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Original Article

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Bioequivalence of the pharmacokinetics between tofacitinib aspartate and tofacitinib citrate in healthy subjects

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ABSTRACT

Tofacitinib is an oral disease-modifying anti-rheumatic drug to selectively inhibit Janus kinases. Tofacitinib is a representative small molecule inhibitor that is used to treat many diseases including rheumatoid arthritis and various autoimmune conditions. Unlike biological agents, tofacitinib has several advantages, including the ability to be administered orally and a short half-life. This study aimed to evaluate the bioequivalence of the pharmacokinetics (PK) between tofacitinib aspartate 7.13 mg (test formulation) and tofacitinib citrate 8.08 mg (reference formulation; Xeljanz®) in healthy subjects. A randomized, open-label, single-dose, 2-sequence, 2-period, 2-treatment crossover trial was conducted in 41 healthy volunteers. A total of 5 mg of tofacitinib as the test or the reference formulation was administered, and serial blood samples were collected up to 14 hours after dosing for PK analyses. The plasma concentration of tofacitinib was determined by ultra-performance liquid chromatography-tandem mass spectrometry. A non-compartmental analysis was used to estimate the PK parameters. A total of 35 subjects completed the study and the study drug was well-tolerated. The mean maximum concentration (C_{max}) and area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}) for the test formulation were 52.67 ng/mL and 133.86 ng•h/mL, respectively, and 50.61 ng/mL and 133.49 h•ng/mL for the reference formulation, respectively. The geometric mean ratios (90% confidence intervals) of the C_{max} and AUC_{last} between the 2 formulations were 1.041 (0.944–1.148) and 1.003 (0.968–1.039), respectively. Tofacitinib aspartate exhibited bioequivalent PK profiles to those of the reference formulation.

Trial Registration: ClinicalTrials.gov Identifier: NCT04278391

Keywords: Bioequivalence; Pharmacokinetics; Tofacitinib

INTRODUCTION

Rheumatoid arthritis (RA) is a prevalent chronic autoimmune disease that affects joints throughout the body. RA symptoms usually begin in the small joints of the hands and feet before proceeding to the large joints. RA causes inflammation of the synovium that damages to the joints and bones, resulting in their deformation. The patient experiences physical

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disability and deterioration in their quality of life due to chronic joint pain and deformation of the joint over time [1]. The goals of treatment are to reduce pain, decrease inflammation, and slow the progression of the disease, thereby reducing physical disability and improving the patient's quality of life [2]. Patients diagnosed with RA start treatment with conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. If there is not a sufficient therapeutic response to the conventional DMRADs, the patient is usually treated with biologic DMARDs or Janus kinase (JAK) inhibitors [3,4]. The available biologic DMARDs include a selective co-stimulation modulator (abatacept), an interleukin-6 inhibitor (tocilizumab), and several tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, golimumab, and certolizumab). Biologic DMARDs require intravenous or subcutaneous injection, making it difficult to administer them to patients [5].

Tofacitinib, a small-molecular drug, has several advantages over biologic DMARDs, including its short half-life and the ability to be taken orally. It has been approved as a single treatment or for use in combination therapy with DMARDs in patients with moderate to severe active RA who do not respond to methotrexate [6,7]. Tofacitinib is known to block the activity of inflammatory cytokines by blocking JAK-1 and JAK-3 signaling [8]. Several clinical trials have shown that tofacitinib is effective compared to placebo when administered to patients who have not received affective treatment with other anti-rheumatoid or biological agents [9-11]. Therefore, tofacitinib may be preferable to expensive biologics that require injection or conventional treatments that only relieve pain. On this basis, several companies have recently expanded the indications of tofacitinib to include active ulcerative colitis and psoriasis arthritis [12,13]. The recommended dose of tofacitinib is 5 mg twice a day [14]. The dose may be increased depending on the patient's clinical condition.

Daewoong Pharmaceutical Co., Ltd. (Seoul, Korea) developed new tablets containing tofacitinib aspartate. This new formulation has been expected to expand its position in the market for RA drugs. For use as an alternative without concerns regarding differences in pharmacokinetics (PK), bioequivalence must be verified between 2 formulations. This is particularly important, since the salt may alter the rate of absorption. The purpose of this study was to evaluate the PK bioequivalence between tofacitinib aspartate 7.13 mg (test formulation, tofacitinib 5 mg) and tofacitinib citrate 8.08 mg (reference formulation, tofacitinib 5 mg; Xeljanz®) in healthy subjects.

METHODS

Subjects and study design

Eligible subjects were Korean male volunteers between 19 and 45 years of age. Volunteers were judged to be in good health based on their previous medical history, physical examination, laboratory tests, vital signs, 12-lead electrocardiogram (ECG) test, and chest X-ray examination. Subjects were excluded if these criteria indicated a history of clinically significant diseases or known hypersensitivity to tofacitinib. Subjects were also excluded if they could not abstain from drinking alcohol, smoking, or drug use throughout the study. Subjects were also excluded if they could not stop taking previously prescribed medications during the screening period.

This was a randomized, open-label, single-dose, 2-sequence, 2-period, 2-treatment crossover study. The test formulation was tofacitinib aspartate 7.13 mg (Tofacitinib 5 mg) manufactured

by Daewoong Pharmaceutical Co., Ltd., Seoul, Republic of Korea. The reference formulation was Xeljanz® 5 mg tablet, containing tofacitinib citrate 8.078 mg (Tofacitinib 5 mg), manufactured by Pfizer Pharmaceuticals Korea, Ltd., Seoul, Republic of Korea. Eligible subjects were randomly assigned into 2 sequence groups, and each group received a single dose each of the test and the reference formulations in reverse order. Therefore, one sequence group was given the test formulation in period 1 followed by the reference in period 2, while the other sequence group which was given the reference formulation in period 1 followed by the test formulation in period 2. The intra-subject variability of the main PK parameters of tofacitinib was reported as up to 25% [11]. When test/reference geometric mean ratios were assumed 0.95 to 1.05, the minimal number of subjects that could identify a variance of ≥ 20%, if any, in the pharmacokinetic profile of Tofacitinib at a significance level (α) of 0.05 with a power (1-β) of 80% was 14. Considering the possible dropouts rate of 30% during the study, the planned sample size was 40 subjects in total, 20 subjects per group. There was a 7-days washout period between period 1 and period, which more than 5 times the terminal half-life ($t_{1/2}$) of tofacitinib (3.2 ± 0.8 hours) [15]. During each period, the subjects were administered either the test or reference drug with 150 mL of water in the fasted state. Blood samples were collected at the following time points: 0 (pre-dosing), 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 14 hours after dosing.

The study protocol was approved by the Institutional Review Board of CHA Bundang Medical Center (Seongnam, Korea). The study was conducted at the Clinical Trials Center of CHA Bundang Medical Center in compliance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and local laws and regulations. All volunteers were provided detailed written and verbal information about the study and were asked to provide written informed consent before being screened for eligibility. This study was registered on ClinicalTrials.gov (http://clinicaltrials.gov, Identifier: NCT04278391).

Determining the plasma tofacitinib concentration

Blood samples were immediately transferred to K2 EDTA tubes. Plasma was separated by centrifugation at 3,000 rpm for 10 minutes at ≤ 4 °C and stored below −70 °C until analysis.

The plasma concentration of tofacitinib was determined by ultra-performance liquid chromatography (UPLC, Waters ACQUITY UPLC™ System, Waters Co., Milford, MA, USA)-tandem mass spectrometry (MS/MS, Waters Xevo™ TQ MS, Waters Co.). Stock standard solution (100 μg/mL of tofacitinib in 50% methanol) was used as a reference standard. The samples were analyzed on a Waters ACQUITY UPLC® BEH C18 column (1.7 μm, 2.1 mm ID × 50 mm L; Waters Co.) using acetonitrile and 0.1% ammonium acetate in distilled water (80:20, v/v) as the mobile phase within 0.4 mL/min.

This method was validated over the concentration range of 0.5–250 ng/mL for tofacitinib. The lower limit of quantitation (LLOQ) was 0.5 ng/mL. The intra- and inter-batch precision (coefficient of variance [CV]) and accuracy ranged from 1.6–6.4 and 97.9–103.0%, respectively. All validation results were in compliance with the EMA Guideline on Bioanalytical Method Validation [16].

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Pharmacokinetic analysis

Pharmacokinetic analysis was performed by non-compartmental methods using Phoenix WinNonlin software version 8.0 (Certara Co., Princeton, NJ, USA). Maximum plasma concentration after dose (C_{max}), and time to C_{max} (T_{max}) were determined directly from the concentration-time data. The elimination rate constant (k_e) was estimated by performing a linear regression analysis on the data points included in the terminal phase of the log-linear plot of the concentration-time data. The elimination half-life ($t_{1/2}$) was calculated as $0.693/k_e$. The area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}) was calculated using the linear trapezoidal linear interpolation method. The plasma concentration-curve from time 0 to infinity (AUC_{inf}) was calculated by adding AUC_{last} to the extrapolated area beyond the last measurable plasma concentration (C_{last}), $AUC_{last} + C_{last} / k_e$. The apparent clearance (CL/F) was calculated as $Dose/AUC_{inf}$. The apparent volume of distribution (V_d/F) was calculated as $(CL/F)/k_e$.

Safety assessment

Throughout the study, safety was assessed based on adverse events (AEs), concomitant medications, physical examination, vital signs, clinical laboratory tests, chest X-ray examinations, and electrocardiograms. AEs were spontaneously reported by the subjects or solicited by the investigators using non-leading questions. Clinical laboratory tests were performed at pre-dose baseline and 7 days after the last study drug was administered.

Statistical analysis

All statistical analyses were performed by using SAS version 9.4 software (SAS Institute Inc. Cary, NC, USA), and Phoenix WinNonlin software version 8.0 (Certara Co., Princeton, NJ, USA). A general linear mixed-effects model was developed using log-transformed data to compare the PK parameters (AUC_{last} and C_{max}) between treatments. Period, sequence, and treatment were fixed effects while subjects nested in the sequence was a random effect. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of the AUC_{last} and the C_{max} between tofacitinib aspartate and tofacitinib citrate were estimated for the PK parameters. Bioequivalence testing was concluded if the 90% CI of the GMR for the PK parameters was entirely contained within the conventional bioequivalence range of 0.8–1.25. Numerical data between the 2 formulations were compared using the independent t-test or Mann-Whitney U test. Categorical data were compared using the χ^2 or Fisher's exact test.

RESULTS

Demographic characteristics

A total of 41 subjects were randomly placed into 2 sequence groups, and 6 subjects (2 subjects from the sequence A group and 4 from the sequence B group) withdrew consent. The demographic characteristics and safety analyses were conducted in 36 subjects who received at least one dose of the investigational drug. The mean ±standard deviation (range) of BMI values was 24.0 ± 2.2 (18.2–26.9) kg/m^2. There were no significant differences in the mean age, height, weight, and BMI between the sequence groups (**Table 1**).

Pharmacokinetic analysis

The pharmacokinetic set consisted of the 35 subjects who completed all blood sampling to calculate PK parameters. The pharmacokinetic parameters for the reference and test compounds are shown in **Table 2**. The mean plasma concentration-time profiles for

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Table 1. Demographic characteristics of the study subjects

Parameters	Sequence 1 (RT) (n = 19)	Sequence 2 (TR) (n = 17)	All subjects (n = 36)	*p*-value[a]
Age (yr)	24.05 ± 3.98	24.82 ± 4.99	24.42 ± 4.44	0.610
Height (cm)	177.67 ± 5.87	176.13 ± 5.40	176.94 ± 5.62	0.419
Weight (kg)	76.66 ± 9.58	73.92 ± 8.66	75.37 ± 9.13	0.373
BMI (kg/m^2)	24.24 ± 2.34	23.77 ± 2.14	24.02 ± 2.23	0.539

Data presented as mean ± standard deviation. R: Reference, Tofacitinib citrate 8.078 mg; T: Test, Tofacitinib aspartate 7.13 mg.
BMI, body mass index.
[a]Independent t-test between the sequence groups.

tofacitinib for the 2 formulations were superimposable (**Fig. 1**). Systemic exposure to tofacitinib after a single dose of 5 mg tofacitinib was bioequivalent between the test and the reference formulations. The GMRs (90% CI) of the C_{max} and AUC_{last} between the test and the reference formulations were 1.041 (0.944–1.148) and 1.003 (0.968–1.039), respectively. Also, the C_{max} and AUC_{last}, fell within the bioequivalence range of 0.800–1.250. Both graphs of the formulations showed very similar patterns. Also, both formulations were quickly absorbed (T_{max}: 0.75 hours in both) and eliminated ($t_{1/2}$: 2.59 hours in the test, and 2.58 hours in the

Table 2. Pharmacokinetic parameters of tofacitinib in 35 subjects after they received a single dose of tofacitinib 5 mg of the test and the reference formulations

Variables	Test (n = 35)		Reference (n = 35)		Geometric mean ratio (90% CI)*
	Mean ± SD	CV (%)	Mean ± SD	CV (%)	
C_{max} (ng/mL)	55.07 ± 16.45	29.87	52.50 ± 14.52	27.66	1.041 (0.944–1.148)
AUC_{last} (ng·h/mL)	136.22 ± 25.40	18.65	136.27 ± 28.59	20.98	1.003 (0.968–1.039)
AUC_{inf} (ng·h/mL)	139.90 ± 26.89	19.22	139.83 ± 29.93	21.40	1.004 (0.968–1.040)
AUCextra† (%)	2.13 (1.20–5.64)		2.37 (1.47–4.99)		
$t_{1/2}$ (h)	2.59 ± 0.36	13.90	2.58 ± 0.26	10.08	
CL/F (L/h)	148.41 ± 30.32	20.43	149.35 ± 31.43	21.04	
Vd/F (L)	546.37 ± 93.46	17.10	550.38 ± 96.89	17.60	
T_{max}[a] (h)	0.75 (0.33–2.00)		0.75 (0.33–2.00)		

Reference (R), Tofacitinib citrate 8.078 mg; Test (T), Tofacitinib aspartate 7.13 mg. All values, except for AUCextra and T_{max}, are presented as the arithmetic mean ± SD and coefficient of variation (%).
SD, standard deviation; CV, coefficient of variance; CI, confidence interval; C_{max}, maximum plasma concentration of drug; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; AUCextra(%), % extrapolated AUC_{last} which was calculated as [(AUC_{inf}–AUC_{last})/AUC_{inf}]; $t_{1/2}$, terminal elimination half-life; CL/F, apparent clearance; Vd/F, apparent volume of distribution; T_{max}, time to reach the maximum blood concentration after administration of drug.
*Geometric mean ratio of test/reference, exponentiation of least square mean difference (90% CI) of logarithmic transformed C_{max} and AUC values; †Median value [min–max].

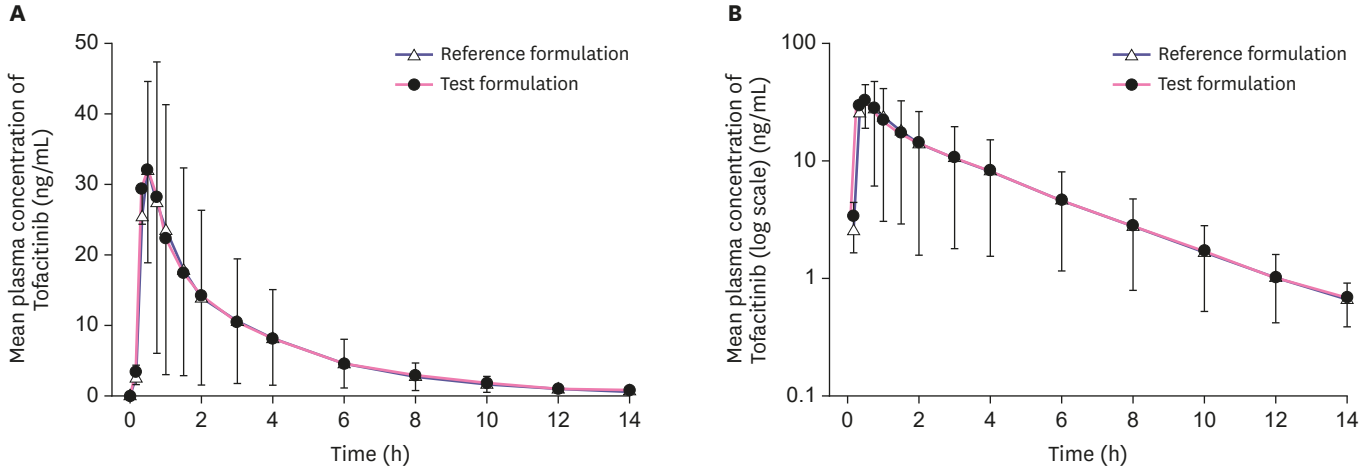

Figure 1. Mean ± standard deviation plasma concentration-time profiles of Tofacitinib after single doses of the reference (white triangles) and test formulations (black circles) in healthy subject (A, linear scale; B, log scale).

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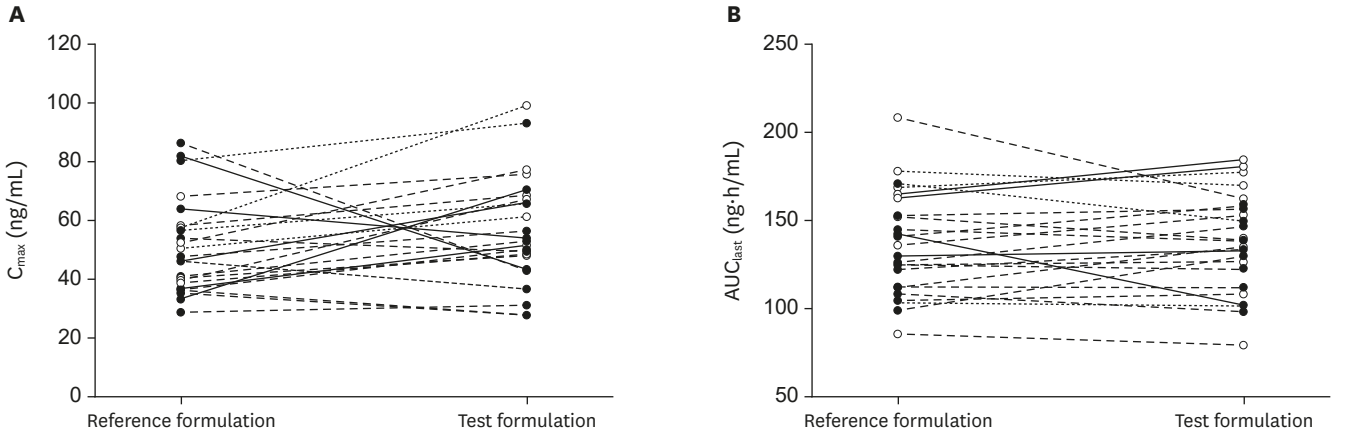

Figure 2. Individual (A) C_{max} and (B) AUC_{last} of Tofacitinib after single doses of the reference and test formulations of Tofacitinib in healthy subjects.
C_{max}, maximum plasma concentration of drug; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration.

Table 3. Number of subjects (percentage of subjects) with adverse events after single oral administrations of tofacitinib 5 mg of the test and the reference formulations

Adverse events	Test (n = 35)	Reference (n = 36)	All subjects (n = 36)	*p*-value*
Subjects with adverse events	2 (5.71)	3 (8.33)	5 (13.89)	1.000
Proteinuria	2 (5.71)	2 (5.56)	4 (11.11)	1.000
Alanine aminotransferase increased	0	1 (2.78)	1 (2.78)	1.000
Blood triglycerides increased	0	1 (2.78)	1 (2.78)	1.000

Values are presented as number (%).
Reference, Tofacitinib citrate 8.078 mg; Test, Tofacitinib aspartate 7.13 mg.
*Fisher's exact test between the test and the reference formulations.

reference). There was no noticeable within-subject difference between C_{max} and AUC_{last} regarding the reference and test formulations (**Fig. 2**).

Safety

There were 4 AEs associated with the reference formulation, and 2 AEs after treatment with the test formulation. The following AEs were observed: proteinuria (2 cases associated with the reference formulation, and 2 cases associated with the test formulation); an increase in alanine aminotransferase (one case treated with the reference formulation, 68 IU/L); and an increase in blood triglycerides (one case treated with the reference formulation, 350 mg/dL). There were no significant differences in the frequency of AEs between the sequence groups (**Table 3**). All AEs were mild and resolved spontaneously within a few hours or days. There were no drug-related AEs or serious AEs. No clinically significant changes were observed in the clinical laboratory test results (except AEs), vital signs, chest X-ray examinations, ECG measurements, or physical examinations.

DISCUSSION

This study was conducted to compare the PK and safety profiles of 2 formulations containing a single 5 mg dose of tofacitinib. We showed that the test formulation (tofacitinib aspartate 7.13 mg) had bioequivalent PK characteristics to the reference formulation (tofacitinib citrate 8.08 mg). This conclusion was supported by the finding that the C_{max} and AUC_{last} GMRs (90% CI) were within the conventional bioequivalence criteria following the administration of each formulation. Also, the mean plasma concentration-time profiles of the 2 formulations were

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superimposable from pre-dose to 14 hours after dosing (**Fig. 1**). Moreover, the safety profiles were not different between the 2 formulations. Finally, these results indicate that the test formulation of tofacitinib can be used as an alternative to the reference formulation without a significant difference in systemic exposure and safety.

The sample size and design of this study were appropriate to evaluate the bioequivalence of 2 drugs and their safety profiles. Based on the previous report regarding the intra-subject variability of tofacitinib C_{max} (25%), the minimum sample size was calculated as 28 subjects. Forty-one subjects were enrolled and 35 subjects completed the study. The number of subjects was sufficient to minimize β-errors (type II), and the randomization of study groups was sufficiently balanced to avoid bias associated with sequence allocation. The PK sampling time points were well established to observe the T_{max} and systemic exposure, which was supported by the fact that the AUC_{extra} (%), was ~3% or less in the test and reference formulations.

According to a report issued by the Ministry of Food and Drug Safety in the Republic of Korea, the approved drug with the modified salt accounted for about 6 percent among the approval of improved drugs during the past decade (2009–2019) [17]. The test drug was developed by modifying the citrate of the reference drug to aspartate. Both types of salts are widely used as drug excipients [18,19]; for instance, magnesium and lithium are widely administered in salt forms. Magnesium with citrate or aspartate both showed excellent solubility and bioavailability [20,21]. Also, different salts (citrate, aspartate, and other salts) exerted similar effects on the absorption of lithium [22]. Furthermore, it has been reported that AEs associated with magnesium and lithium fundamentally depended upon the active ingredients themselves [22-24]. As in the previous cases, both tofacitinib formulation using aspartate and citrate had the equivalent PK characteristics and excellent safety profiles.

In conclusion, tofacitinib aspartate showed similar PK profiles to tofacitinib citrate. The GMR as well as the 90% CIs of the C_{max} and AUC_{last} fell completely within the bioequivalence criteria (80–125%).

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