Wiley
Journal of Clinical Pharmacy and Therapeutics
Volume 2024, Article ID 7914586, 8 pages
https://doi.org/10.1155/2024/7914586

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Research Article

Bioequivalence and Safety of Two Formulations of Tofacitinib Citrate Tablets in Healthy Chinese Volunteers under Fasting and Fed Conditions: Randomized, Open-Label, 2-Period, Single-Dose, Crossover Trials

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Received 19 June 2023; Revised 19 March 2024; Accepted 22 March 2024; Published 23 May 2024

Academic Editor: Irina B. Bondareva

Purpose. To evaluate the bioequivalence of two different tofacitinib citrate tablets formulations among healthy Chinese subjects under fasting and fed conditions and to observe the safety of test preparation and reference preparation in healthy subjects. *Method*. This randomized, open-label, 2-period, crossover, bioequivalence study included 64 healthy Chinese subjects (fasting: $n = 32$, fed: $n = 32$). The subjects were assigned to receive a single 5-mg dose of the test or a reference tofacitinib citrate tablets. Blood samples were collected at predose and up to 24 hours after dosing. Area under the plasma concentration time curve from zero to the last measurable concentration ($AUC_{0\text{-}t}$), the area from time zero to infinite ($AUC_{0\text{-}\infty}$), and maximum plasma concentration (C_{max}) were used for bioequivalence assessment. Safety assessment was conducted by vital signs, physical examination, laboratory examination, and 12-lead electrocardiogram during the study, from the time the subject receiving the test drug to the end of the last visit. *Results*. Under fed condition, the 90% CIs of the geometric mean ratios of the test/reference for tofacitinib citrate tablets were 98.40–104.16% for $AUC_{0\text{-}t}$, 89.96–116.70% for C_{max}, and 98.50–104.15% for $AUC_{0\text{-}\infty}$. Under fasting condition, the 90% CIs of the geometric mean ratios of the test/reference for tofacitinib citrate tablets were 93.65–101.60% for $AUC_{0\text{-}t}$, 90.06–109.15% for C_{max}, and 93.88–101.51% for $AUC_{0\text{-}\infty}$. There were no serious events. *Conclusion*. The 90% CI for the geometric mean ratio (test/reference) of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were within the range of 80.00%–125.00%, indicating that the test formulation was equivalent to the reference formulation in healthy Chinese subjects under both fasting and fed conditions. They are similar in terms of safety. This trial is registered with CTR20190366.

1. Introduction

Rheumatoid arthritis (RA) is a complex autoimmune inflammatory disease with systemic sequelae [1] and is a chronic inflammatory autoimmune disease, causing joint swelling, tenderness, and synovial joint destruction, which can lead to serious joint malformation and functional dysfunction, multiple organs and system damage, and even premature death, with a high disability rate [2], seriously affecting the quality of life. As an autoimmune disease, the individual progression of RA patients varies greatly, so there is a lack of a single effective universal treatment drug. Controlling symptoms and preventing joint injury are the focus of treatment. At present, anti-inflammatory drugs, antirheumatic drugs, steroid drugs, biologics, combination therapy, and immune reconstitution are the main categories of drugs used for the treatment of RA in clinical practice. In common drug treatment plans, disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid drugs, and other relieving drugs are mainly used to alleviate patient pain and alleviate various symptoms. Conventional synthetic

DMARDs (csDMARDs; e.g., methotrexate and sulfasalazine) and biological DMARDs (bDMARDs; TNF inhibitors and IL-6 inhibitors) have been the mainstay of disease management in patients with RA [3]. However, despite various treatment modalities and the recommended treat-to-target approach for disease management, many patients still do not achieve therapeutic targets, indicating an unmet need for additional therapies [3]. In recent years, the research and application of targeted small molecule drugs have become one of the major advances in RA treatment.

Tofacitinib is a new oral small molecule JAK3 inhibitor, which has been used to treat RA patients and has achieved good clinical effects [4]. In November 2012, it was approved by the US FDA for the first time. It is suitable for the treatment of adult patients with moderate to severe active RA who cannot tolerate methotrexate or have insufficient response to methotrexate [5]. It can be used alone or in combination with methotrexate or other nonbiological antirheumatic drugs [5]. It was approved in Japan on March 25, 2013, for the treatment of adult patients with RA who do not respond well to existing therapies [6]. In 2016, European League Against Rheumatism (EULAR) suggested that tofacitinib should be listed as related to TNF-α biological agents such as inhibitors and IL-6 inhibitors that have a similar status as therapeutic drugs. In March 2017, it was approved in Europe to be combined with methotrexate in the treatment of adult patients with moderate to severe RA who have insufficient efficacy or cannot tolerate one or more DMARDs. Tofacitinib can be used as a single agent when methotrexate is not applicable or patients cannot tolerate methotrexate [7]. Approved in China in March 2017, it is applicable to adult patients with moderate to severe active RA whose efficacy of methotrexate is insufficient or intolerable. It can be used in combination with methotrexate or other nonbiological antirheumatic drugs to improve the condition [8]. In 2017, the new indication psoriatic arthritis was approved [9]. It is now available worldwide. But the expensive treatment cost limits the clinical application of tofacitinib to a certain extent, when only the original research drug of tofacitinib citrate tablets are available for sale in the domestic market. The research of generic for tofacitinib will save treatment costs for patients and generate good social and economic benefits.

The aim of this study was to evaluate the bioequivalence between a preparation of tofacitinib citrate tablets developed by Jiangxi Qingfeng Pharmaceutical Co. Ltd. and the reference preparation of tofacitinib citrate tablets (Xeljanz®) developed by Pfizer Manufacturing Deutschland Gmbh in healthy Chinese volunteers and observed the safety of both.

2. Subjects and Methods

2.1. Ethical Considerations. The protocol and the informed consent form were approved by the Ethics Committee of Shanghai Pudong New Area People's hospital, China, and registered with http://www.chinadrugtrials.org.cn/ (CTR20190366). The study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki. All subjects signed informed consent before participation.

2.2. Subjects. Sixty-four healthy subjects were enrolled in this study. Subjects were male or female healthy Chinese and aged 18 years or older with the body mass index in the range between 19 and 26 kg/m^2. All subjects got complete medical test and examination prior to receiving the study medication, including medical history, physical examination, vital signs, 12 lead electrocardiogram, chest radiograph, urine drug screening, alcohol breath test, nicotine test, and clinical laboratory test. Sexually active subjects were required to use protocol-specified effective contraceptive methods during study drug administration and 3 months after study drug administration.

Subjects were excluded from the study if they met any of the following criteria: (1) any clinically significant physical disorders; (2) history of cardiovascular, liver, kidney, endocrine, digestive system, blood system, mental illness, and nervous disease; (3) a personal or family history of inherited immunodeficiency; (4) clinically significant infection within 3 months; (5) drug abuse and drug dependence; (6) history of malignancy or malignancy; (7) have received live or attenuated live vaccines during the 6 weeks prior to screening or are scheduled to receive these vaccines during treatment or within 6 weeks after the last study drug administration; (8) smoking, alcohol, or drug abuse; (9) allergic constitution and allergy to tofacitinib or its excipients; (10) blood donation or participation in clinical research during the past 3 months; (11) cannot follow a uniform diet; (12) difficulty in blood collection, patients who cannot tolerate venipuncture, and people with a history of needle sickness and blood sickness; (13) excessive intake of tea, coffee, or other caffeinated beverage; (14) intake of drinks or foods rich in caffeine or grapefruit or ingesting any beverage or food rich in caffeine or grapefruit within 48 hours before the first administration of the study; (15) ingestion of drugs within 30 days before study drug administration; and (16) pregnancy or lactation.

2.3. Drugs and Reagents. The test preparation, a tofacitinib citrate tablet, 5 mg (batch no: 20181009), was provided by Jiangxi Qingfeng Pharmaceutical Co. Ltd. and the reference preparation, tofacitinib citrate tablet, 5 mg (batch no: T33184), was purchased from Pfizer Manufacturing Deutschland GmbH; both drugs were stored in not more than 30°C storage.

2.4. Study Design. This study consists of two independent clinical trials (the fasting bioequivalence study and fed bioequivalence study); both of them were open-label, randomized, single-dose, two-period, crossover, bioequivalence studies including 32 healthy subjects. The same subjects could participate in only one of the trials. According to the bioequivalence trail data and relevant literature, the intraindividual variation (intra CV %) of tofacitinib AUC was 5–7% and the intraindividual variation of C_{max} was 12%~25% [10]. This trail was a randomized, two-period, two-sequence single dose crossover study, with pharmacokinetic parameters (AUC, C_{max}) as the main analysis indicators. The sample size was calculated by SAS 9.4 software, assuming one side α was set at 0.05, the power (1-β) was set at 0.8, intra CV was 25%, the geometric mean ratio

(GMR) was set as 0.95, and bioequivalence interval was 80.00%~125.00%, with a sample size of 27. Considering the dropout of the subjects, 32 subjects need to be enrolled in both fasting and fed condition trials.

2.5. Fasting Bioequivalence Study. 32 subjects were hospitalized in the study site the night before drug administration and were randomized into the TR group or the RT group, with 16 subjects in each group. The sequence of subjects receiving the test or reference preparation in the study will be determined by the random number obtained from the randomization table. SAS software (version 9.4) is used to set the number of random seeds, and the block randomization method is used to randomly assign the enrollment number to the TR group and the RT group in a 1 : 1 ratio to generate a randomization table of subjects. The randomization data are reproducible. All doses of the study drug were administered in the fasted state (following at least 10 hours overnight fast). The TR group took the test drug in the first period and the reference drug in the second period. The RT group took the reference drug for the first period and the test drug for the second period. The washout period was 7 days. Each oral dose was administered with 240 mL of room-temperature water.

2.6. Fed Bioequivalence Study. This study was conducted with another 32 subjects. The procedure was similar to the fasting study except that following a high-fat (providing about 50% of the calories in food), high-calorie (about 800–1000 kilocalorie) diet. Among them, protein provides about 150 calories, carbohydrate about 250 calories, and fat about 500–600 calories before administering test and reference tablets.

2.7. Blood Sampling. Under fasting condition, the venous blood samples (3 mL) were collected at 0 min, 10 min, 20 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 24 h after dosing. Under fed condition, blood samples (3 mL) were collected at 0 min, 15 min, 30 min, 45 min, 1 h, 1.25 h, 1.5 h, 1.75 h, 2 h, 2.5 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 24 h after dosing. Blood samples were centrifuged immediately at 1700 g and 4°C for 10 minutes to obtain the plasma and stored at −80°C until analysis.

2.8. Safety Assessment. Subjects were monitored throughout the study for safety signals. Safety assessments consisted of monitoring and recording adverse events (AEs). Safety assessment was conducted by vital signs, physical examination, laboratory examination, and 12-lead electrocardiogram. AEs included serious AEs and nonserious AEs, including the time from the subject taking the test or reference drug to the end of the last visit.

2.9. Analytical Methods. The plasma concentration of tofacitinib citrate was analyzed by the Shimadzu LC-20AD system (Kyoto, Japan) coupled with an Applied Biosystems/MDSSciex (TRIPLE QUAD 6500, Tronto, Ontario, Canada). Chromatography was performed on a AQUASIL C18 (Thermofisher, Waltham, MA, USA) (2.1×100 mm, 3 μm), using a mobile phase of water containing 2 mm ammonium acetate (solvent A) and methanol containing 50% acetonitrile (solvent B) at a flow rate of 0.4 mL·min^{-1}. The total LC analysis time per injection was 5.0 min with gradient elution as follows: 35–45% B at 0–2.4 min, 45–95% B at 2.4–2.5 min, 95% B at 2.5–3.6 min, 95–35% B at 3.6–3.7 min, and 35% B at 3.7–5.0 min. The column temperature was maintained at 50°C and a total of 15 μL sample volume was injected into the system. The linear range of the calibration curve for tofacitinib was 0.200–100 ng/mL, with a lower limit of quantitation (LLOQ) of 0.200 ng/mL.

The multiple reaction monitoring (MRM) transition was carried out at m/z 313.2–173.2 and m/z 316.2–176.2 for tofacitinib and tofacitinib-d3 (IS), respectively, in the positive ionization mode. The optimal instrument parameters of the mass spectrometer were as follows: curtain gas (CUR), 30 psi; collision gas (CAD), 6 units; temperature (TEM), 550°C; ion source Gas 1 (GS1), 45 psi; ionspray voltage, 5000 V; and ion source Gas 2 (GS2), 55 psi. The dwell time, declustering potential (DP), and collision energy (CE) were 20 msec, 90 V, and 90 V for tofacitinib and IS.

2.10. Pharmacokinetic and Statistical Analysis. C_{max} and T_{max} were obtained directly from the experimental data. AUC from time zero extrapolated to infinity ($AUC_{0\sim\infty}$) was determined by summing the areas from time zero to the time of the last quantifiable concentration ($AUC_{0\sim t}$) by trapezoidal and logtrapezoidal methods and the extrapolated area. The extrapolated area was determined by dividing the last detectable concentration by the slope of the terminal log-linear phase. Pharmacokinetic parameters were estimated using the noncompartment method. Pharmacokinetic parameters were calculated by Phoenix WinNonlin software (version 6.4), and statistical analysis was performed by SAS 9.4 software. Logarithmically transformed pharmacokinetic parameters including C_{max}, $AUC_{0\sim t}$, and $AUC_{0\sim\infty}$were analyzed by analysis of variance (ANOVA) using a linear mixed-effects model. In the analysis of variance model, sequence, formulation, and period were used as fixed effects, and the subjects (within sequence) were used as random effect. Descriptive statistics for continuous variables are presented using the mean ± standard deviation unless otherwise specified. According to FDA guidelines, the accepted 90% confidence interval (CI) range of the ratio test/reference for these parameters for assuming bioequivalence was 80.00–125.00%.

3. Results

3.1. Demographic Characteristics. A total of 64 healthy adult subjects were enrolled in this study, 32 each in the fasting and fed condition. The Chi-square test was used for gender distribution and the Student's *t*-test was used for age, weight, height, and BMI mean value comparisons by SPSS software (version 26). The demographic details (mean ± SD) and *P*

Table 1: Demographic characteristics of subjects.

Demographics	Fasting ($n = 31$[a])	Fed ($n = 31$[b])	P value*
Male/female, n	22/9	24/7	0.562
Age, y	30.74 ± 6.91	29.35 ± 6.00	0.401
Weight, kg	62.02 ± 6.22	62.66 ± 5.99	0.681
Height, cm	165.94 ± 8.03	166.84 ± 6.35	0.626
Body mass index (BMI) kg/m^2	22.52 ± 1.75	22.51 ± 1.62	0.981

Data were presented as the mean ± SD. [a]One subject withdrew from the clinical trial after collecting blank blood and before administration. [b]One subject withdrew from the clinical trial before collecting blank blood. *P value means the probability value.

value are presented in Table 1. There is no significant difference in demographic characteristics between fasting and fed conditions.

3.2. Pharmacokinetic Parameters and Bioequivalence. Tofacitinib citrate was absorbed after a single oral dose administration, with a median T_{max} of 0.75 h under fasting conditions and 2.8 h under fed conditions. The main pharmacokinetic parameters of tofacitinib citrate under fasting and fed conditions are summarized in Table 2. The mean plasma concentration-time and semilogarithmic curves of tofacitinib citrate after a single dose under fasting and fed conditions are presented in Figure 1. The geometric mean ratio (90% CI) of the test/reference tables for tofacitinib citrate under fasting and fed is summarized in Tables 3 and 4. The results of ANOVA of two formulations of tofacitinib citrate tablets both under fasting and fed conditions are shown in Table 5. There were no administration sequence, period, and formulation factor effects under both fasting and fed conditions ($P > 0.05$). As is shown in Tables 3 and 4, the 90% CI for the geometric mean ratio (test/reference) of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were within the range of 80.00%–125.00%, indicating that the test formulation was equivalent to the reference formulation in healthy Chinese subjects under both fasting and fed conditions.

3.3. Safety Assessment. Among the 62 subjects, 9 (29%) subjects experienced 10 mild AEs in fasting condition. 7 (22.6%) subjects experienced 8 mild AEs in the fed condition. All participants who reported AEs are summarized in Table 6. All adverse events had a severity of 1 or 2. No subjects dropped out of the trial due to serious AEs, and no serious AEs occurred. One subject dropped out of the trial due to hypotension, but it was not a serious AE. The subject's blood pressure returned to normal levels in 1.5 hours when hypotension occurred and no other serious properties occurred. Except for one subject lost visits with high uric acid, the outcomes of all other adverse events were cured or improved.

4. Discussion

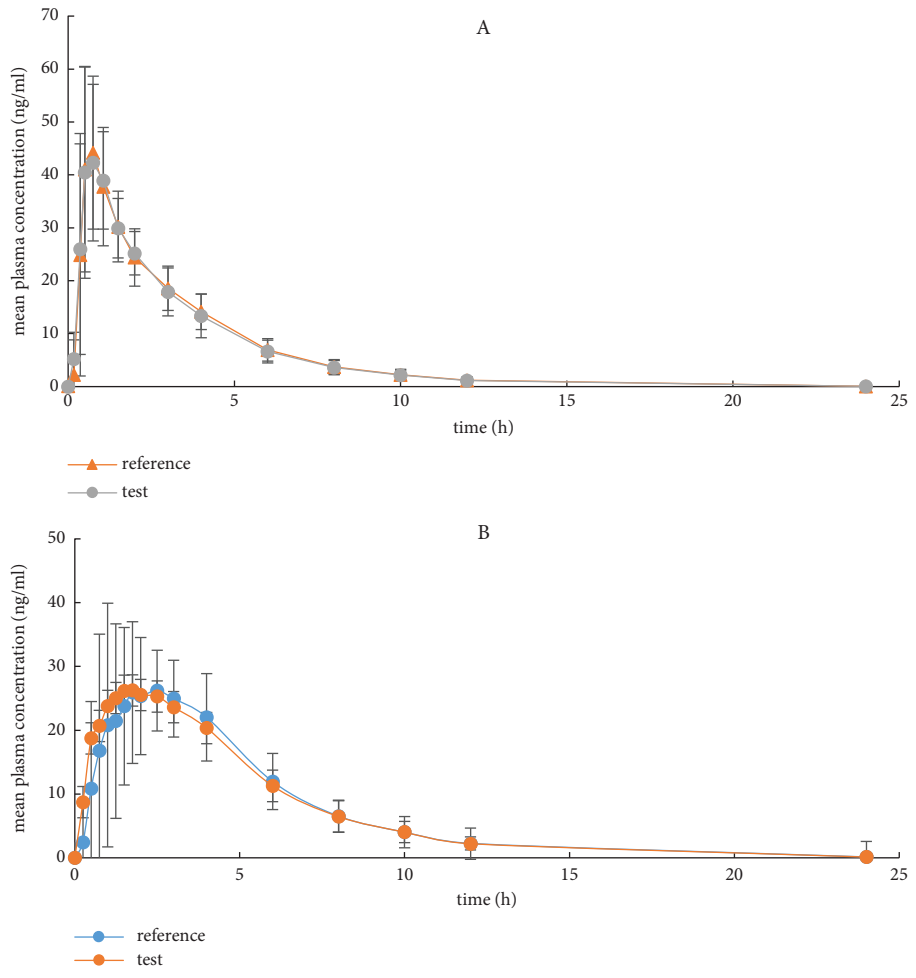
This clinical trial aimed to show the pharmacokinetic bioequivalence of a new tofacitinib citrate tablet, manufactured by Jiangxi Qingfeng Pharmaceutical Co., Ltd., (Jiangxi, China), with the reference product. Food can affect the bioequivalence of the test and reference preparations. According to the original research instruction of tofacitinib citrate tablets in reference to the FDA guidelines for bioequivalence studies, the Technical Guidelines for the Bioequivalence Study of Generic Chemical Drugs with Pharmacokinetics parameters as the Final Evaluation Index, it is recommended that this product be evaluated on fasting and fed conditions in healthy volunteers. Table 2 indicated that the food had a minimal impact on the pharmacokinetics of tofacitinib citrate. Under fed conditions, the C_{max} of tofacitinib citrate decreased by approximately 25%, $AUC_{0\text{-}\infty}$ of tofacitinib citrate increased by approximately 10%, T_{max} of tofacitinib citrate was delayed 0.75 h, and $t_{1/2}$ of tofacitinib citrate was increased from 2.4 h to 2.8 h. The possible reason for these differences is that high-fat food can reduce the rate of gastric emptying and prolong the retention time of drugs in the stomach, which increases the proportion of drugs dissolved before entering the small intestine, thus delaying the rate of drug absorption and prolonging the onset time of drugs. A high-fat high-calorie meal is recommended by the US Food and Drug Administration as the test meal in food effect studies because it will exert the largest effects on gastrointestinal physiology and therefore may have the greatest impact on drug absorption and disposition. In a high-fat high-calorie meal, fat contributes to approximately 50% of the meal's total caloric content. Generally, high-fat food can significantly retard gastric emptying compared with a low-fat diet [11].

Previous studies demonstrated that the pharmacokinetic profile of tofacitinib is characterized by rapid absorption, T_{max} are within 0.5–1.5 h, and $t_{1/2}$ are within 2–3.5 h [12, 13]. In our study trial, the values of C_{max} and T_{max} are similar to previous studies and food affection on exposure of tofacitinib. The value of C_{max} in average decreased by 25.90%, and it is similar to previous studies [12–14]. In our study, the value of AUC_{0-t} and $AUC_{0-\infty}$ was in average increased by 16.57% and 14.08%, respectively, after a high-fat diet in the fasted state, which is similar to the previous study [13]. However, another study showed that a high-diet had no effect on AUC_{0-t} and $AUC_{0-\infty}$ [14]. In our study trial, the value of $t_{1/2}$ was in average delayed 0.45 h after a high-fat diet, and it is different to the previous studies [12, 14]; the previous study showed that there was no significant difference in the value of $t_{1/2}$. But in another study [13], it was also proven that a high-fat diet can extend $t_{1/2}$ about 0.2 h. Overall, a high-fat diet can affect the pharmacokinetic behavior of tofacitinib. A high-fat diet can delay the absorption of tofacitinib and result in a significant decrease in C_{max}, as well as a delayed in C_{max} and an extension of $t_{1/2}$.

Table 2: Main pharmacokinetic parameters after a single 5 mg dose of test and reference tofacitinib citrate tablets under fasting and fed conditions.

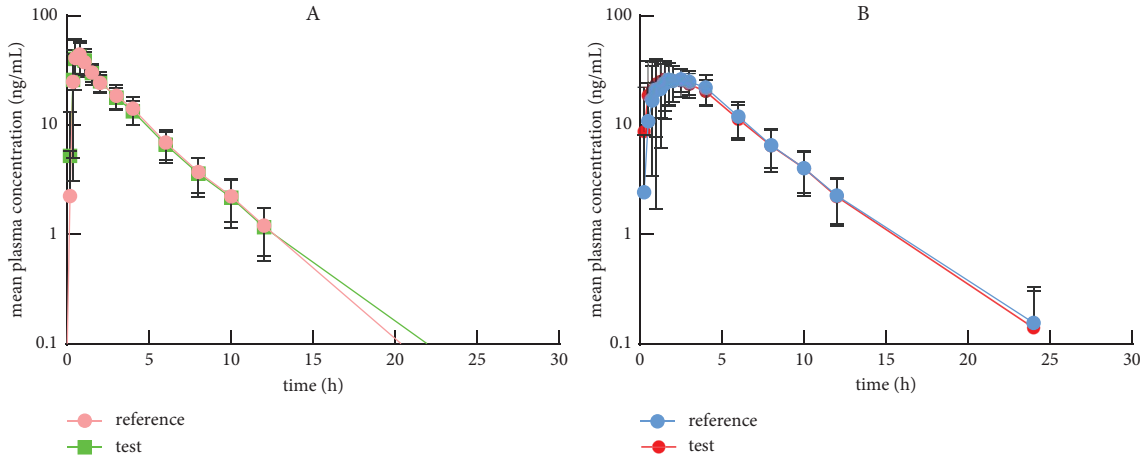
Parameters	Fasting		Fed	
	Test ($N = 30$[a])	Reference ($N = 31$[b])	Test ($N = 30$[c])	Reference ($N = 30$[c])
AUC_{0-t} (ng·h/mL)	135.77 ± 31.63	137.82 ± 23.33	158.43 ± 29.90	157.42 ± 34.39
$AUC_{0-\infty}$ (ng·h/mL)	139.00 ± 32.12	141.07 ± 23.84	161.86 ± 28.90	160.73 ± 33.62
C_{max} (ng/mL)	50.49 ± 13.67	50.83 ± 13.48	38.07 ± 10.94	37.01 ± 10.56
$^{\#}t_{1/2}$ (h)	2.40 ± 0.52	2.43 ± 0.51	2.84 ± 0.61	2.89 ± 0.63
*kel (1/h)	0.30 ± 0.05	0.30 ± 0.05	0.26 ± 0.06	0.25 ± 0.06
$^{*}T_{max}$ (h)	0.75 (0.33, 2.00)	0.75 (0.33, 3.00)	1.5 (0.5, 4)	2.25 (0.75, 4)

Data were presented as the mean ± SD. [a]One subject withdrew from the clinical trial after collecting blank blood and before administration in period 1 and one subject vomited drugs intentionally after medication in period 2 but completed the first period of drug administration which took reference drug and PK blood collection. [b]One subject withdrew from the clinical trial after collecting blank blood and before administration in period 1. [c]One subject withdrew from the study before collecting blank blood in period 1, and one subject dropped out of the trial due to adverse events after the first period of medication and 4 blood samples were collected. $^{\#}t_{1/2}$ is the elimination half-life. *kel is the elimination rate constant. $^{*}T_{max}$ is expressed as the median (range).



(a)

Figure 1: Continued.



(b)

Figure 1: Means (±standard deviation) plasma concentration-time profiles of tofacitinib citrate tablets under fasting (A) and fed (B) conditions after an oral dose of 5 mg test tablet and reference tablet. (a) Mean plasma concentration-time curves. (b) Semilogarithmic mean plasma concentration-time curves.

Table 3: Bioequivalence between the test (*T*) and reference (*R*) tofacitinib citrate tablets in healthy Chinese subjects under fasting condition.

Parameters	Number	Geometric means and ratios			90% CI (%)	CV (%)
		T	*R*	*T*/*R* (%)		
AUC_{0-t} (ng·h/mL)	31	132.21	135.54	97.55	(93.65, 101.60)	9.3
C_{max} (ng/mL)	31	48.53	48.95	99.14	(90.06, 109.15)	22.2
$AUC_{0-\infty}$ (ng·h/mL)	31	135.41	138.71	97.62	(93.88, 101.51)	8.9

*: CV (%): within-subject coefficient of variation. CI: confidence interval.

Table 4: Bioequivalence between the test (*T*) and reference (*R*) tofacitinib citrate tablets in healthy Chinese subjects under fed condition.

Parameters	Number	Geometric means and ratios			90% CI (%)	CV (%)
		T	*R*	*T*/*R* (%)		
AUC_{0-t} (ng·h/mL)	30	155.73	153.82	101.24	(98.4, 104.16)	6.5
C_{max} (ng/mL)	30	36.60	35.72	102.46	(89.96, 116.70)	30.3
$AUC_{0-\infty}$ (ng·h/mL)	30	159.39	157.36	101.28	(98.5, 104.15)	6.4

*: CV (%): within-subject coefficient of variation. CI: confidence interval.

Table 5: Effects of ANOVA test of two preparations under fasting and fed conditions.

Condition	Parameters	$LnAUC_{0-t}$	LnC_{max}	$LnAUC_{0\sim\infty}$
Fasting	Sequence	0.1233	0.1111	0.1185
	Formulation	0.3087	0.8802	0.3037
	Period	0.9138	0.7996	0.9412
Fed	Sequence	0.1762	0.7520	0.1730
	Formulation	0.4666	0.7530	0.4431
	Period	0.3549	0.7316	0.3081

Based on the information of the original research drug [15], the coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. T_{max} was extended by approximately 1 hour. That is why there was a difference in the sampling schedule between fasting and fed trials.

In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5′-diphospho-glucuronosyltransferases (UGTs). Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19 [15]. Therefore, fasting on ingredients such as grapefruit, smoking and drinking were prohibited during the trail.

Table 6: Adverse events in the subjects while taking the test or reference formulation of tofacitinib citrate tablets under fasting and fed conditions.

Adverse events	Fasting n (%)		Fed n (%)	
	Test ($N = 31$[a])	Reference ($N = 31$[a])	Test ($N = 31$[b])	Reference ($N = 30$[c])
Serum uric acid higher	2 (6.45)	4 (12.9)	1 (3.23)	0
High white blood cell count in urine	0	1 (3.23)	0	0
Catarrh tympanitis	1 (3.23)	0	0	0
Triglycerides high	1 (3.23)	0	0	0
Low neutrophil count	0	1 (3.23)	0	0
The electrocardiogram ST-T changes	0	0	0	1 (3.33)
Ventricular pre-excitation type A	0	0	1 (3.23)	0
Hypotension	0	0	2 (6.45)	0
Total bilirubin in serum increased	0	0	1 (3.23)	0
Conjugated bilirubin in serum increased	0	0	1 (3.23)	0
Urine occult blood	0	0	0	1 (3.33)

n: number of adverse events. N: the number of subjects at risk. [a]One subject voluntarily withdrew from the trial after the collection of blank blood samples in the first period. [b]One subject voluntarily withdrew from the trial before the collection of blank blood samples in the first period. [c]One subject withdrew informed consent after completing the first period of drug administration who took the test drug and PK blood collection.

According to standard bioequivalence guidelines [16–18], the basis for bioequivalence is the 90% CI for the geometric mean ratio (test/reference) of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were within the range of 80.00%–125.00%. In this study, the 90% CI of the test/reference ratios for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were within the acceptance range for bioequivalence under fasting and fed conditions. That is, the two formulations are considered to be bioequivalent.

5. Conclusion

Based on the pharmacokinetic and statistical results of the study, the test tofacitinib citrate tablet is bioequivalent to the reference tofacitinib citrate tablet under both fasting and fed conditions. They are similar in terms of safety.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yanping Liu wrote the paper manuscript and was the clinical trial drug administrator; Yuping Ning, Yan Shi, and Juanmin Tao were Clinical Research Nurse and were responsible for blood collection; Man Xu designed the clinical trial protocol; Yafen Dong performed reviewing and editing; Jun Ma and Yan Qiu organized the implementation. Yuping Ning and Yan Shi contributed equally to this work.

Acknowledgments

We gratefully acknowledge the subjects who participated in the study and the staff of the clinical trial units who carried out the study. We sincerely thank Shanghai Xihua Testing Technology Service Co., Ltd. for their support in analyzing the samples. This research was funded by the Academic Leaders Training Program of Pudong Health Bureau of Shanghai (Grant no. PWRd2021-01) and the Outstanding Leaders Training Program of Pudong Health Bureau of Shanghai (Grant no. PWRl2020-08).

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