Efficacy and drug retention of tofacitinib in rheumatoid arthritis: from the nationwide Korean College of Rheumatology Biologics Registry

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Abstract

Objective

Janus kinase inhibitors are expected to change the management patterns and prognosis of chronic rheumatic diseases. This study aimed to evaluate the efficacy, drug retention, and adverse events of tofacitinib, a Janus kinase inhibitor, for rheumatoid arthritis (RA) using a Korean nationwide database.

Methods

Data of patients with RA receiving tofacitinib were extracted from the Korean College of Rheumatology Biologics and Targeted Therapy registry, including clinical characteristics and disease activity markers for RA. Outcomes of clinical efficacy, drug survival rate, and safety profiles were compared between biologic disease-modifying anti-rheumatic drug (bDMARD)-naive and -failure patients. Mann-Whitney U-test, logistic regression analysis, Kaplan-Meier analysis, and log-rank test were used in data analysis.

Results

Three hundred patients with RA received tofacitinib therapy (16.3% male; mean age 55.4±11.9 years); 91 patients were bDMARD-naive. Baseline disease activity markers and proportions of patients who were taking conventional synthetic DMARDs were not different between bDMARD-naive and bDMARD-failure patients. American College of Rheumatology responses and disease activity score-28 did not differ between bDMARD-failure and -naive patients at the 1-year follow-up. The drug retention rate of tofacitinib did not differ between bDMARD-failure (155 per 2.4 years) and -naive patients (89 per 1.9 years) (log-rank test, p=0.202). In logistic regression, the positivity of RF and ACPA were associated with reduced drug retention (p=0.01 and 0.02, respectively). Totally 83 (27.7%) of patients had adverse, and 14 (4.7%) patients had herpes zoster infection.

Conclusion

Nationwide real-world data showed that tofacitinib therapy is effective in patients with RA independent of previous use of a bDMARD. The drug retention of tofacitinib did not differ between bDMARD-failure and -naive patients, and RF or ACPA positivity may be associated with reduced discontinuation of tofacitinib.

Key words

rheumatoid arthritis, Janus kinase inhibitor, tofacitinib, drug retention

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that presents with chronic synovitis, leading to joint destruction and systemic complications (1). Control of systemic inflammation is critical to prevent disability and mortality in patients with RA, as synovial inflammation causes joint damage. As novel drugs have been developed and available options that can produce better results have increased during the last two decades, treatment strategies that prevent joint deformities while minimising complications are becoming more important (2). The guidelines for the management of RA, including the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR), recommend the use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic (ts)-DMARDs in cases of established RA with moderate to high disease activity after one or more conventional synthetic (cs)-DMARDs (1, 3). Janus kinase (JAK) inhibitors are called tsDMARDs, and several JAK inhibitors, including tofacitinib, baricitinib, and upadacitinib, have been developed and approved for the treatment of chronic inflammatory diseases, including RA.

JAKs are involved in intracellular tyrosine kinase signalling transduction pathways of cytokines in various cells, such as myeloid cells and activated B and T cells (4). The binding of cytokines activates them, resulting in the activation of signal transducers and activators of transcription (STAT) proteins. Activated STATs move to the nucleus and modulate the transcription of target genes, which is a critical JAK-STAT pathway in lymphocyte development and immune response. JAKs comprise JAK1, JAK2, JAK3, and Tyk2, and each kinase has distinct cytokine receptors with specific functions. Tofacitinib has an inhibitory potency against all JAK family kinases with enhanced selectivity for JAK1/JAK3, while baricitinib inhibits JAK1/JAK2 (5, 6). Tofacitinib inhibits the release of proinflammatory cytokines, including interleukin (IL)-6 and IL-8, from $CD4^+$ T cells and synovial fibroblasts, and reduces signs of arthritis and suppresses cytokines in inflammatory arthritis models (7, 8). In clinical trials, phase II and III studies of tofacitinib have proven its efficacy and safety among patients with moderate-to-severe active RA, leading to its approval by the Food and Drug Administration (2012) and European Medicines Agency (2017) (9, 10).

Tumour necrosis factor (TNF) inhibitors have been used as a first-line bDMARD for RA, but more than 30% of patients have failed to achieve remission or low disease activity by TNF inhibitor therapy (11). Numerous patients with RA have required a switch to other b/tsDMARDs, including other TNF inhibitors, IL-6 inhibitors, and JAK inhibitors, and the outcomes related to drug switching have been studied (12). The results of each study differed depending on the drugs or the study patients, but many studies concluded that TNF inhibitors were not preferred in cases of refractory RA to second-line TNF inhibitors (13). As an alternative interpretation, it might be more reasonable to switch to bDMARDs or tsDMARDs with different mechanisms in cases of more than second-line treatment. In accordance with the ACR and EULAR guidelines, JAK inhibitors are now available for use in patients who have failed csDMARDs in many countries. As the use of JAK inhibitors increases, the results of clinical trial data and real-world data are being published on these issues. JAK inhibitors are expected to change the management patterns and prognosis of patients with RA. Therefore, this study aimed to evaluate the efficacy, drug retention, and adverse events of tofacitinib, which is generally the first-line JAK inhibitor in most countries, between biologic-naive and -failure patients with RA.

Materials and methods

Data source and collection

The Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) registry is a collection of clinical data from a nationwide, multicentre cohort of patients with rheumatic diseases (14, 15). Patients with RA who were ≥18 years of age and treated with csDMARDs or b/tsDMARDs were

enrolled from 58 hospitals in South Korea in December 2012 (KOBIO-RA), and total number of enrolled patients with RA was 3,201 at March 2021. The present study collected data from patients with RA treated with tofacitinib as first- or further-line bDMARDs or tsDMARDs in the KOBIO-RA registry between September 2015 and March 2021. In South Korea, patients with RA can receive cost support for bDMARDs or tsDMARDs by the public health insurance system if they have an inadequate response to at least two csDMARDs for >6 months. First-line bDMARDs or tsDMARDs eligible for support include all bDMARDs, except rituximab, and second-line bDMARDs or tsDMARDs can be used if first-line bDMARDs show an inadequate response in controlling disease activity of RA or adverse events. Tofacitinib was approved as a second-line treatment for patients who have an inadequate response or adverse events to anti-TNF agents in April 2014; it was approved as a first-line agent for patients who have an inadequate response to at least two csDMARDs for >6 months from July 2017 in South Korea (16).

In the KOBIO-RA registry, data were collected from medical records and assessments of physicians who treated each patient during routine clinical practice. Demographics, previous or current use of medications, medical history, comorbidities, extra-articular manifestations, and laboratory test results including positivity for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) were collected. The disease activity score in 28 joints (DAS28), erythrocyte sedimentation rate (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) were collected to evaluate the efficacy of tofacitinib in RA (17, 18). In addition, the Routine Assessment of Patient Index Data 3 was used to assess the change in the functional capacity of patients with RA. Drug retention, the period until definitive treatment interruption, and reasons for discontinuation were collected and analysed. Reasons for discontinuation included effectiveness, inefficacy, adverse events, and other reasons, such as patient preference, change of hospital, and financial reasons.

Table I. Comparison of clinical characteristics between bDMARD-failure patients and bDMARD-naive patients among patients treated with tofacitinib.

Characteristics	All patients n=300	bDMARD-failure n=209	bDMARD-naive n=91	*p*-value
Age at start (yrs)	55.3 ± 11.9	54.9 ± 12.2	56.0 ± 11.1	0.48
Male	47 (15.7%)	31 (14.8%)	16 (17.6%)	0.55
BMI	23.2 ± 3.6	22.9 ± 3.4	23.8 ± 4.0	0.07
Smoking history				0.64
Ex-smoker	19 (6.3%)	15 (7.2%)	4 (4.4%)	
Current smoker	27 (9.0%)	18 (8.6%)	9 (9.9%)	
Never	254 (84.7%)	176 (84.2%)	78 (85.7%)	
ESR	42.7 ± 30.1	42.4 ± 31.1	43.2 ± 27.8	0.83
CRP	1.7 ± 2.6	1.6 ± 2.2	1.9 ± 3.5	0.31
Tender joint count	7.6 ± 5.8	7.5 ± 6.1	7.7 ± 5.0	0.82
Swollen joint count	6.0 5.3	5.8 5.7	6.3 4.4	0.47
SDAI	27.3 ± 11.4	27.3 ± 12.1	27.3 ± 9.5	0.99
CDAI	25.6 ± 10.8	25.7 ± 11.6	25.4 ± 8.8	0.80
DAS28-ESR	5.3 ± 1.2	5.2 ± 1.3	5.4 ± 1.0	0.30
DAS28-CRP	4.6 ± 1.1	4.6 ± 1.2	4.7 ± 1.0	0.36
RAPID3	15.0 ± 5.3	15.1 ± 5.4	15.0 ± 5.1	0.89
Previous DMARDs	265 (88.3%)	177 (84.7%)	88 (96.7%)	<0.01
Glucocorticoids use	251 (83.7%)	174 (83.3%)	77 (84.6%)	0.77
Positivity of RF	217 (80.1%)	152 (82.6%)	65 (74.7%)	0.13
Positivity of ACPA	181 (84.2%)	117 (86.7%)	64 (80.0%)	0.2

bDMARDs: biologic disease-modifying anti-rheumatic drugs; BMI: Body Mass Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; RAPID3: Routine Assessment of Patient Index Data 3; DMARDs: disease-modifying anti-rheumatic drugs; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody.

The study protocol and data collection form of the KOBIO registry were approved by the institutional review boards of Ajou University Hospital (number [no.]: AJIRB-MED-SUR-12-356) and each ethics committee at the participating hospitals. In addition, the current study protocol and data collection form were approved (no.: AJIRB-MED-SUR-21-048). All procedures were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all participants provided written consent to participate in the registry.

Statistical analysis

Regarding demographic and clinical data, continuous variables are presented as mean ± standard deviation, and categorical variables are expressed as number and percentage. For group comparisons, Mann-Whitney U-test was used to analyse continuous variables, and the chi-square test was used to analyse categorical variables. Logistic regression analysis was used to identify the clinical factors associated with drug discontinuation of tofacitinib in patients with RA; data are presented as odds ratio (OR) with 95% confidence interval (CI). Drug retention curves for tofacitinib were constructed using the Kaplan-Meier method, and data were compared using the log-rank test. The observation time was from the start of tofacitinib treatment to drug discontinuation. All statistical analyses were two-sided and performed using SAS statistical software (v. 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at $p<0.05$.

Results

Comparison of baseline clinical characteristics between the patient groups

Among 300 patients with RA treated with tofacitinib, 209 patients were included in the bDMARD-failure group, and 91 patients were included in the bDMARD-naive group (Table I). Among them, 44 patients (14.7%) were treated with tofacitinib as monotherapy. Patients' mean ages were 54.9±12.2 and 56.0±11.1 years, proportions of male patients were 31 (14.8%) and 16 (17.6%), and proportions of current

smokers were 18 (8.6%) and 9 (9.9%) in the bDMARD-failure and -naive groups, respectively. Inflammatory markers, including ESR and C-reactive protein (CRP), and disease activity markers, including SDAI and CDAI, did not differ between the groups, and the levels of DAS28-ESR were 5.2±1.3 and 5.4±1.0 in the DMARD-failure and -naive groups, respectively. While 174 (83.3%) and 77 (84.6%) patients were treated with glucocorticoids in the bDMARD-failure and -naive groups, respectively, 177 (84.7%) and 88 (96.7%) patients were previously treated with csDMARDs in the bDMARD-failure and -naive groups, respectively (p<0.001). This is because csDMARDs are often discontinued for various reasons in patients receiving previous bDMARD therapy. In total, 152 (82.6%) and 65 (74.7%) patients had RF in the bDMARD-failure and -naive groups, respectively, and 117 (86.7%) and 64 (80.0%) patients had ACPA positivity in the bDMARD-failure and -naive groups, respectively. In the bDMARD-failure group (n=209), 32 (15.3%) patients failed one type of bDMARD, and 157 (75.1%) patients failed two types of bDMARDs. The bDMARD, which was used before starting treatment with tofacitinib, was tocilizumab in 60 (28.7%) patients, adalimumab in 39 (18.7%), etanercept in 30 (14.4%), abatacept in 27 (12.9%), and golimumab in 25 (12.0%).

Comparison of efficacy of tofacitinib between the patient groups

The proportions of patients with RA treated with tofacitinib who had ACR20, ACR50, and ACR70 responses did not differ between the bDMARD-failure and -naive groups at the 1-year follow-up (Table II). The proportions of patients who had an ACR20 response, ACR50 response, and ACR70 response were 117 (76.5%) and 70 (80.5%); 80 (52.3%) and 55 (63.2%); and 35 (22.9%) and 28 (32.2%) in the bDMARD-failure and -naive groups, respectively. The mean levels of ESR and CRP, DAS28-ESR (3.0 [range, 2.4–3.9] and 3.1 [range, 2.2–3.7], respectively), and DAS28-CRP (2.3 [range, 1.8–3.2] and 2.15 [range, 1.6–2.9], respectively)

Table II. Efficacy of Tofacitinib between bDMARD-failure patients and bDMARD-naive patients with tofacitinib at 1-year follow-up.

	Overall	bDMARD-failure	bDMARD-naive	*p*-value*
ACR 20, n (%)	187 (77.9)	117 (76.5)	70 (80.5)	0.68
ACR 50, n (%)	135 (56.3)	80 (52.3)	55 (63.2)	0.14
ACR 70, n (%)	63 (26.3)	35 (22.9)	28 (32.2)	0.14
ESR, mm/hr	23.0 (12.0, 37.0)	21 (11. 4)	26 (12, 4)	0.27
CRP, mg/dL	0.2 (0.05, 0.7)	0.22 (0.04, 0.71)	0.18 (0.07, 0.66)	0.9
DAS28-ESR	3.0 (2.4, 3.8)	3.0 (2.4, 3.9)	3.1 (2.2, 3.7)	0.49
DAS28-CRP	2.2 (1.7, 3.1)	2.3 (1.8, 3.2)	2.15 (1.6, 2.9)	0.09

*p-value was based on Chi-squared test.
bDMARDs: biologic disease-modifying anti-rheumatic drugs; ACR20: American College of Rheumatology-20%; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints.

Table III. Logistic regression of clinical factors for drug discontinuation of tofacitinib in patients with RA .

Parameters	Estimate	95% Confidence	Intervals	*p*-value
Age at start (yrs)	0.96	0.9	1.03	0.27
Sex (male)	3.39	0.55	21.07	0.19
BMI	0.95	0.73	1.25	0.72
ESR	0.98	0.95	1.02	0.35
CRP	1	0.72	1.39	1.0
Tender joint count	1.02	0.89	1.18	0.75
Swollen joint count	1.0	0.85	1.18	0.99
SDAI	0.99	0.92	1.07	0.83
CDAI	0.99	0.91	1.08	0.82
DAS28-ESR	0.76	0.39	1.49	0.43
DAS28-CRP	0.85	0.4	1.81	0.67
RAPID3	0.9	0.77	1.05	0.19
Previous bDMARDs failure (1st line *vs*. 2nd line (ref.))	0.18	0.38	7.98	0.47
Corticosteroid use	0.71	0.08	6.52	0.76
Positivity of RF	0.06	0.01	0.55	0.01
Positivity of ACPA	0.11	0.02	0.71	0.02
No. of DMARDS (as continuous variable)	1.29	0.47	3.51	0.62

BMI: Body Mass Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; RAPID3: Routine Assessment of Patient Index Data 3; bDMARDs: biologic disease-modifying anti-rheumatic drugs; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody.

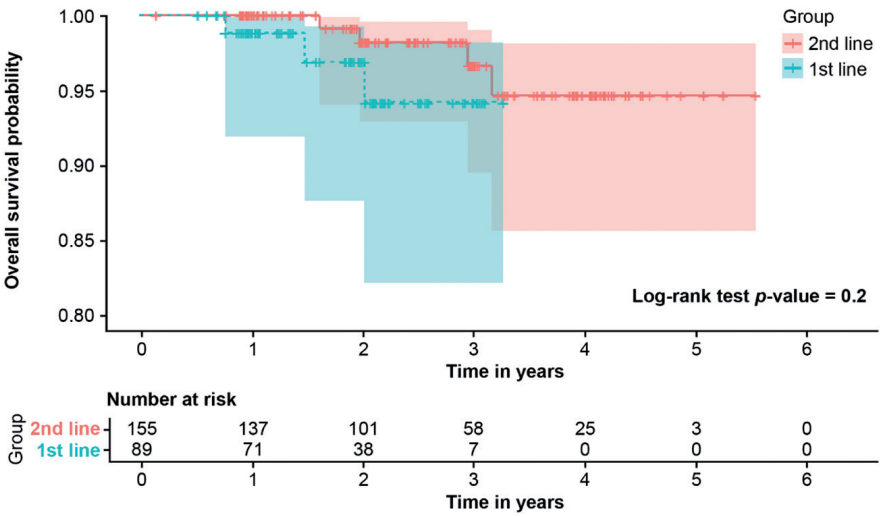

Fig. 1. Kaplan-Meier plot comparing drug retention rates of tofacitinib in different patient groups. Comparison of drug retention rates between patients who received tofacitinib as first-line biologic or targeted synthetic disease-modifying anti-rheumatic drug therapy and those who did not (log-rank test, p=0.201).

Table IV. Adverse events of tofacitinib in patients with rheumatoid arthritis.

Disease category	Disease	Overall n (%)	bDMARD-failure n (%)	bDMARD-naive n (%)
Gastrointestinal disorders	Gastroenteritis	1 (1.2)	1 (1.5)	-
	Nausea	2 (2.4)	1 (1.5)	1 (5.6)
	Nausea and vomiting	1 (1.2)	1 (1.5)	-
	Heartburn	1 (1.2)	-	1 (5.6)
General disorders and administration site conditions	Investigation reaction	10 (12)	10 (15.4)	-
	Generalised oedema	1 (1.2)	1 (1.5)	-
	Orofacial oedema	1 (1.2)	1 (1.5)	-
Infections and infestations	Herpes zoster	14 (16.9)	12 (18.5)	2 (11.1)
	Other bacterial infection	5 (6)	5 (7.7)	-
	Mycobacteria tuberculosis infection	1 (1.2)	1 (1.5)	-
	Genital herpes	1 (1.2)	-	1 (5.6)
	Herpes simplex	1 (1.2)	-	1 (5.6)
	Influenza	1 (1.2)	1 (1.5)	-
	Influenza A virus infection	2 (2.4)		2 (11.1)
	Tonsillitis	2 (2.4)	1 (1.5)	1 (5.6)
Metabolism and nutrition disorders	Hyperlipidaemia	15 (18.1)	9 (13.8)	6 (33.3)
Musculoskeletal and connective tissue disorders	Myalgia	2 (2.4)	2 (3.1)	-
	Sjögren's syndrome	5 (6)	4 (6.2)	1 (5.6)
Nervous system disorders	Dizziness	1 (1.2)	1 (1.5)	-
	Upper respiratory infection	3 (3.6)	3 (4.6)	-
	Upper respiratory tract inflammation	1 (1.2)	1 (1.5)	-
Skin and subcutaneous tissue disorders	Folliculitis	3 (3.6)	3 (4.6)	-
	Pruritus	1 (1.2)	-	1 (5.6)
	Psoriasis	2 (2.4)	2 (3.1)	-
	Skin rash	2 (2.4)	2 (3.1)	-
Investigations	Transaminitis only	2 (2.4)	2 (3.1)	-
Total		83	65	18

bDMARDs: biologic disease-modifying anti-rheumatic drugs.

did not differ between the bDMARD-failure and -naive groups after 1 year of tofacitinib treatment.

Drug retention between the patient groups

Seven patients, including four bDMARD-failure and three bDMARD-naive patients, discontinued tofacitinib and were switched to other drugs. The reasons for switching were inefficacy in six patients and physician's decision in one bDMARD-naive patient. Drug retention data were analysed in a total of 244 patients over a mean of 2.1 (range, 1.1–3.0) years; there were 155 and 89 bDMARD-failure and -naive patients, respectively, and their mean treatment durations were 2.4 (range, 1.5–3.6) and 1.9 (range, 1.0–2.2) years, respectively. The drug retention rate of tofacitinib did not differ between the bDMARD-failure and -naive groups, as shown in Figure 1 (log-rank test, p=0.202).

Clinical factors associated with drug discontinuation oftofacitinib

In logistic regression analysis of clinical factors, drug discontinuation of tofacitinib was associated with positivity of RF (OR = 0.06, 95% CI: 0.01–0.55, p=0.01) and ACPA (OR=0.11, 95% CI: 0.02–0.71, p=0.02), although age, sex, ESR, CRP, SDAI, CDAI, DAS28, and previous bDMARD failure were not (Table III). Multiple regression analysis was not possible because the number of drug discontinuation cases was too small for analysis.

Adverse events in patients with tofacitinib

In total, 83 cases of adverse events, including 65 bDMARD-failure and 18 bDMARD-naive patients, were reported during tofacitinib therapy. Among 300 patients treated with tofacitinib, 14 (4.7%) patients had herpes zoster infection, two (2.2%) patients were bDMARD-naive, and 12 (6.0%) patients were in the bDMARD-failure group (Table IV). Additionally, 15 (5%) patients had hyperlipidaemia, six (6.6%) were bDMARD-naive, and nine (4.5%) bDMARD-failure patients had hyperlipidaemia. Ten (5.0%) and five (2.5%) bDMARD-failure patients had investigation reactions and bacterial infections, respectively, while no bDMARD-naive patients had either. None of the patients had a thromboembolic event during tofacitinib therapy.

Discussion

In this study, tofacitinib therapy showed ACR20, ACR50, and ACR70 responses in 77.9%, 56.3%, and 26.3% of patients with RA, and the mean DAS28-ESR and CRP levels at follow-up were 3.0 and 2.2, respectively. Thus, tofacitinib was effective in bDMARD-naive and -failure patients. Drug retention between the bDMARD-failure and -naive groups was similar after 2 years.

Tofacitinib has been shown to be effective in controlling the disease activity of RA through several randomised clinical trials and retrospective data from clinical practice (19-23). Most data confirmed that the use of tofacitinib could control disease activity in patients with moderate-to-severe active RA compared to TNF inhibitors or other bDMARD or tsDMARD therapy. Unlike

TNF inhibitors, tofacitinib did not show a significant difference between monotherapy and combination therapy with csDMARDs, including methotrexate (MTX) (22). Tofacitinib monotherapy was effective in achieving low disease activity or remission, similar to TNF inhibitors in combination with MTX.

In this study, the efficacy of tofacitinib in RA was confirmed using real-world registry data. The proportions of patients achieving ACR 20/50/70 responses (77.9%/56.3%/26.3%) are higher compared to some studies with same dose of tofacitinib (5 mg twice) such as the Oral Rheumatoid Arthritis (ORAL) study (73.5%/48.8%/27.0%) or a pooled data from patients from the Asia-Pacific region (69.2%/36.9%/15.1%) (24, 25). However, they are not higher compared to some others, including the data of Yamanaka H, *et al*. (88.6%/65.5%/42.5%) or Wollenhaupt *et al*. (81.2%/61.3%/39.8%) (26, 27). A study analysing 144 patients who were treated with tofacitinib showed that the proportion of patients who achieved low disease activity or remission (DAS28 ≤3.2) was higher in the biologic agent-naive group than in the pre-exposed group (28). A prospective study compared the proportions of biologic-naive patients (n=36) and biologic-experienced patients (n=77) who were treated with tofacitinib (29). Although the baseline CDAI and proportion of patients with a high CDAI (>22) did not differ between the groups, the proportions of those who achieved CDAI 50 were higher in the biologic-naive group than in the biologic-experienced group, and mean CDAI was higher in the biologic-experienced group than in the biologic-naive group at 6 months. A study of 247 patients with RA treated with tofacitinib found that DAS28 ≤3.2 was associated with being biologic naive and negativity for RF, even after adjustment for disease duration, which differed between biologic-naive and biologic-experienced patients (30). However, the proportion of patients who achieved an ACR response and the mean DAS28 level after tofacitinib treatment were similar between bDMARD-failure and bDMARD-naive groups in this study, suggesting that failure of bDMARD was not associated with the efficacy of tofacitinib, contrary to previous studies' results.

Generally, JAK inhibitors are recognised as more potent agents because they were effective even in the patients, who were refractory to bDMARDs. The South Korea public health insurance covers most of drug price (90%) for seropositive patients, but it is not allowed to switch drugs between JAK inhibitors and to reuse the previously failed biologics or tsDMARDs. Therefore, after drug switching of tofacitinib to bDMARDs, tofacitinib cannot be prescribed again. This insurance condition might have affected the retention rate of tofacitinib in this study. Rheumatologists would have explained to the patients that tofacitinib is a potent drug and the retreatment of tafacitinib is not permitted after drug switching in RA. If current treatment is effective without significant adverse events, the patient's opinion could be greatly reflected in the switching or retention of the drug.

There are some data regarding drug retention of tofacitinib, and the current study showed relatively higher than other data. A study using an Australian dataset suggested that treatment persistence was similar between other bDMARDs and tofacitinib, regardless of monotherapy or combination therapy (31). In a comparison of RA patients with other bDMARDs or tsDMARDs (n=964) and tofacitinib (n 139), tofacitinib had similar event-free survival rates to other bDMARDs, but better drug survival than other agents among first- and second-line users (32). A comparison of drug maintenance between TNF inhibitors and bDMARDs or tsDMARD with other modes of action revealed that tofacitinib had a higher drug maintenance rate than TNF inhibitors for 3 years (33). A study using the eXel patient support programme in Canada compared tofacitinib persistence according to the number of prior bDMARDs (34). Tofacitinib discontinuation was more frequent in bDMARD-experienced patients than in bDMARD-naive patients, and 55.8% of bDMARD-naive patients and 45.4% of post- ≥3 bDMARD patients maintained treatment for 2 years. Tofacitinib persistence was associated with age ≥56 years, not ≤45 years, and 15–20 years of disease duration before starting tofacitinib not <5 years. Data analysis of Turkish patients treated with tofacitinib (n=247) showed that discontinuation rates did not differ between biologic-naive and biologic-experienced groups (log-rank, p=0.23), and there was no relevant factor for predicting better drug retention (30). In the present study, tofacitinib retention rates were similar between bDMARD-failed and -naive patients. There could be an external factor influencing the drug survival of tofacitinib that is not related to the efficacy and safety of the drug or the characteristics of the disease. The health insurance conditions described above might have affected the retention rate of tofacitinib between both biologic-naive and -experienced groups, because they had limited options compared to those who used tofacitinib as the first bDMARD or tsDMARD.

The positivity of RF and positivity of ACPA were associated with drug retention of tofacitinib in our study. In open label and extension studies for 9.5 years, positivity of ACPA and positivity of both RF and ACPA were associated with reduced tofacitinib discontinuation in RA (35). A study revealed that the negativity of RF and negativity of ACPA were associated with superior drug survival among 151 patients with RA treated with tofacitinib for 3 years (p=0.05 and 0.025, respectively) (36). In a study comparing the efficacy and safety of tofacitinib between groups divided by positivity of autoantibodies, ACR responses and discontinuation rates were similar, while DAS28 remission rates and 36-Item Short Form Survey physical functioning were lower in the ACPA-negative group than in the ACPA-positive group (37). In the current study, patients who had RF or ACPA maintained tofacitinib treatment more than those who did not. Korea public health insurance supports only seropositive patients with RF or ACPA, so seronegative RA patients pay about a three-fold higher cost of tofacitinib compared to seropositive RA patients. Tofacitinib is an expensive drug depending on seropositivity, and this might have affected the retention rate.

Based on the safety data, 14 (4.7%) patients had herpes zoster infection, and five (1.7%) and three (1%) patients in the bDMARD-failure group had bacterial and upper respiratory infections, respectively. In phases I–III clinical trials, the incidence rates of herpes zoster infection in RA patients with tofacitinib therapy were 4.0 in global 16,839 patient -years (pys), 8.0 in Japanese 1,705 pys, and 8.4 in Korean 779 pys (38, 39). Herpes zoster infection has been prevalent in East Asian patients treated with tofacitinib, and genetic variants that were associated with the onset of herpes zoster in RA or psoriatic arthritis patients with tofacitinib were prevalent in East Asian and European populations (40). The higher incidence rate of herpes zoster infection in clinical trials and clinical practice suggests that patients receiving tofacitinib in countries with a high incidence of herpes zoster infection, *e.g.* Korea, should be warned against the risk of herpes zoster infection and advised to receive zoster vaccination. In addition, 15 (5%) patients had hyperlipidaemia in this study, and several previous clinical trials and observational studies have shown increased low-density lipoprotein cholesterol levels in tofacitinib therapy (19, 41). Although dyslipidaemia could develop in patients treated with tofacitinib, the incidence of significant cardiovascular disease has rarely been found, except for thromboembolism (42). It is necessary to evaluate the long-term consequences of such deteriorated lipid metabolism using further data from clinical practice.

This study has some limitations. The duration of tofacitinib treatment was too short, and the number of the patients who discontinued tofacitinib was small to be analysed using logistic regression. Our study lacked detailed analysis, such as a comparison of drug survival between patients divided by the number of failed bDMARDs or multiple regression analysis against drug discontinuation. In addition, socioeconomic factors, such as the national insurance standards and financial conditions of the patients, were not collected or analysed. However, this study collected and analysed nationwide clinical data and other important data of tofacitinib, which is a drug with a lack of information in clinical practice.

Conclusions

Nationwide real-world data showed that tofacitinib therapy is effective in patients with RA independent of previous use of a bDMARD. The drug retention of tofacitinib did not differ between bDMARD-failure and -naive patients. Moreover, RF or ACPA positivity may be associated with reduced discontinuation of tofacitinib. Lastly, among 300 patients with RA who had been treated with tofacitinib, 4.7% had herpes zoster infection, and 5% had hyperlipidaemia.

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