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Efficacy and safety of different Janus kinase inhibitors combined with methotrexate for the treatment of rheumatoid arthritis: a single-center randomized trial

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Abstract

Objective To compare the efficacy and safety between baricitinib (BARI) and tofacitinib (TOFA) for the treatment of the rheumatoid arthritis (RA) patients receiving methotrexate (MTX) in clinical practice.

Methods This retrospective study recruited 179 RA patients treated with BARI (2–4 mg/d) or TOFA (10 mg/d) at The First Affiliated Hospital of Guangxi Medical University from September 2019 to January 2022. The rate of low disease activity (LDA) was used as the primary end point. Secondary end points included the Disease Activity Scale-28 (DAS-28)-C-reactive protein (CRP); the rate of DAS28-CRP remission; visual analogue scale (VAS) for pain, swollen joint, and tender joint counts; and adverse events at the 6-month follow-up. Several factors affecting LDA achievement were also analyzed.

Results Seventy-four patients were treated with BARI and 105 were treated with TOFA, including 83.24% females, with a median (IQR) age of 56.0 (53.0–56.0) years old and disease duration of 12.0 (6.0–12.0) months. There was no difference of the rate of LDA between the BARI and TOFA treatment groups. All disease indices in the two groups were significantly improved, including a significantly lower VAS in the BARI group ($P < 0.05$), reflecting the drug efficacy after 1 and 6 months of treatment. The incidence of adverse reactions was similar in these two groups.

Conclusion The treatment efficacy and safety of BARI and TOFA in the RA patients were similar, but BARI was more effective in pain relief than TOFA. An older baseline age was more likely to achieve LDA in the BARI group, while a low baseline erythrocyte sedimentation rate (ESR) was more likely to achieve LDA in the TOFA group.

Keywords Rheumatoid arthritis, Baricitinib, Tofacitinib, Janus kinase (JAK) inhibitors, Disease Activity Scale-28 (DAS-28)

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to destruction of bone and joints, systemic complications, and disability [1]. The use of disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biological DMARDs (bDMARDs), is crucial for controlling inflammation, preventing structural damage, and reducing RA-related symptoms [2]. However, some RA patients inadequately respond to treatment with bDMARDs, and a novel class of antirheumatic drugs, Janus kinase (JAK) inhibitors, has been used to address this issue [3].

The JAK family comprises JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2, which are multidomain nonreceptor tyrosine kinases. Among the several JAK inhibitors developed, tofacitinib (TOFA) is a pan-JAK inhibitor that inhibits JAK 1, 2, and 3 [4]; meanwhile baricitinib (BARI) is a JAK1 and JAK2 inhibitor, with moderate inhibitory activity against TYK2, but less efficacy againstJAK3 [5]. The effectiveness of TOFA and BARI in the treatment of RA has been established in many randomized controlled trials [6–8]. TOFA was recommended by Chinese guidelines in 2018 as a combination therapy for RA patients with no response to csDMARDs [9]. For example, a comparison study found a longer persistence in the RA patients who switched to TOFA from a bDMARD than in those who switched to a bDMARD [10]. Additionally, compared to adalimumab, BARI was found to be faster and more effective in relieving the RA-caused pain in the RA patients with inadequate response to methotrexate (MTX) [11].

Although similar discontinuation rates and safety profiles have been observed for TOFA and BARI, respectively, in real-world studies [12], their efficacy in treating RA patients in China remains unknown. This study aimed to evaluate the efficacy and safety BARI and TOFA in treating RA patients in a real-world setting in China, providing a reference for their clinical use.

Methods

Patients

This study recruited RA patients who received treatment at the Department of Rheumatology and Immunology of The First Affiliated Hospital of Guangxi Medical University during the period from September 2019 to January 2022. The inclusion criteria were as follows: the RA patients were diagnosed, according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [13] and were treated with BARI or TOFA combined with MTX (10–15 mg once a week). The exclusion criteria were as follows: (1) patients who had received advanced therapies (bDMARDs or JAK inhibitors other than TOFA and BARI) within 3 months; (2) patients who have systemic complications; (3) patients who also had other autoimmune diseases or other diseases and special conditions, such as tumors, tuberculosis, severe infection, pregnancy, or lactation; and (4) patients with a lymphocyte count < 500 cells/mm^3, neutrophil count < 1000 cells/mm^3, or hemoglobin level < 9 g/dL.

The collected basic information of the recruited patients included age, disease duration, sex, glucocorticoid dosage at baseline, and previous medical history (including hyperuricemia, type II diabetes, hyperlipemia, latent tuberculosis infection, hypertension, or hepatitis B). The follow-up period was 6 months.

Laboratory data

The following clinical laboratory parameters were collected: routine blood test results, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function, renal function, and rheumatoid factor at baseline and at 1 month and 6 months after treatment.

Evaluation of the treatment efficacy

The primary end point was the rate of low disease activity (LDA) at 6 months. Disease Activity Scale-28(DAS-28) was calculated based on the equation: DAS28-CRP = 0.56 × SQRT (TJC28) + 0.28 × SQRT (SJC28) + 0.36 × ln (CRP + 1) + 0.014 × (VAS-GH) + 0.96. A DAS28-CRP score of ≤ 3.2 represented the achievement of low disease activity (LDA).

The major secondary end points included the DAS28-CRP score, swollen joint count (SJC), visual analog scale (VAS) pain score, and tender joint count (TJC), and rate of remission at 6 months. A DAS28-CRP score of ≤ 2.6 was defined as remission.

Among these measurements, VAS is a validated, subjective measure for acute and chronic pain, the scores of which are quantified by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain," indicating the degree of pain (from 0 to 10).

Evaluation of treatment safety

Any adverse events and their severity during the course of treatment were recorded for evaluation, such as leukopenia: white blood cell count < 4×10^9/L after treatment; increasing alanine aminotransferase (ALT)/aspartate aminotransferase (AST): ALT and/or AST > 40 U/L after treatment; and increasing creatinine (CREA): CREA > 84 μmol/L (female) or > 90 μmol/L (male); and venous thromboembolism (VTE) after treatment.

Treatment groups

The recruited patients were assigned into two treatment groups, according to the treatment at baseline:

BARI (2–4 mg/day) or TOFA (10 mg/day). All of the patients received the combination therapy with MTX (10–15 mg/qw). After 6 months of treatment, a comparison of the disease activity between the patients with DAS28-CRP ≤ 3.2 and those with DAS28-CRP > 3.2 was performed by multivariate logistic regression analysis for each treatment group, respectively, thereby identifying the factors contributing to LDA.

Statistical analysis

The demographics and characteristics of the recruited patients were collected for comparison, in which the results were expressed as the mean ± standard deviation, median with interquartile range (IQR), or number (%) of patients. The Student's t-test or Mann–Whitney U test was used to test the difference between groups, and Pearson's chi-squared test was used to compare the differences between categorical variables. A *P*-value of <0.05 was considered a statistically significant difference. The factors related to remission were identified using binary logistic regression analysis. SPSS software (V.20.0) was used for data analysis in this study, including the DAS28-CRP score at baseline and after 1 month and 6 months of treatment.

Results

Patients

In total, 179 patients with a median age of 50 years old were recruited into this study. There were 74 patients (63 females and 11 males) in the BARI group, while 105 patients were in the TOFA group (86 females and 19 males). The demographic and baseline clinical characteristics of the patients in these two groups before treatment were compared, showing no significant differences in terms of sex, age, RA duration (12 months), TJC, SJC, VAS, ESR, CRP, DAS28-CRP, routine blood tests (hemoglobin level, platelet count, white blood cell count, neutrophil count, and lymphocyte count, liver and kidney function, and rheumatoid factors ($P>0.05$; Table 1).

Efficacy

The parameters associated with disease activity, such as DAS28-CRP, TJC, SJC, VAS, remission rate, and LDA achievement rate were significantly improved after 1 month of treatment and further improved after 6 months of treatment in both the BARI and TOFA groups ($P<0.05$)(Table 2). The DAS28-CRP categories at baseline, 1 month, and 6 months after BARI and TOFA treatment are shown in Fig. 1. The time-dependent differences in several indices, including TJC, SJC, VAS, ESR, CRP, and DAS28-CRP, between the two treatment groups were also compared. There was no significant difference in the primary end point of the rate of LDA at 6 months between the two treatment groups ($P>0.05$) (Fig. 2a). Also, there was no significant difference in secondary end points between both groups, including TJC, SJC, DAS28-CRP, ESR, CRP, level of DAS28-CRP, or the rate of DAS28-CRP remission (Fig. 2b). The results showed that only VAS remained significantly different between the two groups after 6 months of treatment ($P=0.0001$).

Factors contributing to LDA achievement

The factors associated with LDA achievement were identified by both univariate analysis and multivariate logistic regression analysis, by a comparison of the associated factors between the patients with DAS28-CRP ≤ 3.2 and those with DAS28-CRP > 3.2 after 6 months of treatment in both groups (Table 3). The explanatory variables included sex, age, duration of RA, white blood cell count, neutrophil count, lymphocyte count, hemoglobin level, ESR, and rheumatoid factors. Analysis found that in the BARI group, an older baseline age was more likely to achieve LDA; meanwhile, in the TOFA group, a low baseline ESR level was more likely to achieve LDA.

Safety

As shown in Table 4, there was no statistically significant difference in the incidence of adverse reactions between the two treatment groups. In the BARI group, three patients stopped treatment due to adverse events (one case of pneumonia, one case of herpes zoster, and one case of liver dysfunction); while in the TOFA group, five patients abandoned treatment due to adverse events (three cases of pneumonia and two cases of liver dysfunction). During the period of treatment, no patients in either treatment groups developed VTE or cancer. However, several patients had latent tuberculosis infection, but they did not develop tuberculous after treatment. Several chronic HBV carriers did not develop hepatitis B reactivation. There was one patient in the BARI group who developed myocardial infarction after 6 months of treatment, but she had a history of chest tightness and chest pain for two years and did not achieve clinical remission.

Discussion

The main manifestation of RA, a chronic autoimmune disease, is erosive polyarthritis, which results in disability and a poor quality of life. RA also causes other immune complications involving the skin, lungs, and cardiovascular system, leading to an increase in mortality [8]. To quickly minimize disease activity and achieve clinical remission in the RA patients, it is necessary to treat them with DMARDs as early as possible to reduce joint destruction [14]. JAK inhibitors are novel tsDMARDs that can effectively control the progress of RA [15]. It has been reported that treatment with TOFA is effective in RA patients, even those who had an inadequate response

Table 1 The baseline characteristics of the RA patients who received tofacitinib or baricitinib

Variable	Baricitinib (*n* = 74)	Tofacitinib (*n* = 105)	*P*-value
Age (years)	50.0 (33.0–58.8)	50.0 (42.5–56.5)	0.48
Sex, *n* (% female)	63 (85.1%)	86 (81.9%)	0.57
RA duration (months)	12.0 (7.0–36.0)	12.0 (6.0–60.0)	0.82
glucocorticoid dosage at baseline(mg)	2.0(0–4.0)	0(0–4.0)	0.14
Number of patients with previous use of DMARDs			
1 class	31(41.9%)	50(47.6%)	0.49
2 classes	38(51.4%)	51(48.6%)	0.71
3 classes	5(6.8%)	4(3.8%)	0.37
Hyperuricemia (n)	2(2.7%)	0	0.09
Type II diabetes(n)	1(1.4%)	2(1.9%)	0.78
Hyperlipemia(n)	0	2(1.9%)	0.23
Latent tuberculosis infection(n)	2(2.7%)	3(2.9%)	0.95
Hypertension(n)	0	2(1.9%)	0.64
Hepatitis B indicates antigen carriage(n)	4(5.4%)	4(3.8%)	0.61
TJC	6.0 (2.0–11.8)	6.0 (2.0–12.0)	0.36
SJC	5.5 (2.0–12.0)	6.0 (2.0–12.0)	0.57
VAS	5.5 (4.0–8.0)	5.5 (3.0–8.0)	0.28
DAS28-CRP	4.6 (3.7–6.2)	4.9 (3.7–6.0)	0.72
WBC ($\times 10^9$/L)	7.5 (6.7–9.8)	7.3 (6.1–9.4)	0.36
HGB (g/L)	113.7 ± 15.2	116.8 ± 11.5	0.11
PLT ($\times 10^9$/L)	331.7 (271.0–434.7)	334.7 (274.0–423.8)	0.91
NEU ($\times 10^9$/L)	5.3 (4.2–6.9)	5.0 (3.8–6.7)	0.54
LYM ($\times 10^9$/L)	1.8 (1.3–2.2)	1.7 (1.3–2.0)	0.33
AST (U/L)	24.5 (19.0–30.0)	25.0 (21.0–29.5)	0.50
ALT (U/L)	12.0 (10.0–20.0)	14.0 (9.0–22.0)	0.78
CREA (μmol/L)	53.0 (46.0–65.8)	54.0 (46.5–65.0)	0.64
CRP (mg/L)	16.9 (4.9–53.9)	22.7 (8.3–61.4)	0.46
RF positive	67(90.5%)	94(91.3%)	0.90
ESR (mm/h)	57.5 (35.0–82.8)	62.0 (40.0–91.0)	0.23

RA: rheumatoid arthritis, TJC: tender joint count, SJC: swollen joint count, VAS: visual analog scale, DAS28: disease activity score in 28 joints, CRP: C-reactive protein, WBC: white blood cell, HGB: hemoglobin, PLT: blood platelet, NEU: neutrophil, LYM: lymphocyte, AST: aspartate transaminase, ALT: alanine transaminase, CREA: creatinine, UA: uric acid, RF: rheumatoid factor, and ESR: erythrocyte sedimentation rate

to tumor necrosis factor inhibitors [7, 16–18]. Treatment with BARI also has been demonstrated to reduce disease activity in the RA patients who had an inadequate response or intolerance to csDMARDs and bDMARDs [8, 19–21]. Moreover, treatment with either BARI or TOFA has been proven to be effective in the RA patients who were refractory to bDMARDs [22, 23]. However, there has been no direct comparison of their effectiveness [24]. Our study showed that in both the BARI and TOFA groups, TJC, SJC, ESR, CRP, DAS28-CRP remission rate, and LDA achievement rate were significantly improved after 1 month and 6 months of treatment. Our findings were similar to those reported by real-world studies in Japan and Brazil, indicating that both BARI and TOFA can achieve a satisfactory treatment efficacy in RA patients.

The safety and efficacy of BARI and TOFA have been compared using the meta-analysis method in several studies. For example, the administration of TOFA at a dose of 5 mg/d was more effective than BARI at 4 mg/d [24]. However, in another study, treatment with BARI (4 mg/d) was demonstrated to be more effective than TOFA (5 mg/d) [25]. In addition, a real-world study found that the BARI group had a lower Clinical Disease Activity Index (CDAI) and a significantly higher rate of remission, compared to those in the TOFA group [26]. The primary end point was the rate of low disease activity (LDA) at 6 months, as detailed in the "Evaluation of the treatment efficacy" section. It's worth noting that the 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis conditionally recommends LDA as a minimal initial therapeutic goal over remission. In the context of China, methotrexate remains the first-line treatment for rheumatoid arthritis. To our knowledge, there hasn't been a direct comparison between BARI and TOFA when combined with

Table 2 Changes in patient baseline characteristics at 1 month and 6 months after baricitinib or tofacitinib

	Baricitinib group		Tofacitinib group					
	1 month ($n=71$)	6 months ($n=105$)	1 month ($n=50$)	6 months ($n=95$)	Z/t	P^a	Z/t	P^b
DAS28-CRP	2.8 (2.0–3.3)	2.17 (1.62–3.09)	2.7 (1.9–3.8)	2.12 (1.50–2.90)	-0.01	0.99	-1.05	0.29
TJC	1.00 (0–2.00)	0.00 (0.00–2.00)	2.00 (0–3.8)	0.0 (0.00–2.0)	-1.33	0.18	-0.84	0.40
SJC	2.00 (0–3.00)	1.00 (0.00–2.00)	1.0 (0–3.00)	0.0 (0.0–2.0)	-0.73	0.46	-0.30	0.76
VAS	3.0 (2.0–3.0)	2.00 (1.00–3.00)	2.9 (2.0–4.0)	1.0 (1.00–2.0)	-1.56	0.12	-3.87	0.00
CRP (mg/L)	3.9 (1.2–11.6)	2.70 (0.95–13.05)	3.0 (1.0–10.0)	2.30 (0.7–8.6)	-1.18	0.24	-1.19	0.24
ESR (mm/h)	34.0 (23.0–47.0)	30.00 (17.50–45.50)	31.5 (21.3–50.8)	27.00 (17.50–40.50)	-0.27	0.79	-0.70	0.49
RF (IU/mL)	60.0 (27.2–105.5)	59.10 (28.25–106.95)	73.3 (35.8–132.6)	66.30 (44.65–117.95)	-0.98	0.33	-0.89	0.37
WBC ($\times10^9$/L)	7.1 (5.7–8.3)	6.6 (5.5–8.0)	6.9 (5.5–9.2)	6.6 (5.3–7.9)	-0.38	0.71	-0.60	0.55
HGB (g/L)	118.8 (106.1–124.0)	116.5 ± 12.7	120.1 (109.1–129.8)	122.3 ± 14.6	-1.46	0.15	-2.32	0.02
PLT ($\times10^9$/L)	308.0 (267.0–359.0)	331.0(268.7–379.0)	276.0 (229.0–328.5)	264.0 (222.0–331.0)	-2.57	0.01	-3.44	0.001
NEU ($\times10^9$/L)	4.2 (3.2–5.4)	4.1 (3.2–5.5)	4.4 (3.4–6.2)	4.1 (3.2–5.3)	-1.00	0.31	-0.58	0.56
LYM ($\times10^9$/L)	1.8 (1.6–2.5)	1.7 (1.3–2.0)	1.6 (1.3–2.2)	1.6 (1.3–2.0)	-1.73	0.08	-0.66	0.51

DAS28-CRP disease activity score using 28 joints C-reactive protein, TJC: tender joint count, SJC: swollen joint count, VAS: visual analog scale, CRP: C-reactive protein

a, Comparison of baseline characteristics after 1 month of treatment between the baricitinib and tofacitinib groups

b, Comparison of baseline characteristics after 6 months of treatment between the baricitinib and tofacitinib groups

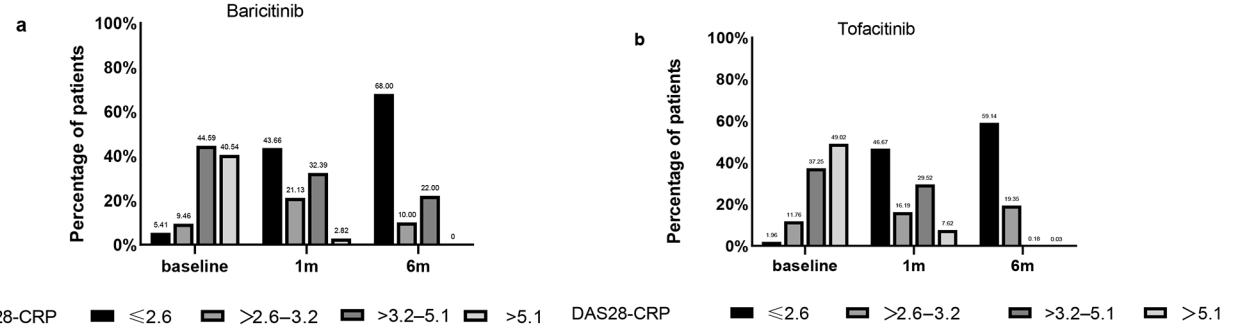

Fig. 1 Percentages of the rheumatoid arthritis patients in the baricitinib (a) and tofacitinib (b) groups with the disease activity score in 28 joints, C-reactive protein (DAS28-CRP) score ≤ 2.6, > 2.6–3.2, > 3.2–5.1, and > 5.1 at baseline and after 3 and 6 months of treatment

methotrexate in the Chinese setting. This gap in the literature prompted our single-center study. In our study, one index (VAS at 6 months) remained significantly different between the two groups, suggesting that treatment with BARI could achieve greater pain reduction than TOFA treatment. JAK1 and JAK2 inhibitors also have antinociceptive effects that are independent of at least certain aspects of the inflammatory process [27]. The inactivation of the JAK2-dependent cytokine granulocyte-macrophage colony-stimulating factor might be a possible mechanism of action of JAK1 and JAK2 inhibitors, which may be associated with pain relief [28]. Another possible mechanism is inhibition of the signaling pathways related to the JAK2-dependent signal transducer and activator of transcription 3, which may be involved in neuropathic pain [29]. In Fautrel's study, no significant difference in pain relief was observed between treatment with 4 mg of BARI and 5 mg of TOFA (two times per day) [30]. Our study showed that there were no significant differences in the primary and secondary end points of clinical outcome between the two groups, including the rate of DAS28-CRP LDA achievement, the rate of DAS28-CRP remission, TJC, SJC, DAS28-CRP, ESR, CRP, and the level of DAS28-CRP at 1 month and 6 months. Nevertheless, our results are different from those in a Japanese study [26]. They found that the BARI group had a significantly lower CDAI and Simple Disease Activity Index (SDAI) as well as a significantly higher rate of CDAI remission, rate of SDAI remission, and SDAI-LDA achievement at 24 weeks, indicating better clinical outcomes in the BARI-treated RA patients.

In a Japanese study [26], the patients in the TOFA group who received more bDMARDs were more likely to develop drug resistance which is defined as patients with

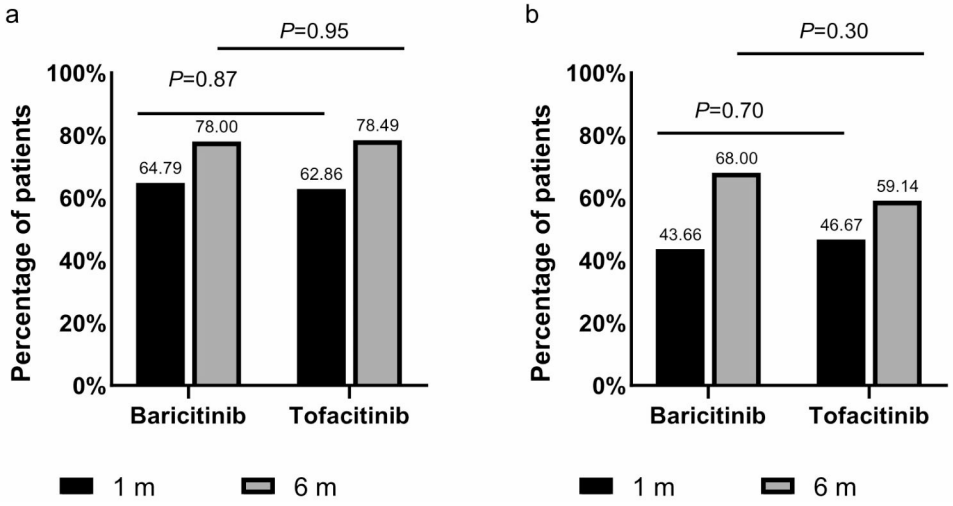

Fig. 2 Comparison of the rates of disease activity score in 28 joints, C-reactive protein (DAS28-CRP) remission (a) and DAS28-CRP-low disease activity (LDA) achievement (b) between the two groups after 1 month and 6 months of treatment. Numbers represent the percentages of all patients (%)

Table 3 Identification of the factors contributing to LDA achievement after baricitinib or tofacitinib treatment

	Baricitinib		**Multivariate analysis**		**Tofacitinib**		**Multivariate analysis**	
	Univariate analysis				**Univariate analysis**			
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Age	1.00–1.11	0.04	1.01–1.17	0.04	0.96–1.04	0.94		
Sex	#				#			
Disease duration	0.97–1.00	0.08			0.99–1.01	0.87		
WBC	0.42–0.95	0.03	0.26–5.21	0.83	0.63–1.03	0.08		
NEU	0.38–0.90	0.02	0.09–1.94	0.27	0.51–0.91	0.008	0.54–1.08	0.13
LYM	0.43–6.27	0.47			0.88–6.62	0.09		
HB	0.95–1.06	0.80			#			
PLT	0.98–1.00	0.015	0.98–1.00	0.10	0.99–1.00	0.09		
ESR (mm/h)	#				0.93–0.98	0.001	0.93–0.99	0.01
RF (IU/mL)	0.98–1.00	0.14			0.99–1.00	0.13		

#Due to *P*-value being < 0.05 in the Hosmer–Lemeshow test, logistic regression analysis was not performed

LDA: low disease activity, WBC: white blood cell, NEU: neutrophil, LYM: lymphocyte, HGB: hemoglobin, PLT: blood platelet, and RF: rheumatoid arthritis

high disease activity at baseline and without achievement of LDA after drug introduction at week 24. However, in the BARI group, none of the factors was found to be associated with drug resistance. In our study, an older baseline age was found to be associated with a greater achievement of LDA in the BARI group, while a low baseline ESR level was more likely to achieve LDA in the TOFA group. Our recent findings present an innovative discovery. Elderly patients might benefit more from using BARI, since they appear to be more sensitive to the inhibition of JAK1 and JAK2, which aids in achieving LDA with BARI. However, further research is required in this area. Additionally, patients with lower ESR levels might be better candidates for TOFA treatment. A study [31] has indicated a positive correlation between ESR and inflammation levels in biopsies. A lower baseline ESR suggests reduced inflammation, making patients in the TOFA group more likely to achieve LDA. Nevertheless, this hypothesis warrants further investigation.

In our study, the incidence of herpes zoster infection in both treatment groups was similar. The numbers of white blood cells and neutrophils decreased significantly, but ALT/AST increased significantly in both treatment groups, in which adverse events occurred after treatment. In addition, no VTE or tumors occurred in either treatment group. Our results were the same as those in a Japanese study [26]. However, in a Brazilian study, there were two patients who received BARI and then developed deep vein thrombosis [32]. It also has been reported that treatment with JAK inhibitors may increase the risk of VTE [33, 34]. Meanwhile, Cohen et al. summarized a series of experiments for identifying the risk factors of VTE, and their results could not conclude that JAK inhibitors can definitely increase the risk of VTE [35]. Therefore, further study is needed. Moreover, another

Table 4 Safety and laboratory data after baricitinib or tofacitinib treatment (1–6 months)

Variable	Baricitinib (*n* = 74)	Tofacitinib (*n* = 105)	*P*-value
Safety data			
Any adverse event after the start of therapy, *n* (%)	25 (33.8%)	46 (43.8%)	0.18
Adverse event resulted in discontinuation of treatment, *n* (%)	3 (4.1%)	5 (4.8%)	0.82
Infection, *n* (%)	7 (9.5%)	12 (11.4%)	0.67
Herpes zoster, *n* (%)	3 (4.1%)	4 (3.8%)	0.93
Leukopenia	1 (1.4%)	7 (6.7%)	0.09
Increasing CREA	0	3 (2.86%)	0.14
Increasing ALT/AST	10 (13.51%)	15 (14.29%)	0.88
Cancer, *n* (%)	0	0	1.00
Major adverse cardiovascular event, *n* (%)	1 (1.35%)	0	0.23
Venous thromboembolism, *n* (%)	0	0	1.00
Laboratory data—median change from baseline			
WBC ($\times 10^9$/L)	-0.9**	-0.7**	0.55
HGB (g/L)	4.0	6.5*	0.18
PLT ($\times 10^9$/L)	-0.6	-70.7**	0.001
NEU ($\times 10^9$/L)	-1.1**	-0.95**	0.56
LYM ($\times 10^9$/L)	-0.2	-0.12	0.51
AST (U/L)	3.0*	3.0**	0.59
ALT (U/L)	4.0*	4.0**	0.77
CREA (μmol/L)	2.0	4.0	0.11
Glucocorticoid dosage (mg) after 1 month	2(0–4)	0(0–4)	0.21
Glucocorticoid dosage(mg) after 6 months	0(0–2)	0(0–2)	0.71

The data are presented as numbers and percentages of the patients with adverse events

Laboratory values are reported as the median change from baseline at 6 months

*$P \leq 0.05$ for the comparison of the within-group change from baseline

**$P \leq 0.01$ for the comparison of within-group change from baseline

study has found that RA patients are more likely (about 2–3 times) to develop VTE than those without RA [36]. In contrast, no venous thrombosis was observed in our study, which might be due to the short follow-up time.

In our study, there was one patient who had a myocardial infarction in the BARI group. It has been reported that the disease activity in RA patients might be associated with cardiovascular events [37]. The incidence rates of major adverse cardiovascular events and myocardial infarction were 0.5 and 0.2, respectively, in another study [38]. In addition, the most common type of major adverse cardiovascular event among the RA patients who received TOFA was nonfatal myocardial infarction [39]. Also, there was one patient in our study who had chest tightness and pain for one year prior to the treatment with BARI. However, it is not clear whether the disease activity or the BARI treatment was associated with her myocardial infarction. Accordingly, JAK inhibitors are not recommended for RA patients with cardiovascular risk, in accordance with the Federal Drug Administration alert.

In our study, the patients with latent tuberculosis in the both BARI and TOFA groups were treated with one or two types of antituberculosis drugs in combination with JAK inhibitors for 2–3 months. None of these patients developed tuberculosis. A larger sample size may be needed in further studies to confirm the efficacy of the combination therapy in RA patients with latent TB.

Nevertheless, our study still has some limitations that must be addressed. First, only a short-term follow-up period (6 months for BARI and TOFA) was available due to some patients who returned to their local hospitals when their condition was stable. Therefore, it is necessary to extend the observation time to determine the safety of BARI and TOFA in the treatment of RA. Second, radiographic follow-up was not assessed in this study. Finally, the decision and reason for discontinuation (e.g., lack of efficacy or remission) were made and explained by different physicians, and there were no standardized criteria. In spite of these limitations, the effectiveness of both BARI and TOFA was proven in our study, suggesting that both of them may be equally effective.

Overall, this is the largest single-center study to compare the effectiveness of BARI and TOFA in China to date, which showed an equal efficacy of BARI and TOFA in the treatment of RA patients in China. Although the clinical outcome between BARI and TOFA treatment was similar, BARI was better at improving the patient's pain. It should be noted that there might be an additional risk of cardiovascular events when JAK inhibitors are administered to RA patients.

Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BARI	baricitinib
bDMARDs	biological DMARDs
CDAI	Clinical Disease Activity Index
CREA	creatinine
CRP	C-reactive protein
DAS-28	Disease Activity Scale-28
DMARDs	disease-modifying antirheumatic drugs
ESR	erythrocyte sedimentation rate
JAK	Janus kinase
LDA	low disease activity
MTX	methotrexate
RA	rheumatoid arthritis
SJC	swollen joint count
SDAI	Simple Disease Activity Index
TJC	tender joint count
TOFA	tofacitinib
tsDMARDs	targeted synthetic DMARDs
TYK	tyrosine kinase
VAS	visual analogue scale
VTE	venous thromboembolism

Supplementary Information

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Supplementary Material 1

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Authors' contributions
All authors contributed to the study conception and design. In addition, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data and materials in this article are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with a protocol approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University.

Consent for publication
Not applicable.

Competing interests
Xiaoling Liao, Wang Huo, Wen Zeng, Fang Qin, Fei Dong, Wanling Wei, and Ling Lei declare that they have no conflicts of interest.

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