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Unintentional Monotherapy in Rheumatoid Arthritis Patients Receiving Tofacitinib and Drug Survival Rate of Tofacitinib

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Objective: To determine the rate of unintentional monotherapy (UM; switching to monotherapy from combination therapy of patients' own volition) in rheumatoid arthritis patients receiving tofacitinib and to evaluate tofacitinib survival rate.

Methods: This national, multicenter study included patients' data from the TURKBIO Registry. Demographics, clinical characteristics, disease duration and activity, comorbidities, and treatments were analyzed.

Results: Data of 231 rheumatoid arthritis patients (84.8% female, median age, 56 years) were included; 153 were initially prescribed combination therapy and continued to their therapies; 31 were initially prescribed combination therapy but switched to monotherapy on their own volition (UM); 21 were initially prescribed monotherapy and switched to combination therapy; 26 were initially prescribed monotherapy and continued to their therapies. The rate of comorbidities at the time of data retrieval was higher in the UM group than in the combination group (83.3% vs. 60.3%, $p = 0.031$). Presence of comorbidities was a significant factor affecting switching to monotherapy ($p = 0.039$; odds ratio, 3.29; 95% confidence interval, 1.06–10.18). The combination and UM groups did not differ regarding remission rate assessed by Disease Activity Score 28-joint count C-reactive protein (60.5% and 70%, respectively; $p = 0.328$). Drug survival rates of the UM and combination groups did not differ. The median drug survival duration of tofacitinib was 27+ months with 1- and 4-year drug survival rates of 89.6% and 60.2%, respectively, in the UM group.

Conclusions: Although 13.4% of the study population started monotherapy unintentionally, drug survival and remission rates of the UM and combination groups were not different. Comorbidity was a factor affecting transition from combination therapy to monotherapy.

Key Words: adherence, monotherapy, rheumatoid arthritis, survival, tofacitinib

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PRACTICAL CLINICAL MESSAGES

- For patients with comorbidities using multiple medications, adherence to treatment is difficult.
- Comorbidities in rheumatoid arthritis patients should be thoroughly investigated, and monotherapy should be considered when deciding on treatment in cases with multiple comorbidities.
- In conventional synthetic disease-modifying antirheumatic drug–resistant rheumatoid arthritis patients, monotherapy with advanced treatments may be an effective treatment option.

Rheumatoid arthritis (RA), an autoimmune disease presenting with persisting synovitis and multisystem inflammation and leading to destruction of joints and disability at the end, is estimated to affect 0.24% of the world's population.[1,2] Uncontrolled disease may decrease productivity and impair quality of life.[3] Today, the main goal of treatment is to provide sustained clinical remission. Although analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce symptoms, disease-modifying antirheumatic drugs (DMARDs) are the basis of treatment.[2]

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The authors have full control of all primary data and agree to allow the journal to review their data if requested.

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Methotrexate (MTX), a conventional synthetic csDMARD (csDMARD), remains the main drug in the initial treatment of RA. Methotrexate is involved in combination therapies with glucocorticoids or csDMARDs, biological DMARDs (bDMARDs), or targeted synthetic DMARDs (tsDMARDs).[4] The current optimal regimen in RA patients with early or confirmed disease who have no response to csDMARDs is the use of MTX with a bDMARD or a tsDMARD.[4] Nevertheless, in routine practice, nearly 30% of the patients use bDMARDs as monotherapy.[5–7] Reasons for monotherapy include toxicity/intolerance to DMARDs, patients' unwillingness to receive concomitant DMARDs, and physician decision.[8] On the other hand, 3-year drug survival rate is similar in those on monotherapy and combination therapy.[8] Drug survival is an indirect indicator of efficacy of treatment and absence of toxicity.[8]

Although unintentional monotherapy (UM; switching to monotherapy from combination therapy on patients' own volition) generally is not studied, some of the patients are thought to switch to monotherapy unintentionally; that is, although they are prescribed combination therapy, they begin to use monotherapy without telling their physicians. The issue of skipping part of prescriptions by the patients without medical advice may be missed by many researchers. In the present study, the percentage of UM in RA patients who receive tofacitinib was aimed to be determined. Therefore, RA patients using tofacitinib, which is a tsDMARD, in combination therapy or as monotherapy were evaluated. Moreover, various features of the patients who received UM were compared with the features of those who received combination therapy, and drug survival rate of tofacitinib was calculated.

MATERIALS AND METHODS

The present study was designed as a national, multicenter study. Data of the patients were obtained from the TURKBIO Registry, which was approved by the Ministry of Health in July 2013 and is the first nationwide biological registry with the contribution of different rheumatology centers across Turkey (https://www.turkbio.com/). The study was conducted according to the 1964 Helsinki Declaration and its later amendments and approved by the Clinical Research Ethics Committee of Dokuz Eylül University (approval no. 2016/03-05, date: February 11, 2016).

Patients who had received and either discontinued or switched to another biological or nonbiological drug and patients who were still receiving tofacitinib and had at least 2-visit data in addition to the baseline visit data were included in the study. The database of the TURKBIO Registry was used to obtain the following information: demographic features, clinical features, disease duration of RA, Disease Activity Score 28-joint count C-reactive protein (DAS28-CRP), comorbidities, and treatment-related data (including adverse events during the treatment and reasons for drug discontinuation).

Statistical Analysis

Data were analyzed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL). Descriptive statistics are presented as numbers and percentages for categorical variables and as median and 25th percentile (Q1) to 75th percentile (Q3) for numerical variables. The conformity of data to normal distribution was tested using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). A χ^2 test was used to compare multiple groups of categorical variables; if the χ^2 assumptions were not met, the Fisher exact test was used. Comparison of multiple groups of non–normally distributed numerical variables was performed using the Kruskal-Wallis test. To evaluate the factors affecting switching to monotherapy from combination therapy, a logistic regression analysis was performed using the backward likelihood ratio method. A Cox regression model was used to determine the factors affecting survival of drug (tofacitinib). Drug survival was calculated using the Kaplan-Meier method. $p < 0.05$ was considered significant.

RESULTS

Among 318 RA patients fulfilling the study criteria, 231 patients in whom current treatment data were available were included in the analysis. The median age of the patients was 56 years, and 84.8% of the patients were female. General features of the study patients at baseline are shown in Table 1.

Among 231 patients, physicians initially prescribed combination therapy to 184 patients (79.7%) and monotherapy to 47 patients (20.3%). The patients were divided into 4 groups according to the treatment initially prescribed by the physicians and their current treatment.

(1) Combination group (n = 153): The physician initially prescribed combination therapy, and the patients continued to receive combination therapy.

TABLE 1. General Characteristics of the Patients With RA

Characteristics	n	Value
Sex, n (%)	231	
Female		196 (84.8)
Male		35 (15.2)
Age, median (Q1–Q3), y	231	56 (47–63)
Disease duration, median (Q1–Q3), y	223	10.5 (7.2–16.5)
Follow-up duration, median (Q1–Q3), mo	231	13.6 (6.8–25.5)
RF positivity, n (%)	200	131 (65.5)
Anti-CCP positivity, n (%)	190	123 (64.7)
DAS28-CRP, median (Q1–Q3)	231	3.7 (2.6–4.6)
No. previously used bDMARDs, median (Q1–Q3)	231	0 (0–1)
No. previously used csDMARDs, median (Q1–Q3)	231	2 (0–3)
Previous glucocorticoid use, n (%)	231	91 (39.4)

Anti-CCP, anti–cyclic citrullinated peptides; Q1–Q3, 25th percentile to 75th percentile; RF, rheumatoid factor.

TABLE 2. Some Characteristics of the Patients Receiving Unintentional Monotherapy and Reasons for DMARD Therapy Discontinuation

Characteristics (N = 24[a])	n (%)
Extra-articular system involvement related to RA	3 (12.5)
Use of medication for a nonrheumatic disease	19 (79.2)
Presence of comorbidities	20 (83.3)
Comorbidities[b]	
Hypertension	9 (37.5)
Cardiac disease	7 (29.2)
Diabetes mellitus	6 (25.0)
Osteoporosis	3 (12.5)
Other	8 (33.3)
Reasons for DMARD therapy discontinuation (N = 24[a])	n (%)
Not wanting to use many drugs	9 (37.5)
Drug adverse effects	8 (33.3)
Not being able to access the drug	6 (25.0)
Drug becoming ineffective	1 (4.2)

[a] Information of 7 patients could not be obtained.
[b] More than 1 comorbidity can be seen in 1 patient.

(2) Unintentional monotherapy group (n = 31): The physician initially prescribed combination therapy, and the patients received monotherapy of their own volition.
(3) Monotherapy to combination group (n = 21): The physician initially prescribed monotherapy, and then the patients were switched to combination therapy.
(4) Monotherapy group (n = 26): The physician initially prescribed monotherapy, and the patient still continued to receive monotherapy.

According to these findings, the rate of UM among 231 patients was found to be 13.4% (n = 31).

The characteristics of the patients according to the treatment groups are presented in Supplemental Digital Content 1, Table S1 (http://links.lww.com/RHU/A615). The reasons for DMARD therapy discontinuation and some other characteristics of the patients receiving UM are shown in Table 2.

Comparison of the UM group with the combination group revealed no significant difference in terms of sex, follow-up duration, continuing to use tofacitinib, DAS28-CRP scores, previous glucocorticoid use, and concomitant NSAID and prednisolone use. However, the percentage of patients with comorbidities in the UM group (83.3%) was significantly higher when compared with that in the combination group (60.3%, $p = 0.031$). Moreover, the ratio of patients receiving at least 1 bDMARD previously was found to be significantly higher in the combination group (29.4% vs. 9.7%; $p = 0.023$) (Table 3).

No significant difference was found between the patients previously receiving and not receiving bDMARDs in terms of drug survival rate (median, 40+ and 48+ months, respectively; $p = 0.350$). According to the Cox regression model, previous bDMARD use was not found to be a factor affecting survival of drug ($p = 0.353$; hazard ratio, 1.40; 95% confidence interval [CI], 0.69–2.85).

In the logistic regression analysis performed by creating a model including age and presence of comorbidity, the presence of comorbidity was found to be a significant factor affecting switching to monotherapy (UM) from combination therapy ($p = 0.039$; odds ratio, 3.29; 95% CI, 1.06–10.18).

The remission rate at the last visit (60.5% and 70%, respectively; $p = 0.328$) as measured by DAS28-CRP was comparable in both groups.

The Kaplan-Meier analysis performed to determine the drug survival rate of tofacitinib in the UM and combination groups revealed that drug survival rate was similar in the 2 groups (Table 4 and the Figure).

TABLE 3. Comparison of the Patients Receiving Unintentional Monotherapy With the Patients Receiving Combination Therapy

	n	Combination Therapy	n	Unintentional Monotherapy	*p* value
Sex, n (%)	153		31		
Female		130 (85.0)		24 (77.4)	0.300
Male		23 (15.0)		7 (22.6)	
Age, median (Q1–Q3), y	153	54 (45–62)	31	60 (50–64)	0.067
Disease duration, median (Q1–Q3), y	146	10 (7–16)	30	9 (5–18)	0.584
Follow-up duration, median (Q1–Q3), mo	153	12.3 (6.2–23.7)	31	13.6 (6.0–21.6)	0.882
Using tofacitinib, n (%)	153		31		
Continue		123 (80.4)		25 (80.6)	0.974
Discontinue		30 (19.6)		6 (19.4)	
DAS28-CRP, n (%)	152	2.3 (1.75–3.1)	30	2.2 (1.8–3.2)	0.727
Presence of comorbidities, n (%)	131	79 (60.3)	24	20 (83.3)	0.031
Previous glucocorticoid use, n (%)	153	62 (40.5)	31	12 (38.7)	0.851
Previous bDMARD use, n (%)					
Present (≥1 bDMARD)	153	45 (29.4)	31	3 (9.7)	0.023
Absent		108 (70.6)		28 (90.3)	
Previous csDMARD use, n (%)					
Present (≥1 csDMARD)	153	98 (64.1)	31	20 (64.5)	0.961
Absent		55 (35.9)		11 (35.5)	
Concomitant NSAID use, n (%)	136	92 (67.6)	26	19 (73.1)	0.585
Concomitant prednisolone use, n (%)	153	51 (33.3)	31	10 (32.3)	0.908

Q1–Q3, 25th percentile to 75th percentile.

DISCUSSION

The present study aimed to determine the rate of patients who were prescribed combination therapy by their physicians but decided to switch to monotherapy (UM) on their own volition and to investigate the characteristics and outcomes of these patients. For this purpose, real-life data were used, and the rate of UM among patients receiving targeted therapies was found to be 13.4%. The presence of comorbidities is the most common reason for switching from combination therapy to monotherapy unintentionally (UM) rather than remaining on combination therapy. Both tofacitinib drug survival and remission rates were comparable in the UM and combination groups.

Studies that compare tofacitinib monotherapy with tofacitinib combination therapy are limited in number. In their meta-analysis, Buckley et al.[9] failed to draw a conclusion in terms of comparison of effectiveness between tofacitinib monotherapy and combination therapy (tofacitinib + MTX). In their study, Harnett et al.[10] compared monotherapy and combination therapy in terms of treatment adherence, treatment persistence, and all-cause/RA-related costs and obtained no significant differences in all parameters. Kivitz et al.[11] performed a pooled analysis of tofacitinib trials and concluded that fewer safety events might be observed by tofacitinib monotherapy compared with combination therapy and that better risk-benefit profile could be obtained by tofacitinib monotherapy in the patients with active RA who were intolerant to csDMARDs. Although the present study used all patient data from a national registry (TURKBIO Registry), which could lead to missing data, the combination group and the UM group (patients who switched to monotherapy of their own volition after combination therapy) were found similar in terms of age, sex, disease duration, and follow-up duration; thus, the 2 groups were comparable. Previous glucocorticoid use, concomitant NSAID use, and concomitant prednisolone use did not significantly differ between the combination and UM groups. The rate of patients with comorbidity at the time of data collection was higher in the UM group in comparison to that in the combination group (83.3% vs. 60.3%, $p = 0.031$). Based on the logistic regression analysis, presence of a coexisting disease was a significant factor having an impact on switching to monotherapy from combination therapy ($p = 0.039$, odds ratio: 3.29; 95% CI, 1.06–10.18). The ratio of patients receiving at least 1 bDMARD previously was found to be significantly higher in the combination group (29.4% vs. 9.7%; $p = 0.023$). Nevertheless, previous bDMARD use was not found to be a factor affecting survival of drug ($p = 0.353$; hazard ratio, 1.40).

TABLE 4. Drug Survival Rate of Tofacitinib (Kaplan-Meier Analysis)

	Combination Therapy	*p*
Drug survival rate		
6th month	91.5%	0.939
12th month	86.1%	
24th month	75.6%	
36th month	68.4%	
48th month	62.2%	
Drug survival time, median	48+ mo	
	Unintentional Monotherapy	
Drug survival rate		
6th month	89.6%	
12th month	89.6%	
24th month	72.3%	
36th month	60.2%	
48th month	60.2%	
Drug survival time, median	27+ mo	

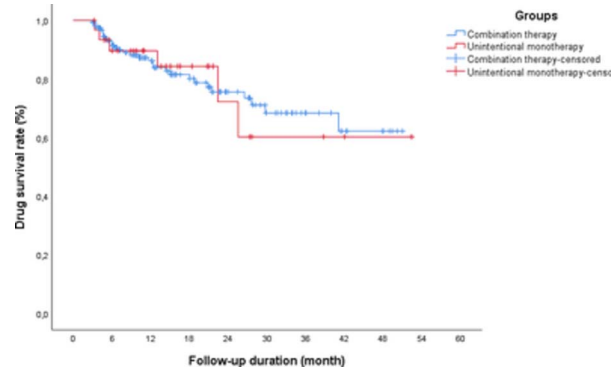

FIGURE. The Kaplan-Meier curve for the drug survival rate of tofacitinib.

The most common patient-reported reason for drug discontinuation in the patients switching to UM was unwillingness to use many drugs (n = 9). Accordingly, the patients having comorbidity and using many drugs made them to prefer monotherapy. Based on the data from the Corrona registry trial, patient-related factors (history of hepatic disease, neutropenia, and malignancy) were found effective in the decision of prescribing bDMARDs as monotherapy.[12]

Randomized controlled studies have frequently concluded that combination therapy is superior to monotherapy; however, information from registry data does not always confirm this situation. According to some observational studies, monotherapy is equivalent to combination therapy in terms of efficacy.[13] In their meta-analysis reviewing randomized controlled studies, Buckley et al.[9] compared monotherapy (novel DMARD) with combination therapy (novel DMARD + MTX) in RA treatment. They found similarity or difference between the efficacies of combination therapy and monotherapy depending on the DMARDs used. Similarly, in their systematic review, Emery et al.[14] concluded that combination therapy seemed to be associated with better outcomes in some patients; however, they reported that both bDMARDs and tsDMARDs were effective in monotherapy. Patient eligibility criteria in randomized trials and populations with different characteristics in real-world studies may lead to obtaining different outcomes.[13] Among the advanced treatment agents, interleukin 6 inhibitors and JAK (Janus kinase) inhibitors were preferred as monotherapy in patients who were ineligible for combination therapy, because they were reported to be more effective in monotherapy as compared with other biologics.[15] In the present study, patients who switched from combination therapy to monotherapy unintentionally (UM) rather than remaining on combination therapy were compared with those who stayed on combination therapy. As a result, the DAS28-CRP remission rate at the last visit of patients was found to be similar in both groups (60.5% and 70%, respectively; $p = 0.328$).

In their study, Finckh et al.[16] reported that among the patients receiving monotherapy, 94% continued to receive monotherapy in the first year and that the median drug survival duration was 25 months (interquartile range, 19–30 months). In the study evaluating the data of 247 individuals from the HURBIO registry study, Bilgin et al.[17] reported that the median duration of tofacitinib treatment was 10.2 months and that overall drug

retention rate of tofacitinib was 63.9% in 1 year. They stated the most common cause of discontinuation as treatment failure. In Australia, tofacitinib was prescribed as monotherapy in 43.4% of 650 RA patients receiving tofacitinib. In these patients, the median tofacitinib survival duration was 34.2 months.[18] Pope et al.[19] analyzed pooled data from 2 long-term, open-label studies in which tofacitinib was used either as monotherapy or in combination therapy for RA treatment. They obtained the mean treatment duration as 3.5 years and the median drug survival as 4.9 years (95% CI, 4.7–5.1 years). They found that 2-year drug survival rate was 75.5%, and 5-year drug survival rate was 49.4%, and the average drug survival was slightly higher in those receiving tofacitinib as monotherapy than those receiving tofacitinib in combination therapy. In that study, 50.7% of the patients discontinued tofacitinib, and the reason was adverse events in 47.2% of the patients and lack/loss of efficacy in 7.1% of the patients. Discontinuation risk was increased with having diabetes at baseline, hypertension, negative anti–cyclic citrullinated peptide, negative rheumatoid factor, and inadequate response to tumor necrosis factor inhibitors. In the present study, the estimated 1- and 4-year drug survival rates were 86.1% and 62.2%, respectively, in the combination group and 89.6% and 60.2%, respectively, in the monotherapy group. The median drug survival was 48+ months in the combination group and 27+ months in the monotherapy group. There was no significant difference between the groups in terms of drug survival ($p = 0.939$).

Given that the present study included patients' data obtained from a national registry (TURKBIO Registry), which leads to missing data, this does not allow us to reach a direct conclusion. The low number of patients, particularly in the monotherapy groups, is another limitation of the study. Future prospective studies are needed to set forth the reasons of patients switching to monotherapy from combination therapy of their own volition.

In conclusion, UM (switching to monotherapy from combination therapy of their own volition) is a treatment modality preferred by a substantial proportion of RA patients. On the other hand, no negative results were found in the drug survival rate or response to treatment in the UM patient group. Comorbidities in RA patients are an important consideration when selecting UM because these patients not only fear the use of multiple drugs but also fear the risks of adverse effects. Individualization of treatment and allowing for flexible prescription due to varying patient characteristics would be advantageous in RA treatment.

REFERENCES

1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73:1316–1322.
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376: 1094–1108.
3. Strand V, Khanna D. The impact of rheumatoid arthritis and treatment on patients' lives. *Clin Exp Rheumatol*. 2010;28:S32–S40.
4. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79:685–699.
5. Lee SJ, Chang H, Yazici Y, et al. Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. *J Rheumatol*. 2009;36:1611–1617.
6. Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. *Ann Rheum Dis*. 2013;72:1897–1904.
7. Yazici Y, Shi N, John A. Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bull NYU Hosp Jt Dis*. 2008;66:77–85.
8. Catay E, Bravo M, Rosa J, et al. Prevalence of biologics monotherapy in a cohort of patients with rheumatoid arthritis in daily clinical practice. *BMC Musculoskelet Disord*. 2016;17:110.
9. Buckley F, Finckh A, Huizinga TW, et al. Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in rheumatoid arthritis patients with inadequate response to conventional DMARDs: a network meta-analysis. *J Manag Care Spec Pharm*. 2015;21: 409–423.
10. Harnett J, Curtis JR, Gerber R, et al. Initial experience with tofacitinib in clinical practice: treatment patterns and costs of tofacitinib administered as monotherapy or in combination with conventional synthetic DMARDs in 2 US health care claims databases. *Clin Ther*. 2016;38:1451–1463.
11. Kivitz AJ, Cohen S, Keystone E, et al. A pooled analysis of the safety of tofacitinib as monotherapy or in combination with background conventional synthetic disease-modifying antirheumatic drugs in a phase 3 rheumatoid arthritis population. *Semin Arthritis Rheum*. 2018;48:406–415.
12. Pappas DA, Reed GW, Saunders K, et al. Characteristics associated with biologic monotherapy use in biologic-naive patients with rheumatoid arthritis in a US registry population. *Rheumatol Ther*. 2015;2:85–96.
13. Choy E, Aletaha D, Behrens F, et al. Monotherapy with biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis. *Rheumatology (Oxford)*. 2017;56:689–697.
14. Emery P, Pope JE, Kruger K, et al. Efficacy of monotherapy with biologics and JAK inhibitors for the treatment of rheumatoid arthritis: a systematic review. *Adv Ther*. 2018;35:1535–1563.
15. Doria A, Zavaglia D. Monotherapy is a relevant option in rheumatoid arthritis treatment: a literature review. *Clin Exp Rheumatol*. 2019;37: 862–871.
16. Finckh A, Tellenbach C, Herzog L, et al. Comparative effectiveness of antitumour necrosis factor agents, biologics with an alternative mode of action and tofacitinib in an observational cohort of patients with rheumatoid arthritis in Switzerland. *RMD Open*. 2020;6:e001174.
17. Bilgin E, Ceylan F, Duran E, et al. Efficacy, retention and safety of tofacitinib in real-life: HUR-BIO monocentric experience. *Turk J Med Sci*. 2021;51:297–308.
18. Bird P, Littlejohn G, Butcher B, et al. Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia. *Clin Rheumatol*. 2020;39:2545–2551.
19. Pope JE, Keystone E, Jamal S, et al. Persistence of tofacitinib in the treatment of rheumatoid arthritis in open-label, long-term extension studies up to 9.5 years. *ACR Open Rheumatol*. 2019;1:73–82.