Original Article

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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Abstract

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

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

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

(72.7%), and JAKi (72.6%) (TNFi vs. ABT; P=0.017) in the TCZ-switched group and TNFi (69.6%) and TCZ (72.4%) (P=0.44) in the ABT-switched group.

Conclusions: Switching to ABT in TCZ-treated patients led to higher retention as compared to TNFi. Switching to TCZ in ABT-treated patients tended to led to higher retention due to effectiveness, although total retention was similar as compared to TNFi.

Key-points

This is the first retrospective, multi-center study aimed to clarify the retention rates of secondary bDMARDs or JAKi in patients with RA who were primarily being treated by TCZ or ABT as the first bDMARDs.

Introduction

The recommendations of the 2016 European League Against Rheumatism (EULAR) stated that CTLA4-Ig [abatacept (ABT)], anti-interleukin (IL)-6 receptor antibody [tocilizumab (TCZ)], and Janus kinase inhibitors (JAKi) were considered to be equivalent to tumor necrosis factor inhibitors (TNFi) for both the phase II and phase III treatment of rheumatoid arthritis (RA) [1]. The findings of this report also stated that there was no difference in the outcomes among these biological disease-modifying antirheumatic drugs (bDMARDs) and JAKi, irrespective of their target. Moreover,

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

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

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

of using a second bDMARDs or JAKi, especially in patients who originally exhibited an inadequate response to ABT or TCZ. As far as we know, there have yet to be any reports showing drug retention of secondary bDMARDs or JAKi in patients who were primarily treated by ABT or TCZ as first bDMARDs. At the present time, reliable evidence is still lacking in these types of cases. Randomized controlled trials (RCTs) often recruits patients with fewer comorbidities than that often seen in real-world settings [11]. Moreover, cohort-based observational studies have increasingly been used to investigate the performance of bDMARDs [12,13,14,15,16]. In these studies, drug retention is considered to be a major index of both the safety and effectiveness [17,18,19].

Based on the findings of our cohort, we have recently reported on the drug retention found among bDMARDs [6,7,20,21], factors associated with the achievement of bDMARDs-free remission [22], and the influence of family history on treatment response [23]. The aim of current multicenter, retrospective study was to clarify within a real-world setting the retention of secondary bDMARDs or JAKi in patients who were primarily treated by ABT or TCZ as the first bDMARDs.

Materials and methods

Patients

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

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

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

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

Statistical analysis

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

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

Results

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

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

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

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

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

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

Table 4 shows the adjusted HR for each of the discontinuation reasons. The HR due to a lack of effectiveness tended to be lower in the TCZ (HR=0.3, P=0.053) versus the TNFi group. In contrast, the HR due to toxic adverse events tended to be higher in the TCZ (HR=2.8, P=0.19) versus the TNFi group, while the HRs for total discontinuation (excluding non-toxic reasons and remission) were similar between the TCZ and TNFi group (HR=0.7, P=0.44).

Discussion

To the best of our knowledge, this is the first time that the retention rates of secondary bDMARDs or JAKi have been documented in patients with RA who were primarily being treated by TCZ or ABT as the first bDMARDs.

Previously, there have only been a few reports that have examined these types of issues with the administration of these drugs. Akiyama et al. examined patients with an insufficient response to TCZ and reported that the drug retention was comparable for both TNFi and ABT after switching [32]. However, only 41.3% of the patients were treated by TCZ as first bDMARDs, with 55.6% of the patients found to have a TNFi failure history, which could have affected these results.

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

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

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

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

Conclusions

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

Figure Legends

Figure 1. Adjusted drug retention due to lack of effectiveness (a) and total drug retention excluding non-toxic reasons and remission (b) in TCZ-switched cases.

Adjusted confounders included age, sex, disease duration, concomitant prednisolone and methotrexate, treatment duration and discontinuation reasons of the TCZ.

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

Figure 2. Adjusted drug retention due to lack of effectiveness (a) and total drug retention excluding non-toxic reasons and remission (b) in ABT-switched cases.

Adjusted confounders included age, sex, disease duration, concomitant prednisolone and methotrexate, treatment duration and discontinuation reasons of the ABT.

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

Availability of data and materials

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

Authors' contributions

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

Compliance with ethical standards

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, Ono Pharmaceutical, and UCB Japan. KE has received payments for lectures from Abbie, Asahi-Kasei, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Janssen, Mitsubishi-Tanabe, Ono Pharmaceutical, Sanofi, and UCB Japan. TH received a research grant and/or speaker fee from Astellas, Chugai, Nippon Shinyaku, Abbvie, Eisai, and Ono Pharmaceutical. YM received a research grant and/or speaker fee from Eli Lilly, Chugai, Pfizer, Bristol-Myers Squibb, and Mitsubishi-Tanabe. MHashimoto and KM are affiliated with a department that is financially supported by four pharmaceutical companies (Mitsubishi-Tanabe, Chugai, Ayumi, and UCB Japan) and the city government (Nagahama City). MHashimoto received a research grant and/or speaker fee from Astellas, Mitsubishi-Tanabe, Eisai, Eli Lilly, and Bristol-Myers Squibb. KM

received a speaking fee, and/or consulting fee from Eisai. TT is affiliated with a department that is financially supported by six pharmaceutical companies (Mitsubishi-Tanabe, Chugai, Ayumi, Astellas, Eisai, and Takeda). TT received a research grant from Chugai, CoverLetter and a speaker fee from Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Abbvie, Bristol-Myers Squibb, Ayumi, Daiichi Sankyo, Eisai, Takeda, and Asahi-Kasei. AO received a speaker fee from Chugai, Ono Pharmaceutical, Eli Lilly, Mitsubishi-Tanabe, Asahi-Kasei, and Takeda. RH received a speaker fee from AbbVie. 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. WY, KN, YS, HA, SJ, and KY have no financial conflicts of interest to disclose concerning this manuscript. These companies had no role in the study design, data collection, data analysis, data interpretation, and preparation of the manuscript.

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 approval by each of the ethics committees of the seven institutes: Kyoto University (2016-03-24/ approved number R053), Osaka University (2015-11-04/ approved number 15300), Osaka Medical College (2014-07-14/ approved

number 1529), Kansai Medical University (2017-11-21/ approved number 2014625), Kobe University (2015-03-20/ approved number 1738), Nara Medial University (2018-01-23/ approved number 1692), and Osaka Red Cross Hospital (2015-09-01/ approved number 644). The board of Osaka University Hospital Ethical Committee waived the requirement for patients' informed consent because of the anonymous nature of the data. Written informed consent was obtained from the participants in other institutes.

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Table 1

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

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 duration of TCZ, and reasons of TCZ discontinuation)

	Reference	HR (95% CI)		P-value
Variable	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

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
Treatment interval (months)	2.2±4.0	1.9±4.8	0.78
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
SASP usage (%)	21.4	17.6	0.78
LEF usage (%)	0.0	0.0	1.0
BUC usage (%)	7.1	20.6	0.10
TAC usage (%)	11.9	8.8	0.73
IGU usage (%)	0.0	8.8	0.085

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

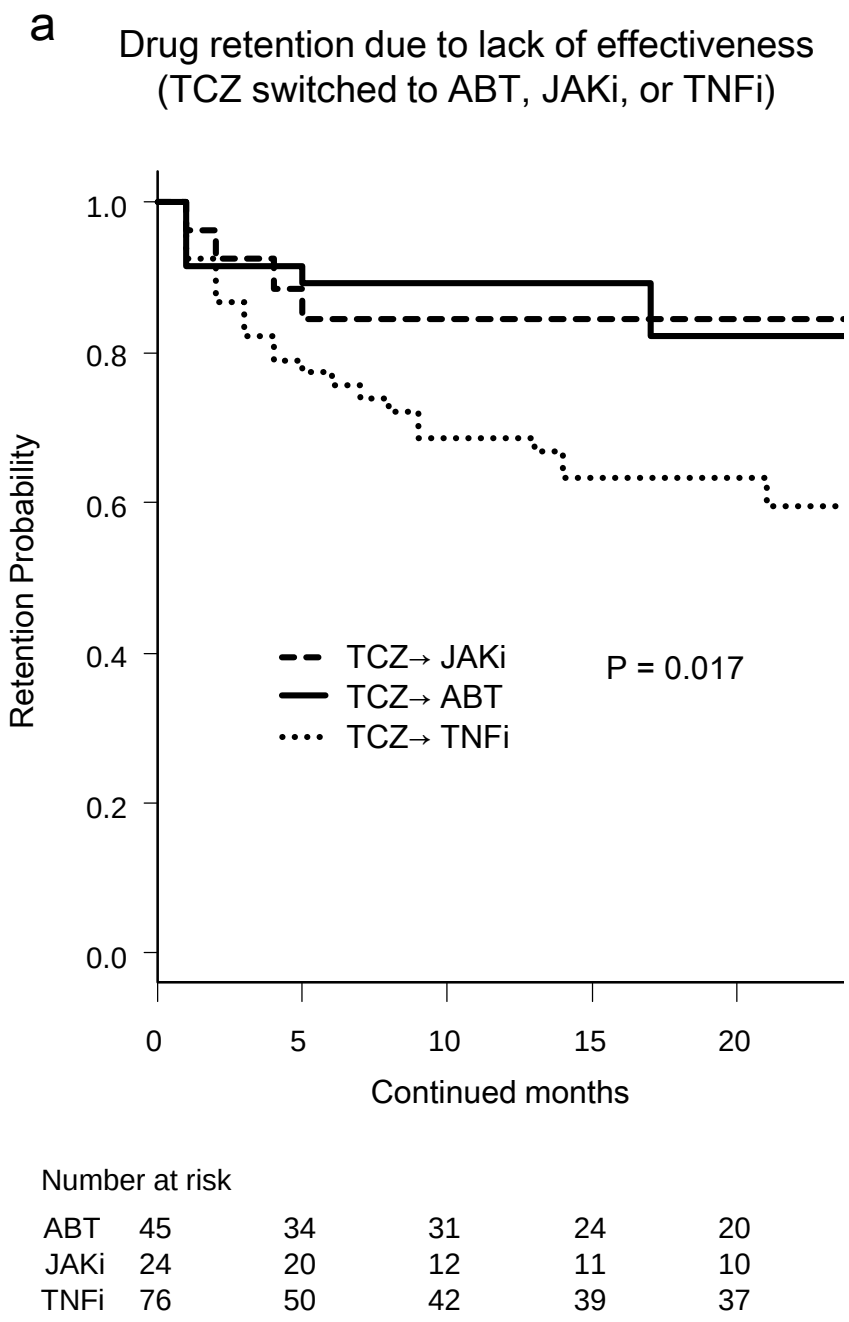
Table 4. Hazard ratio for treatment discontinuation in ABT-switched cases (Cox proportional hazards model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX, treatment duration of ABT, and reasons of ABT discontinuation)

	Reference	HR (95% CI)	P-value
Variable	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)
Retention Probability
1.0
0.8
0.6
0.4
0.2
0.0
TCZ→ JAKi
TCZ→ ABT
TCZ→ TNFi
P = 0.017
0
5
10
15
20
Continued months
Number at risk
ABT 45 34 31 24 20
JAKi 24 20 12 11 10
TNFi 76 50 42 39 37

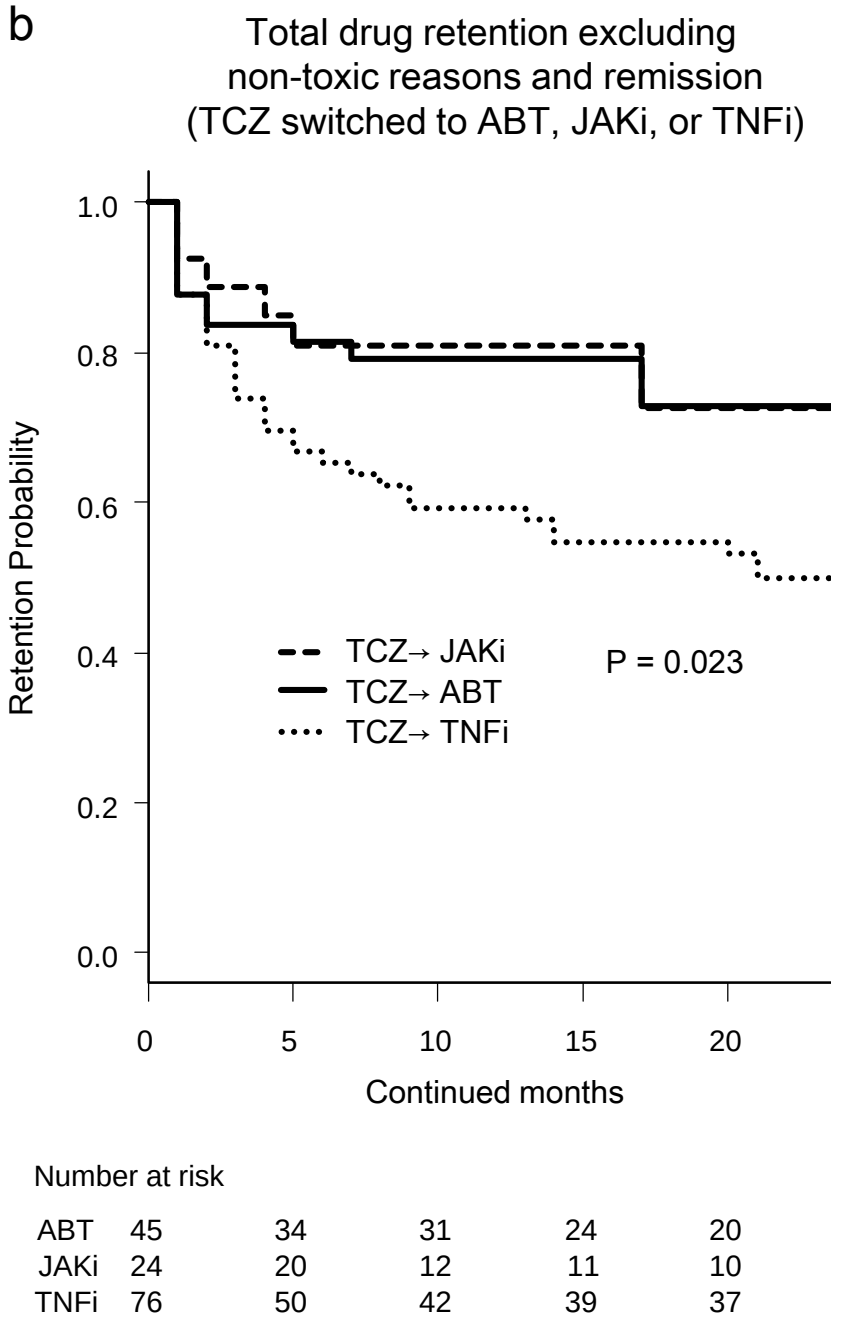
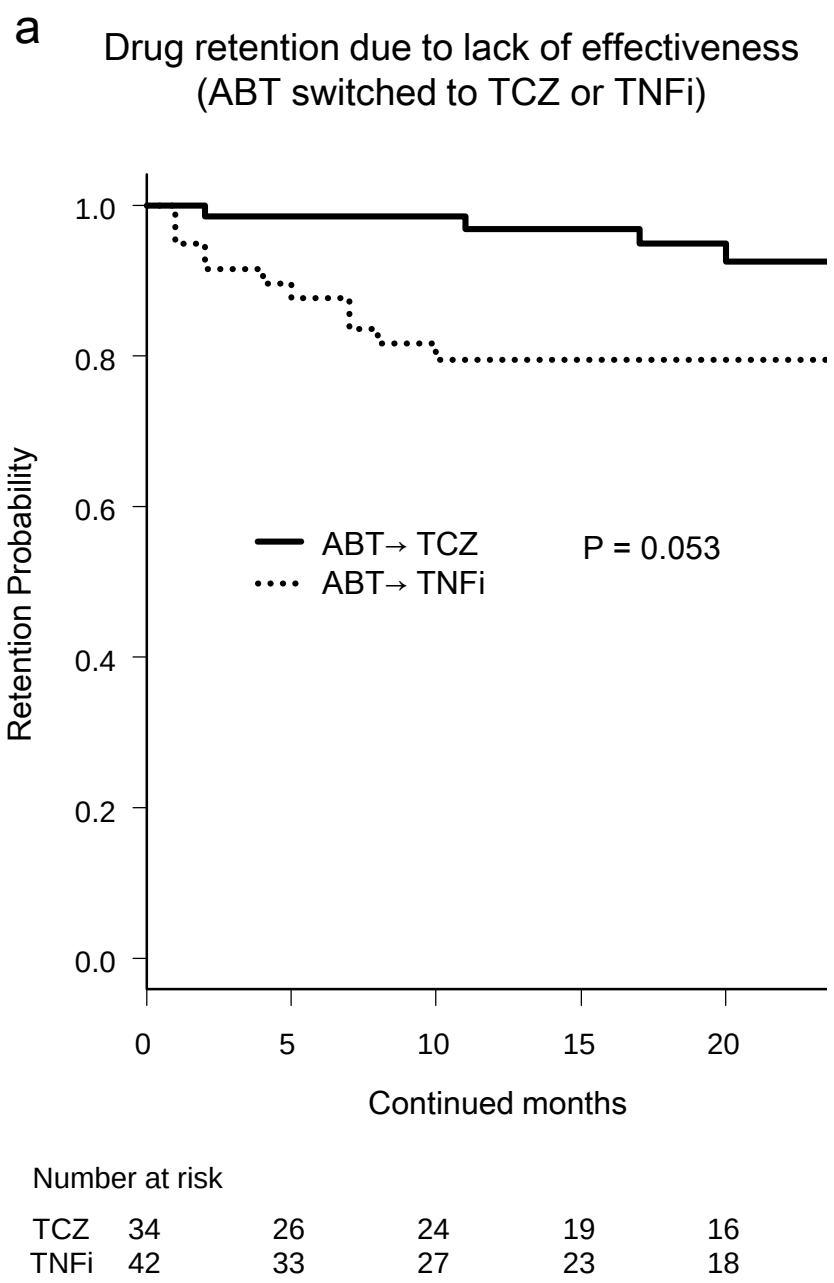
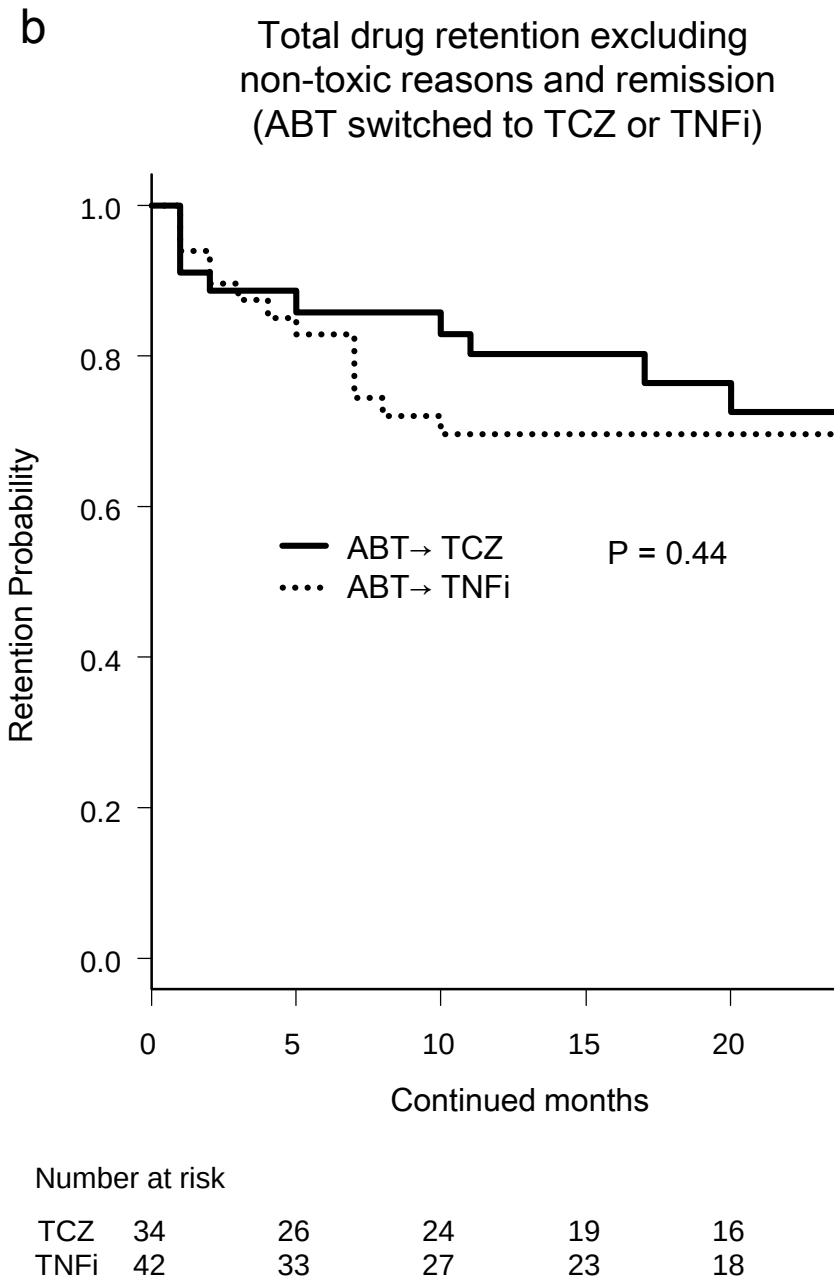

b
Total drug retention excluding
non-toxic reasons and remission
(TCZ switched to ABT, JAKi, or TNFi)
Retention Probability
1.0
0.8
0.6
0.4
0.2
0.0
TCZ→ JAKi
TCZ→ ABT
TCZ→ TNFi
P = 0.023
0
5
10
15
20
Continued months
Number at risk
ABT 45 34 31 24 20
JAKi 24 20 12 11 10
TNFi 76 50 42 39 37

Figure 2


a
Drug retention due to lack of effectiveness
(ABT switched to TCZ or TNFi)
Retention Probability
1.0
0.8
0.6
0.4
0.2
0.0
ABT→ TCZ
ABT→ TNFi
P = 0.053
0
5
10
15
20
Continued months
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)
Retention Probability
1.0
0.8
0.6
0.4
0.2
0.0
ABT→ TCZ
ABT→ TNFi
P = 0.44
0
5
10
15
20
Continued months
Number at risk
TCZ 34 26 24 19 16
TNFi 42 33 27 23 18