>	<b>7.1</b>	<b>20.6</b>	<b>0.10</b>
<b>TAC usage (%)</b>	<b>11.9</b>	<b>8.8</b>	<b>0.73</b>
<b>IGU usage (%)</b>	<b>0.0</b>	<b>8.8</b>	<b>0.085</b>

Values represent mean ± standard deviation. NA = not applicable.

ABT = abatacept, TNFi = tumor necrosis factor inhibitors, TCZ = tocilizumab, GLM = golimumab, ETN = etanercept, IFX = infliximab, ADA = adalimumab, CZP = certolizumab pegol, RF = rheumatoid factor, ACPA = anti-cyclic citrullinated peptide antibody, DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein, CDAI = Clinical Disease Activity Index, HAQ-DI = Health Assessment Questionnaire Disability Index, PSL = prednisolone, MTX = methotrexate, **SASP = salazosulfapyridine**,

LEF = leflunomide, BUC = bucillamine, TAC = tacrolimus, IGU = iguratimod.

Differences between the groups were assessed using a Mann-Whitney U test or Pearson's chi-squared test.

**Table 4. Hazard ratio for treatment discontinuation in ABT-switched cases (Cox proportional hazards model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX, treatment duration of ABT, and reasons of ABT discontinuation)**

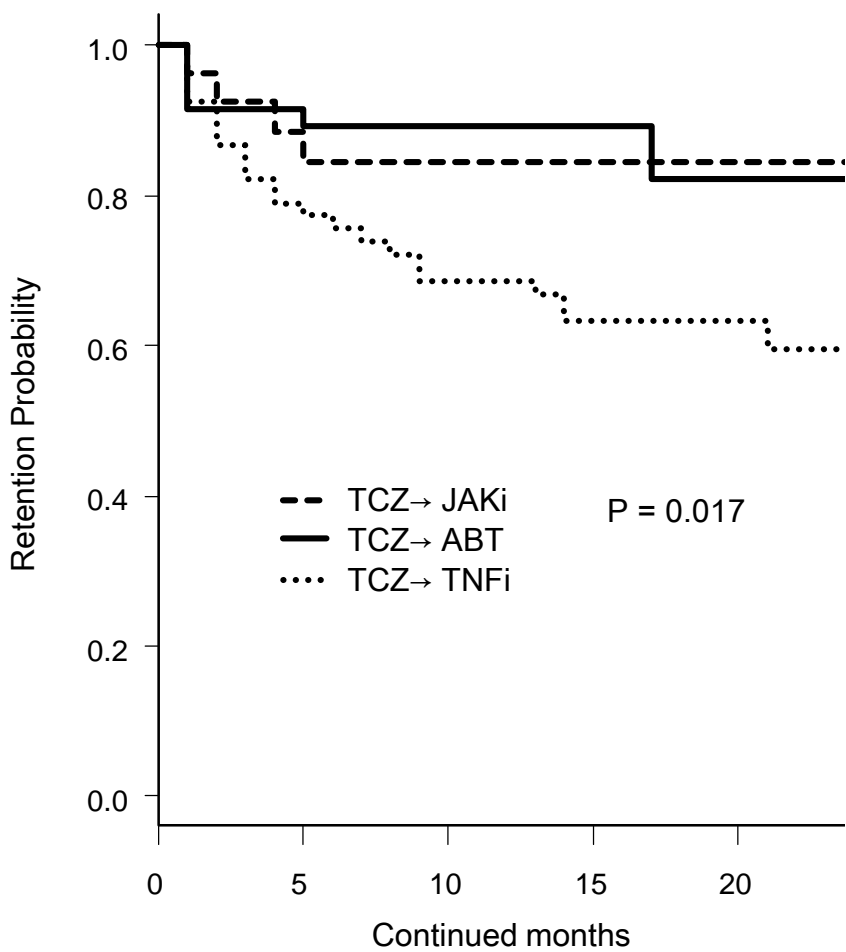
Variable	Reference	HR (95% CI)	P-value
	ABT→TNFi (n=42)	ABT→TCZ (n=34)	
Lack of effectiveness	1	0.3 (0.1-1.0)	0.053
All toxic adverse events	1	2.8 (0.6-13.1)	0.19
Non-toxic events	1	2.1 (0.6-7.7)	0.25
Total discontinuation (excluding non-toxic reasons and remission)	1	0.7 (0.3-1.8)	0.44

ABT = abatacept, PSL = prednisolone, MTX = methotrexate, HR = hazard ratio, 95% CI = 95% confidence interval, TNFi = tumor necrosis factor inhibitors, TCZ = tocilizumab.

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

Figure 1

**a** Drug retention due to lack of effectiveness  
(TCZ switched to ABT, JAKi, or TNFi)

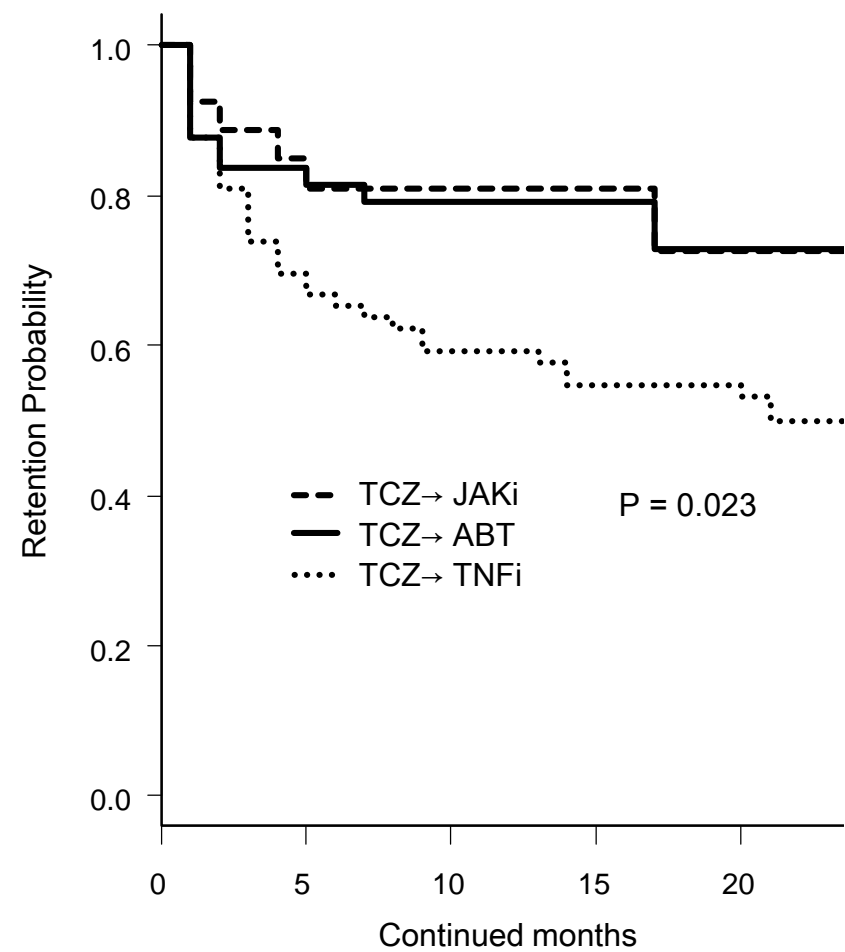


Number at risk

ABT	45	34	31	24	20
JAKi	24	20	12	11	10
TNFi	76	50	42	39	37

**b**

Total drug retention excluding  
non-toxic reasons and remission  
(TCZ switched to ABT, JAKi, or TNFi)



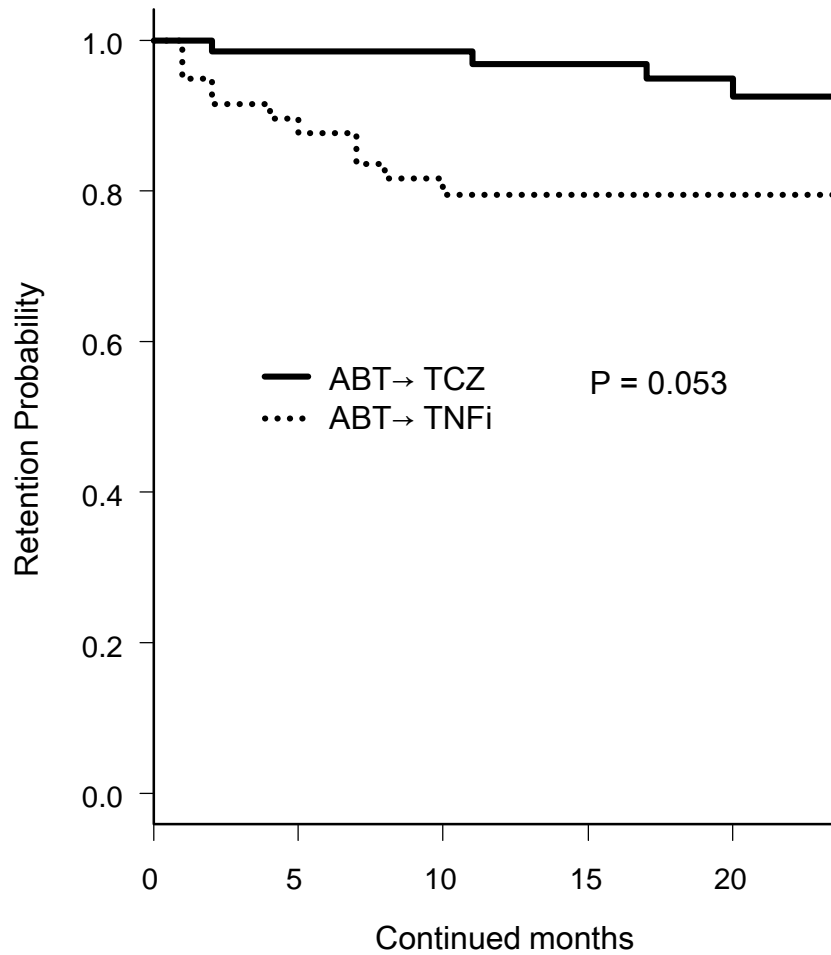
Number at risk

ABT	45	34	31	24	20
JAKi	24	20	12	11	10
TNFi	76	50	42	39	37



Figure 2

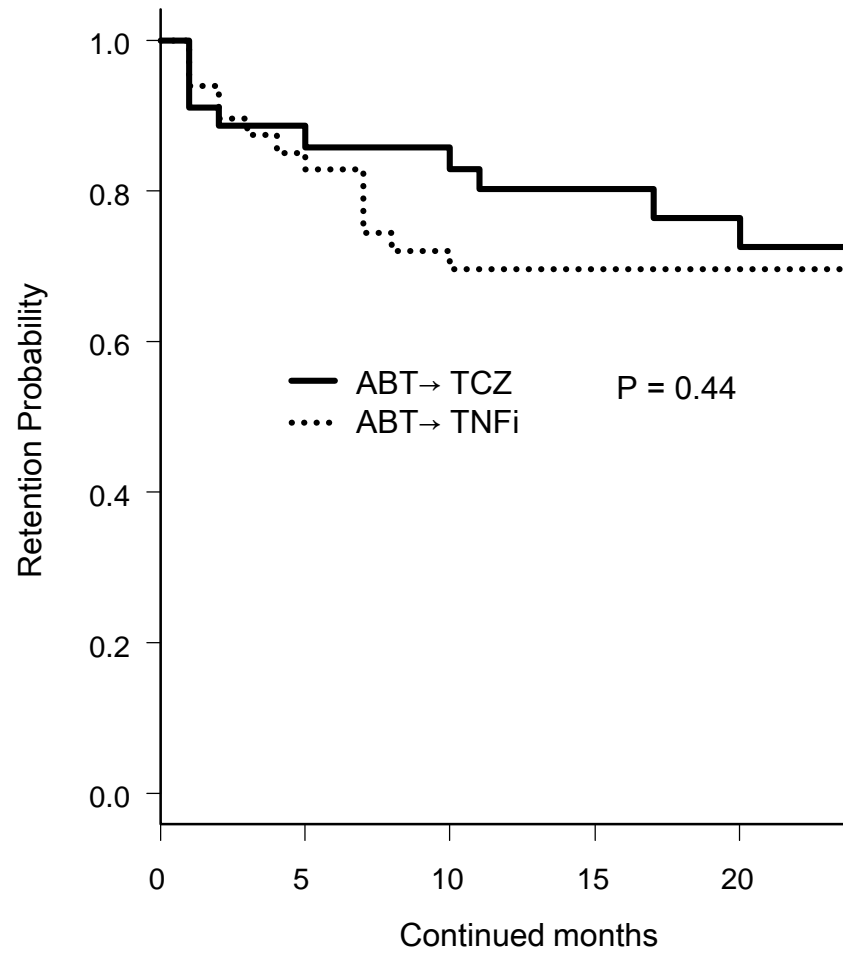
**a** Drug retention due to lack of effectiveness  
(ABT switched to TCZ or TNFi)



Number at risk

TCZ	34	26	24	19	16
TNFi	42	33	27	23	18

**b** Total drug retention excluding non-toxic reasons and remission  
(ABT switched to TCZ or TNFi)



Number at risk

TCZ	34	26	24	19	16
TNFi	42	33	27	23	18