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Application of Physiologically-Based Pharmacokinetic Modeling for the Prediction of Tofacitinib Exposure in Japanese

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Tofacitinib (3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile) is an oral Janus kinase inhibitor that is approved in countries including Japan and the United States for the treatment of rheumatoid arthritis, and is being developed across the globe for the treatment of inflammatory diseases. In the present study, a physiologically-based pharmacokinetic model was applied to compare the pharmacokinetics of tofacitinib in Japanese and Caucasians to assess the potential impact of ethnicity on the dosing regimen in the two populations. Simulated plasma concentration profiles and pharmacokinetic parameters, i.e. maximum concentration and area under plasma concentration-time curve, in Japanese and Caucasian populations after single or multiple doses of 1 to 30 mg tofacitinib were in agreement with clinically observed data. The similarity in simulated exposure between Japanese and Caucasian populations supports the currently approved dosing regimen in Japan and the United States, where there is no recommendation for dose adjustment according to race. Simulated results for single (1 to 100 mg) or multiple doses (5 mg twice daily) of tofacitinib in extensive and poor metabolizers of CYP2C19, an enzyme which has been shown to contribute in part to tofacitinib elimination and is known to exhibit higher frequency in Japanese compared to Caucasians, were also in support of no recommendation for dose adjustment in CYP2C19 poor metabolizers. This study demonstrated a successful application of physiologically-based pharmacokinetic modeling in evaluating ethnic sensitivity in pharmacokinetics at early stages of development, presenting its potential value as an efficient and scientific method for optimal dose setting in the Japanese population.

Recently, many pharmaceutical companies are adopting global development strategies for efficient worldwide marketing, and multi-regional clinical trials are being widely conducted with the objective of minimizing drug lag in a particular region (1). Although many drugs have comparable profiles among populations, ethnic or racial differences may contribute to variability in pharmacokinetics (PK) and pharmacodynamics (PD), and thereby influence the efficacy and safety profiles of a drug between populations (2,3). In fact, numerous differences have been reported in approved dosages for drugs approved in the International Conference on Harmonization (ICH) regions, i.e. the United States, the European Union and Japan, and the dose approved in Japan is known to be often lower than that in the United States or Europe (4-7). The ICH has issued a guidance that recommends evaluation of the impact of ethnic factors, in order to facilitate the use of foreign clinical data in extrapolating to a "new region" and to minimize duplication of clinical studies (8). As listed in "ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data," PK and PD factors of a drug may be influenced not only by intrinsic factors, such as gender, race, age and genetic polymorphism in drug disposition, but also extrinsic factors, such as climate, diet, medical practice, socioeconomic factors and drug compliance, all of which should be taken into consideration for successful global development (8). To encourage pharmaceutical companies to include Japan in global drug development from the early stages of development, the Japanese regulatory authority has issued the "Basic Principles on Global Clinical Trials" which provides guidance on the basic concepts for planning and implementing multi-regional trials in Japan (9). In the meantime, the Japanese regulatory authority also emphasizes the need to ensure adequate tolerability in the Japanese population prior to joining global studies, and the requirement for the inclusion of sufficient domestic clinical trial data in new drug application data packages (9,10). Thus, joining a multi-regional study in a timely manner requires prior assessment of dosage in the participating populations with strong awareness of the ethnic

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sensitivity in factors that define the risk/benefit characteristics, including PK profiles, PD profiles and medical practice (1).

In this context, physiologically-based pharmacokinetic (PBPK) modeling has been developed as a mathematical modeling technique to predict the absorption, distribution, metabolism and excretion (ADME) of chemical substances in humans and other animal species. PBPK modeling provides a mechanistic framework that enables the assessment of inter-individual variability in PK and PD using virtual human populations by integrating general knowledge of the physical chemistry of a drug with human biology, anatomy, physiology and genetics, and is increasingly adopted within the pharmaceutical industry and regulatory authorities as a useful tool to identify critical points to be considered in clinical study design and to inform drug labels (11,12).

Tofacitinib (3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile, Figure 1) is an oral Janus kinase (JAK) inhibitor that shows considerable selectivity to the JAK family of kinases compared to over 82 other kinases tested in the selectivity panel (13,14). Inhibition of JAK1/3 by tofacitinib is proposed to block signaling through the common gamma chain containing receptors for several cytokines, including IL-2, -4, -7, -9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation and function, and inhibition of their signaling may result in suppression of multiple aspects of the immune response (14,15). In addition, cross-over to JAK1 may result in some attenuation of signaling by additional cytokines, such as IL-6 and IFN-γ (14). The primary clearance mechanism of tofacitinib in humans has been shown to be via metabolism by CYP3A4 (approximately 55%) followed by metabolism by CYP2C19 (approximately 15%), and renal excretion as unchanged drug (approximately 30%) (16).

Tofacitinib is being developed globally for the treatment of various inflammatory diseases including rheumatoid arthritis (RA) (17-22), psoriasis (23,24) and inflammatory bowel disease (25), and is currently approved for the treatment of RA in multiple countries, including Japan and the United States, where the approved dosage is 5 mg twice daily (BID) (26,27). Prior to approval of tofacitinib for the treatment of RA, global development strategies were adopted, and multi-regional clinical trials were conducted to collect clinical data in multiple nations including Japanese subjects (28,29). Clinical data in Japanese healthy volunteers and RA patients provided valuable information in the Japanese population in comparison to the Western population, resulting in timely regulatory submission and approval in Japan (27,28). PK profiles in Japanese healthy volunteers have been shown to be similar to those in Caucasian healthy volunteers (28). Moreover, population PK analyses demonstrated that exposure in Japanese RA patients was similar to that in Caucasian RA patients, thereby requiring no dose adjustment in the Japanese population from a PK perspective (26-28).

The objective of this study was to characterize the PK profile of tofacitinib in the Japanese healthy population using PBPK modeling and to compare the profile with that in the Caucasian healthy population. The impact of CYP2C19 genotype on tofacitinib exposure was also evaluated.

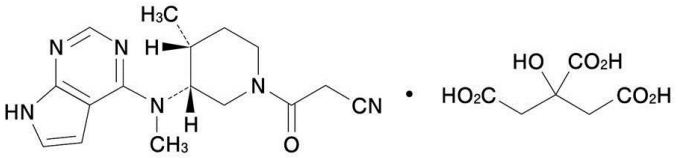

Figure 1. Chemical structure of tofacitinib citrate. (3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo-[2,3-d]pyrimidin-4-yl)amino] piperidin-1-yl]-3-oxopropanenitrile monocitrate (MW: 504.5 D)

METHODS

Clinical data

Study 1 (28,29):

This study was a Phase 1, randomized, subject- and investigator-blind, sponsor-open, placebo-controlled, single- and multiple-dose escalation study in healthy adult male and female Japanese and Western subjects. The primary objectives of the study were to evaluate the PK, safety and tolerability of single and multiple oral doses of tofacitinib in healthy adult Japanese subjects. The study consisted of 2 cohorts, i.e. Cohort A and Cohort B. Cohort A received 3 escalating single doses (1, 5 and 30 mg) of tofacitinib and Cohort B was administered a single dose (15 mg) of tofacitinib followed by a BID dose regimen of 15 mg of tofacitinib for 5 days (single dose on the last day). The subjects took tofacitinib on an empty stomach. Blood samples for PK analysis were collected up to 48 hours after final dosing. Blood samples were collected on Day 0 to investigate the potential relationship between the exposure of tofacitinib and CYP2C19 genotype.

Study 2 (28,29):

This study was a Phase 1, single-dose, randomized, 3-treatment, 3-period cross-over, sponsor-open, placebo-and positive-controlled trial planned for 60 healthy adult volunteers at 2 sites. The primary objective

was to demonstrate the lack of effect of a single 100 mg dose of tofacitinib relative to placebo on QTc interval in Western healthy volunteers. CYP2C19 genotype and PK data were collected from 60 healthy subjects who received a single 100 mg dose of tofacitinib as part of this QT study. The subjects took tofacitinib on an empty stomach. Blood samples for PK analysis were collected up to 24 hours after dosing. The *2, *3, *4, *5, and *17 alleles of the CYP2C19 gene were genotyped and each subject's metabolizer status was classified as: poor metabolizers – *2/*2, *2/*3, or *3/*3 alleles; ultra-rapid metabolizers – *17/*17; or extensive metabolizers – all other allele combinations.

Simulator and Demographic Factors

Simcyp Simulator® (Version 15 Release 1, SimcypTM, Sheffield, UK) was used to predict the plasma drug concentration-time profiles of tofacitinib in virtual Japanese and Caucasian populations. The Japanese and Healthy Volunteers Virtual Population Library provided by Simcyp were used for simulation in the Japanese and Caucasian populations, respectively. Previously reported input parameters for the tofacitinib compound file were used to develop a model in the Japanese population (30). Demographic factors for simulations are summarized in Table I for Study 1 and Table II for Study 2.

Table I. Summary of demographic factors for subjects in Study 1 and in Simcyp generated populations

	Study 1			**Simcyp generated**		
Population	Japanese		Caucasian	Japanese		Caucasian
	Cohort A[a)]	Cohort B[b)]	Cohort A[a)]	Cohort A[a)]	Cohort B[b)]	Cohort A[a)]
N	8	8	9	100	100	100
Age (years)[c)]	34.1±5.8 (24-44)	35.8±6.5 (24-45)	38.0±9.6 (25-52)	34.2±5.6 (24-43)	34.7±5.9 (24-44)	33.0±6.7 (25-52)
Height (cm)[c)]	173.1±6.2 (163.0-182.0)	167.6±7.9 (158.0-176.0)	178.1±10.3 (158.0-191.0)	168.7±6.2 (145.7-184.5)	163.1±8.3 (145.6-184.5)	175.5±7.5 (151.6-192.3)
Weight (kg)[c)]	66.8±8.9 (54.0-81.0)	65.4±12.0 (49.0-80.0)	89.3±11.5 (63.0-106.0)	66.7±10.1 (43.9-104.1)	61.6±10.4 (40.4-95.2)	80.5±14.0 (53.4-126.8)
Proportion of females (%)	0	38	11	0	38	11
Proportion of CYP2C19 PM (%)	12.5	12.5	0	12.5	12.5	0

BID: twice daily, N: number of subjects, PM: poor metabolizer
a) 1, 5, 30 mg single dose
b) 15 mg single dose and 15 mg BID for 5 days
c) Age, height and weight are shown as mean±standard deviation with range.

Table II. Summary of demographic factors for subjects in Study 2 and in Simcyp generated populations

	Study 2[a)]	**Simcyp generated[a)]**
Population	Caucasian/Asian/Other	Caucasian/Japanese
N	60 (30 Caucasians/28 Asians/2 Other)	100 (53 Caucasians/47 Japanese)
Age (years)[b)]	32.7±9.2 (21-51)	33.9±8.9 (21-50) [30.7±8.0 (21-49) in Caucasians, 37.5±8.6 (22-50) in Japanese]
Height (cm)[b)]	167.5±8.9 (151.0-190.0)	165.1±8.7 (145.5-185.4) [167.2±9.2 (151.6-185.4) in Caucasians, 162.6±7.5 (145.5-184.6) in Japanese]
Weight (kg)[b)]	67.0±11.7 (51.0-102.0)	66.7±14.7 (42.4-120.0) [72.9±15.8 (42.4-120.0) in Caucasians, 59.7±9.5 (43.8-86.0) in Japanese]
Proportion of females (%)	46.7 (50.0 in Caucasians and Other/42.9 in Japanese)	53.0 (64.2 in Caucasians/40.4 in Japanese)
Proportion of CYP2C19 PM (%)	10.0	0.00 or 100[c)]

EM: extensive metabolizer, N: number of subjects, PM: poor metabolizer
a) 100 mg single dose
b) Age, height and weight are shown as mean±standard deviation with range.
c) Proportion of CYP2C19 PMs were set to 0% in the EM population and 100% in the PM population.

The demographic databases for Japanese and Healthy Volunteers population files were as provided by Simcyp, except for the hepatic and gastrointestinal abundance levels of CYP3A4 and CYP2C19 protein in the Japanese population file. The default abundance levels of CYP3A4 and CYP2C19 protein in the liver and the gastrointestinal tract, provided by Simcyp, are lower in the Japanese population. However, the effect of

ethnicity on CYP3A4 expression level remains to be fully characterized to date. Furthermore, previous reports have demonstrated that genotype, rather than ethnicity, influences the phenotype of some CYP enzymes including CYP2C19 (31-33). In light of these findings, all abundance levels of hepatic and gastrointestinal CYP3A4 and CYP2C19 protein in Japanese were adjusted to the same values as the Simcyp default Healthy Volunteers Virtual Population Library in this study. Preliminary studies in our laboratory have confirmed that the adjusted Japanese population file produced a better prediction of observed PK profiles in Japanese subjects who participated in the two cohorts of Study 1 (unpublished data).

Simulations

Firstly, simulations were conducted to predict clinically observed PK results in Study 1 and Study 2. The age range, proportion of females, proportion of CYP2C19 poor metabolizers and fasting state were set to match those of Study 1 or Study 2, and virtual populations were generated in Simcyp. As for the prediction of Study 2, a population consisting of both Caucasians and Japanese was generated in Simcyp. The input value for the proportion of Japanese were set to match the proportion of Asian subjects in Study 2 and the remaining proportion of subjects were generated from the Healthy Volunteers Virtual Population Library. Each simulation was conducted for ten clinical trials of ten subjects. Simulated data were compared against reported clinical data in Study 1 and Study 2. Secondly, plasma concentration-time profiles of tofacitinib in populations of either extensive or poor metabolizers of CYP2C19 were simulated to evaluate the impact of CYP2C19 genotype on tofacitinib exposure. The proportion of CYP2C19 poor metabolizers were set to zero for simulation in extensive metabolizers and to 1 for simulation in poor metabolizers. Simulated data were compared against reported clinical data in Study 1 and Study 2. Additional simulations were performed for 5 mg BID dosing in extensive and poor metabolizers of CYP2C19 using the Japanese and Healthy Volunteers Virtual Population Library, as well as in populations with typical proportions of poor metabolizers in the two populations, to evaluate the potential impact of ethnicity on exposure for the clinically approved dosing regimen for the treatment of RA in Japan and the United States. The Japanese and Healthy Volunteers population files described above were also used for the simulation of the clinically approved dosing regimen. The age range, proportion of females and fasting status were adjusted to match those of Study 1 Cohort A for both Japanese and Caucasians as a reference for a typical Phase 1 study. The default values given in Simcyp were used for typical proportions of CYP2C19 poor metabolizers in the Japanese (18%) and Healthy Volunteers (2.4%) population files.

RESULTS

Plasma concentration-time profiles in Japanese and Caucasian healthy volunteers

Simulated and observed plasma concentration-time profiles for single doses of 1, 5, 15 and 30 mg tofacitinib in Japanese are shown in Figure 2, and simulated and observed plasma concentration-time profiles for single doses of 1, 5 and 30 mg in Caucasian healthy volunteers are shown in Figure 3. The respective values for maximum plasma concentrations (C_{max}) and area under plasma concentration-time curve from zero to infinity (AUC_{inf}) are shown in Table III. Observed concentration data points, including the range of standard deviation, were largely within the range of simulated 5^{th} and 95^{th} percentiles. The simulated versus observed ratios in C_{max} across doses studied were 0.743-1.06 in Japanese and 0.732-0.928 in Caucasians. The simulated versus observed ratios in AUC_{inf} across doses studied were 1.29-1.50 in Japanese and 1.11-1.28 in Caucasians. Thus, simulations based on the current model resulted in a reasonable prediction of plasma concentration-time profiles for single dosing in Japanese and Caucasian healthy volunteers. Figure 4 shows simulated and observed plasma concentration-time profiles for multiple doses of 15 mg BID tofacitinib in Japanese. The respective C_{max} and area under the plasma concentration-time curve during a dosing interval (tau) at steady-state (AUC_{tau}) values are shown in Table IV. Observed concentration data points, including the range of standard deviation, were largely within the range of simulated 5^{th} and 95^{th} percentiles. The simulated versus observed ratios were 0.978 for C_{max} and 1.21 for AUC_{tau}, and thus the current model resulted in a good prediction of plasma concentration-time profiles for multiple dosing in Japanese.

Plasma exposure in extensive and poor metabolizers of CYP2C19

Table V shows the comparison of simulated and observed plasma C_{max} and AUC_{inf} values for a single dose of 100 mg tofacitinib in poor versus extensive metabolizers of CYP2C19. Simulated and observed ratios between poor metabolizers versus extensive metabolizers for C_{max} and AUC_{inf} values were similar, demonstrating adequate prediction by the current model. Table VI shows the simulated values for plasma C_{max} and AUC_{inf} values for single doses of 1, 5, 15 and 30 mg tofacitinib in Japanese extensive and poor metabolizers of CYP2C19. The ratios comparing poor versus extensive metabolizers of CYP2C19 were close to 1. Moreover,

the ratios for poor versus extensive metabolizers of CYP2C19 in simulated C_{max} and AUC_{inf} for Japanese subjects in Study 1 as shown in Table VI (1.06 for C_{max} and 1.21 for AUC_{inf}) were similar to the simulated and observed results in Study 2 as shown in Table V (1.06-1.15 for C_{max} and 1.17-1.24 for AUC_{inf}).

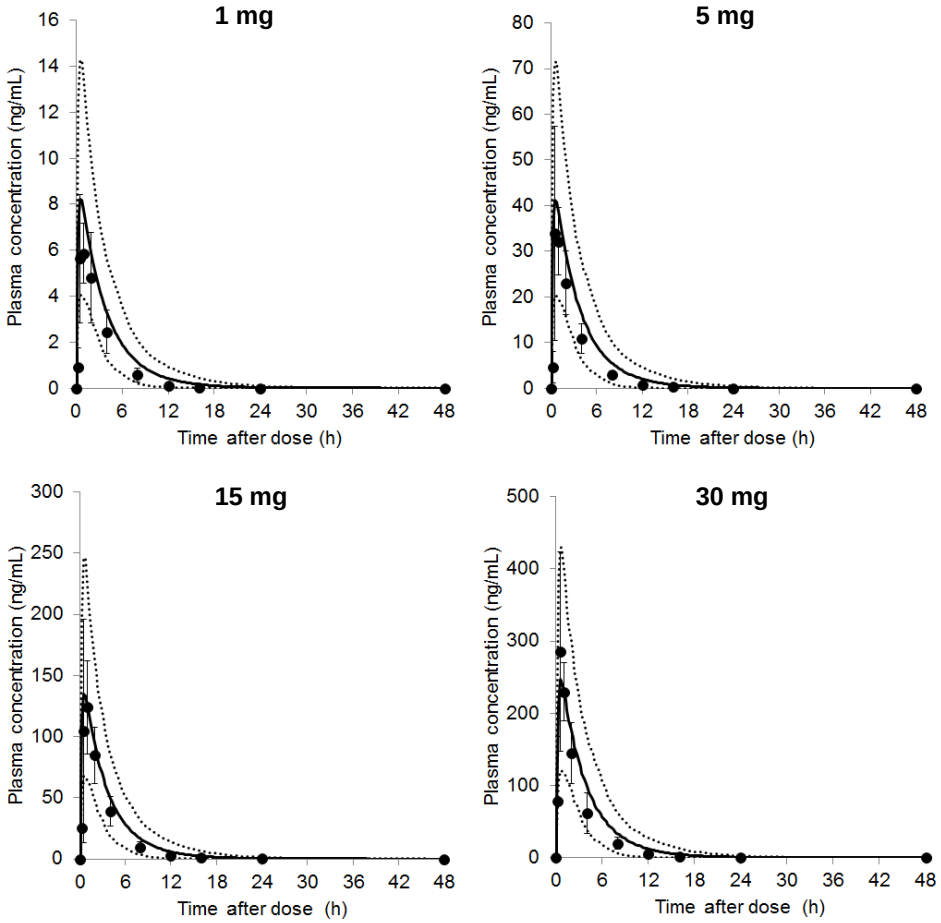

Figure 2. Simulated and observed plasma concentration-time profiles of tofacitinib in Japanese following single dosing (1-30 mg). Solid lines show mean simulated plasma concentrations in the Japanese population. Dotted lines show 5th and 95th percentiles for the simulated plasma concentrations. Filled circles show clinically observed plasma concentrations with standard deviation in Japanese subjects in Cohort A in Study 1.

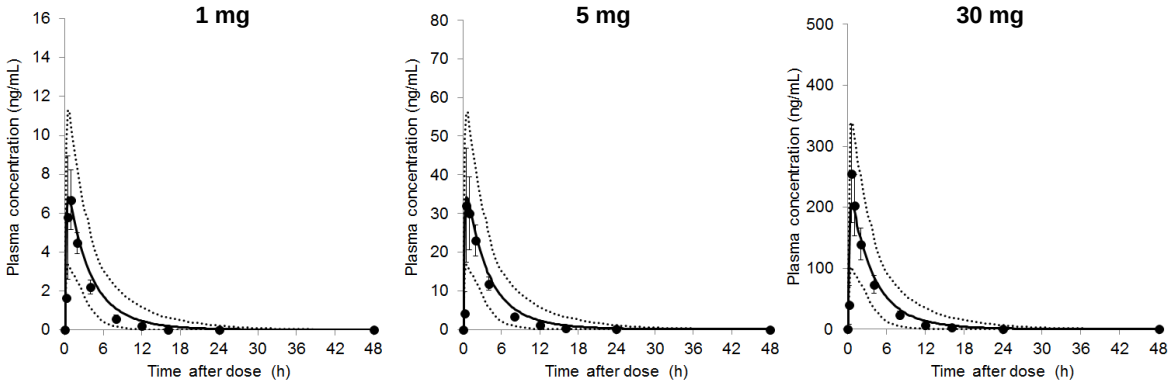

Figure 3. Simulated and observed plasma concentration-time profiles of tofacitinib in Caucasians following single dosing (1-30 mg). Solid lines show mean simulated plasma concentrations in the Caucasian population. Dotted lines show 5th and 95th percentiles for the simulated plasma concentrations. Filled circles show clinically observed plasma concentrations with standard deviation in Caucasian subjects in Cohort A in Study 1.

Table III. Simulated versus observed tofacitinib exposure in Japanese and Caucasians following single dosing (1-30 mg)

Population	PK parameter	Dose	Simulated[a)]	Observed in Study 1[b)]	Ratio (Simulated/Observed)
Japanese	C_{max} (ng/mL)	1 mg	7.79 (38) [7.22-8.40]	7.32 (14)	1.06
		5 mg	38.9 (38) [36.1-42.0]	41.3 (35)	0.942
		15 mg	127 (38) [117-137]	141 (34)	0.901
		30 mg	234 (38) [217-252]	315 (25)	0.743
	AUC_{inf} (ng*h/mL)	1 mg	32.9 (36) [30.5-35.4]	22.0 (28)	1.50
		5 mg	164 (36) [153-177]	111 (22)	1.48
		15 mg	514 (35) [478-554]	399 (32)	1.29
		30 mg	986 (36) [915-1060]	754(26)	1.31
Caucasian	C_{max} (ng/mL)	1 mg	6.47 (38) [6.00-6.98]	7.36 (22)	0.879
		5 mg	32.4 (38) [30.0-34.9]	34.9 (27)	0.928
		30 mg	194 (38) [180-209]	265 (18)	0.732
	AUC_{inf} (ng*h/mL)	1 mg	29.1 (39) [26.8-31.6]	22.8 (11)	1.28
		5 mg	146 (39) [134-158]	119 (14)	1.23
		30 mg	873 (39) [805-947]	788 (16)	1.11

AUC_{inf}: area under plasma concentration-time curve from zero to infinity, C_{max}: maximum plasma concentration, CV: coefficient of variation, PK: pharmacokinetic
a) Simulated PK parameters are shown as geometric means with %CV and 95% confidence intervals.
b) Observed PK parameters are shown as geometric means with %CV.

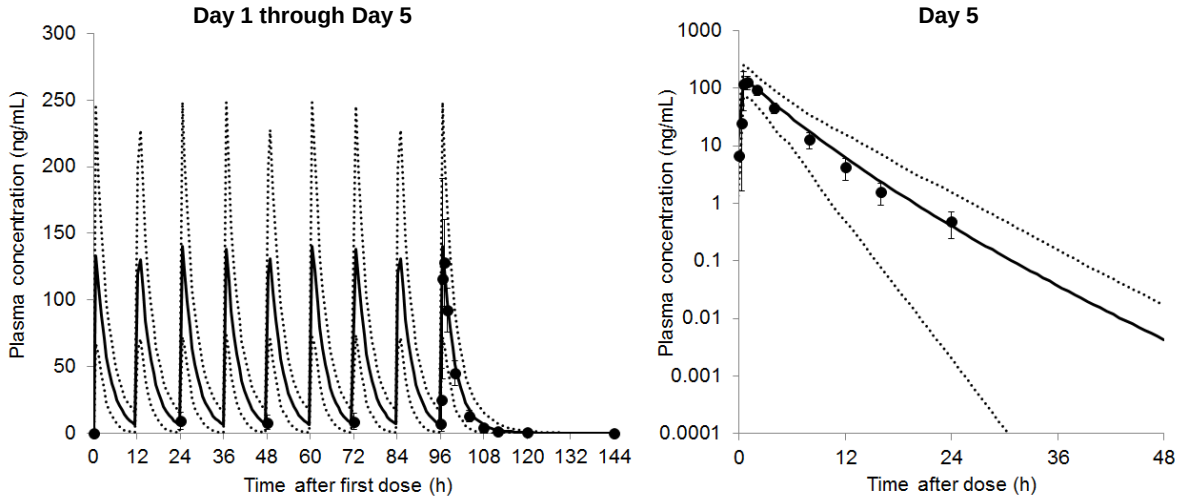

Figure 4. Simulated and observed plasma concentration-time profiles of tofacitinib in Japanese following 15 mg BID dosing for 5 days (only the morning dose was given on Day 5). Solid lines show mean simulated plasma concentrations in the Japanese population. Dotted lines show 5th and 95th percentiles for the simulated plasma concentrations. Filled circles show clinically observed plasma concentrations with standard deviation in Japanese subjects in Cohort B in Study 1.

Table IV. Simulated versus observed tofacitinib exposure in Japanese subjects following 15 mg BID dosing

	Simulated[a)]	Observed in Study 1[b)]	Ratio (Simulated/Observed)
C_{max} (ng/mL)	133 (37) [123-143]	136 (32)	0.978
AUC_{tau} (ng*h/mL)	538 (37) [498-580]	445 (25)	1.21

AUC_{tau}: area under the plasma concentration-time curve during a dosing interval (tau) at steady-state, BID: twice daily, C_{max}: maximum plasma concentration, CV: coefficient of variation, PK: pharmacokinetic
a) Simulated PK parameters are shown as geometric means with %CV and 95% confidence intervals.
b) Observed PK parameters are shown as geometric means with %CV.

Table V. Comparison of simulated and observed tofacitinib exposure in poor versus extensive metabolizers of CYP2C19 following a single dose of 100 mg

PK parameter	Population	Simulated [a)]	Observed in Study 2[b)]	Ratio (Simulated/Observed)	CYP2C19 PM/EM ratio	
					Simulated	Observed in Study 2
C_{max} (ng/mL)	CYP2C19 EM	788 (41) [725-856]	565 (31)	1.39	-	-
	CYP2C19 PM	839 (40) [774-910]	647 (41)	1.30	1.06	1.15
AUC_{inf} (ng*h/mL)	CYP2C19 EM	3290 (38) [3040-3570]	2680 (28)	1.23	-	-
	CYP2C19 PM	4070 (37) [3780-4390]	3130 (12)	1.30	1.24	1.17

AUC_{inf}: area under plasma concentration-time curve from zero to infinity, C_{max}: maximum plasma concentration, CV: coefficient of variation, EM: extensive metabolizer, PK: pharmacokinetics, PM: poor metabolizer
a) Simulated PK parameters are shown as geometric means with %CV and 95% confidence intervals.
b) Observed PK parameters are shown as geometric means with %CV. 52 EMs and 6 PMs of CYP2C19 took part in Study 2.

Table VI. Comparison of simulated tofacitinib exposure in Japanese poor versus extensive metabolizers of CYP2C19 following single dosing (1-30 mg)

PK parameter	Dose	Simulated in CYP2C19 EM[a)]	Simulated in CYP2C19 PM[a)]	PM/EM ratio[a)]
C_{max} (ng/mL)	1 mg	7.72 (38) [7.15-8.33]	8.18 (37) [7.60-8.81]	1.06
	5 mg	38.6 (38) [35.8-41.7]	40.9 (37) [38.0-44.0]	
	15 mg	126 (39) [116-136]	133 (37) [123-144]	
	30 mg	232 (38) [215-250]	245 (37) [228-264]	
AUC_{inf} (ng*h/mL)	1 mg	32.1 (37) [29.7-34.6]	38.8 (34) [36.1-41.6]	1.21
	5 mg	160 (37) [148-173]	194 (34) [181-208]	
	15 mg	502 (36) [465-543]	605(33) [564-649]	
	30 mg	962 (37) [890-1040]	1160 (34) [1080-1250]	

AUC_{inf}: area under plasma concentration-time curve from zero to infinity, C_{max}: maximum plasma concentration, CV: coefficient of variation, EM: extensive metabolizer, PK: pharmacokinetics, PM: poor metabolizer
a) Simulated PK parameters are shown as geometric means with %CV and 95% confidence intervals.

Plasma exposure in Japanese and Caucasians at clinically approved dosage

Simulations were conducted to compare steady state tofacitinib exposure in extensive and poor metabolizers of CYP2C19 in Japanese and Caucasians for 5 mg BID. Simulations were also conducted for 5 mg BID in Japanese and Caucasians with typical proportions of CYP2C19 poor metabolizers. As shown in Figure 5 and Table VII, the simulated plasma concentration-time profiles, as well as simulated C_{max} and AUC_{tau} values, for 5 mg BID were comparable between Japanese and Caucasians. Simulated plasma concentration profiles and PK parameters in Japanese CYP2C19 poor metabolizers with the highest exposure and Caucasian CYP2C19 extensive metabolizers with the lowest exposure were also comparable.

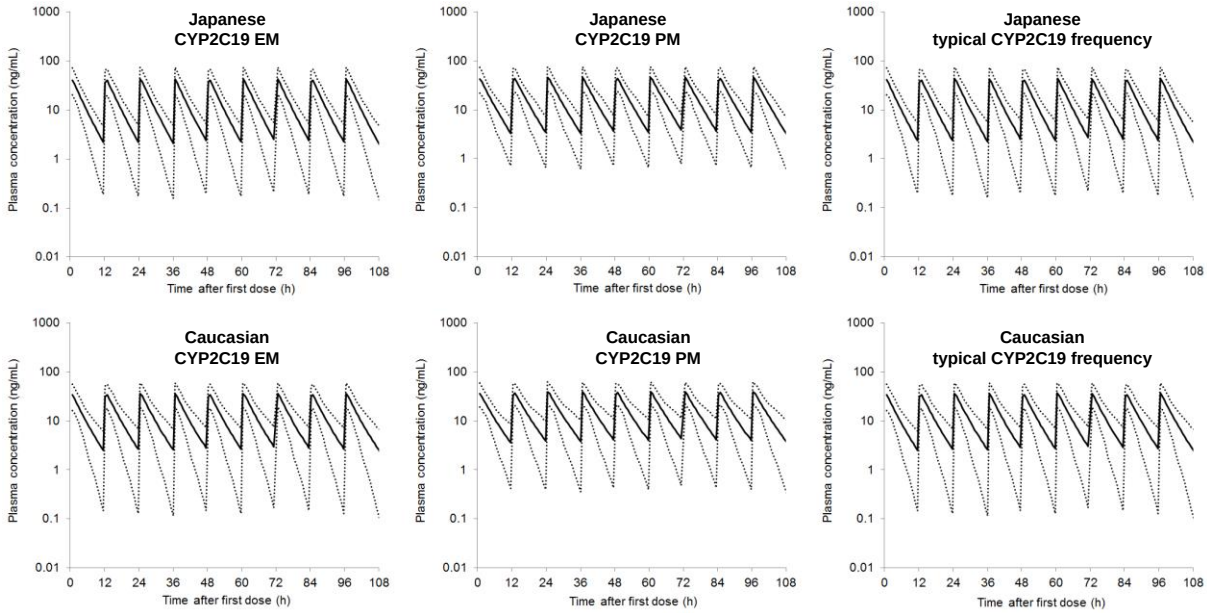

Figure 5. Simulated plasma concentration-time profiles of tofacitinib in Japanese and Caucasian extensive metabolizers and poor metabolizers of CYP2C19 following 5 mg BID dosing. Solid lines show mean simulated plasma concentrations in each population. Dotted lines show 5th and 95th percentiles for the simulated plasma concentrations. Simcyp default values were used for typical proportions of CYP2C19 poor metabolizers in Japanese (18%) and Caucasians (2.4%), respectively.

Table VII. Comparison of simulated tofacitinib exposure in Japanese and Caucasian CYP2C19 extensive metabolizers and poor metabolizers at steady state following 5 mg BID dosing

PK parameter[a)]	Population	CYP2C19 EM or PM	Simulated[b)]	Ratio versus Caucasian EM[c)]
C_{max} (ng/mL)	Japanese	EM	40.5 (37) [37.6-43.6]	1.17
		PM	43.9 (35) [41.0-47.1]	1.27
		Typical PM frequency (18%)	41.0 (36) [38.2-44.1]	1.18
	Caucasian	EM	34.7 (35) [32.3-37.3]	-
		PM	37.8 (34) [35.4-40.5]	1.09
		Typical PM frequency (2.4%)	34.8 (35) [32.4-37.4]	1.00
AUC_{tau} (ng*h/mL)	Japanese	EM	168 (38) [155-182]	1.08
		PM	208 (36) [193-224]	1.33
		Typical PM frequency (18%)	174 (38) [161-188]	1.12
	Caucasian	EM	156 (43) [143-171]	-
		PM	194 (43) [179-211]	1.24
		Typical PM frequency (2.4%)	157 (43) [144-172]	1.01

AUC_{tau}: area under the plasma concentration-time curve during a dosing interval (tau) at steady-state, BID: twice daily, C_{max}: maximum plasma concentration, CV: coefficient of variation, EM: extensive metabolizer, PK: pharmacokinetics, PM: poor metabolizer
a) Simulations were conducted for 5 mg BID dosing for 5 days. Only the morning dose was given on Day 5. PK parameters were calculated for the final dose.
b) Simulated PK parameters are shown as geometric means with %CV and 95% confidence intervals.
c) Ratios are shown as comparison versus Caucasian EM.

DISCUSSION

Tofacitinib is an orally active JAK3 kinase inhibitor which is approved for the treatment of RA in countries including Japan and the United States. Previous studies have shown that the PK of tofacitinib is characterized by rapid absorption with a time to peak concentration of approximately 1 hour after oral administration and a terminal phase half-life of approximately 3 hours (16). In the present simulation using the Simcyp-based PBPK model, observed concentration data points derived from clinical studies were largely within the range of 5th and 95th percentiles across doses and populations studied. The simulated versus observed ratios for C_{max} after single dosing of 1 to 30 mg ranged from 0.743 to 1.06 and 0.732 to 0.928 in Japanese and Caucasians, respectively (Table III). The respective ratios for AUC_{inf} across doses studied ranged from 1.29 to 1.50 and 1.11 to 1.28 in Japanese and Caucasians, respectively. Furthermore, the simulated versus observed ratios for AUC_{tau} and C_{max} after multiple dosing (15 mg BID) were close to 1 in Japanese (Table IV). These results demonstrate that the PBPK model employed in this study provides a reasonable prediction of PK profiles of tofacitinib irrespective of dosing regimen and populations. The present data demonstrates that the simulated and observed plasma concentration-time profiles, as well as PK parameters after both single and multiple dosing were comparable between the Japanese and Caucasians. This finding is consistent with the current tofacitinib labels in Japan and the United States, where there is no recommendation of dose adjustment according to race from a PK point of view.

Clinical relevance of CYPC19 polymorphism to drug metabolism has been well characterized to date (3), and the allele frequencies are reported to be different between the Asian and Caucasian populations, i.e. proportion of poor metabolizers being approximately 18-23% in Asians and 2-5% in Caucasians (2,34). The poor metabolizers possess mutations in the CYP2C19 gene that preclude the expression of normal enzymes, resulting in deficiency of enzyme activity. However, clinical data have demonstrated the contribution of CYP2C19 in tofacitinib elimination to be minor and no obvious differences have been reported in tofacitinib exposure between extensive and poor metabolizers in the Japanese healthy volunteers who took part in Study 1 (28). In Study 2, AUC_{inf} has been reported to be 17% higher in poor metabolizers of CYP2C19 compared to extensive metabolizers (16,28). In the present study, the effect of CYP2C19 genotype on tofacitinib exposure was explored using the current PBPK model to evaluate the need for dose adjustment in poor metabolizers of CYP2C19 (16). The simulated exposure in CYP2C19 poor metabolizers was slightly higher compared to extensive metabolizers (6% for C_{max} and approximately 20% for AUC_{inf}, Table V and Table VI), but the simulated PK parameters were comparable between the extensive and poor metabolizers of CYP2C19 in both populations. Simulations conducted for the clinically approved dosing regimen (5 mg BID) showed that the plasma concentration profiles, as well as simulated C_{max} and AUC_{tau}, were essentially comparable among Japanese and Caucasian extensive and poor metabolizers of CYP2C19 (Figure 5 and Table VII). Exposure in Japanese extensive and poor metabolizers were slightly higher compared to Caucasian extensive and poor metabolizers, respectively. The precise reason for the slight difference remains to be clarified, but it may, at least in part, be attributable to the smaller body weight in the Simcyp generated Japanese population. Nevertheless, the simulated data are consistent with earlier findings that CYP2C19 metabolism is a minor contributor in tofacitinib elimination, and that the difference in PK profiles between extensive and poor metabolizers of CYP2C19 either in Japanese or Caucasians is not clinically significant. Thus, the results of the present simulation are in agreement with the current tofacitinib labels in Japan and the United States, where there is no recommendation of dose adjustment for CYP2C19 poor metabolizers (26,27). Although there are known differences in the frequency of CYP2C19 poor metabolizers between the Japanese and Caucasian populations, it is considered that deficiency of CYP2C19 activity does not have such a large impact on tofacitinib exposure that it requires a dose adjustment.

Although the PBPK model employed in the present study provided adequate prediction of PK profiles in Japanese and in Caucasian healthy volunteers, the simulated exposure in the current model were apparently lower compared to reported values in RA patients. Estimated C_{max} and AUC_{tau} at steady state for tofacitinib 5 mg BID monotherapy in RA patients has been reported to be 60.4 ng/mL and 262 ng·a/mL in Japanese, and 61.9 ng/mL and 263 ng·h/mL in non-Japanese, respectively (28), whereas the simulated results for C_{max} and AUC_{tau} in this study were 41.0 ng/mL and 174 ng·h/mL in Japanese, and 34.8 ng/mL and 157 ng·h/mL in Caucasians with typical proportions of CYP2C19 poor metabolizers, respectively (Table VII). This observation is reasonable considering that tofacitinib exposure in patients with RA or psoriasis is known to be higher compared to healthy volunteers (35). One hypothesis for the difference in apparent oral clearance of tofacitinib between the healthy volunteers and patients is the downregulation of CYP3A4 activity by inflammatory stimuli (36). In fact, elevated levels of cytokines have been reported to downregulate the expression and suppress the activity of CYPs, and interleukin-6 (IL-6) in inflammatory disease states are known to downregulate CYP3A4 activity (37). Since the target patient population of tofacitinib are under inflammation burden from diseases

such as RA or psoriasis, it is likely that the clinically observed differences in exposure between patients and healthy volunteers are attributable to the effects of inflammatory burden (36). Further investigation on the sensitivity of disease-drug interaction in relation to ethnic factors remains to be conducted to fully establish the PBPK modeling of tofacitinib in RA patients (36).

In recent years, many drug labels are known to be informed by PBPK modeling in the designing stages of clinical trials or in providing additional information for dose adjustment (11,38). PBPK modeling can start at very early stages of drug development and can be used to provide information needed for an efficient development strategy by helping to identify potential ethnicity-based differences in PK (1,11). Since clinical data from patients outside of Japan are often available prior to the start of multi-regional clinical trials, PBPK is one of the methods to allow effective use of foreign data in assessment of the necessity to conduct a Phase 1 study and/or a dose ranging study in the Japanese population prior to joining a multi-regional clinical trial, and in defining optimal dosing regimens in Japanese. Although PBPK modeling is not a tool that can replace clinical studies, it can add considerable value to clinical data and allow later studies to become confirmatory rather than just exploratory (11). The currently available physiological data for Japanese are from more limited sources compared to the Caucasian population (39-41). Further collection of demographic, anatomical and physiological data in Japanese healthy volunteers would be valuable in future PBPK modeling to predict the PK profile in Japanese. Although additional studies are essential to clarify the disease-drug interaction for predicting PK profiles in patient populations, the current study indicates the potential usefulness of PBPK modeling in defining an optimal dose and in constructing study designs based on early phase study outcomes in the Japanese population.

In conclusion, tofacitinib PK in Japanese healthy volunteers was adequately predicted by the current PBPK model using Simcyp. Although the prediction of tofacitinib exposure in Japanese patients with RA or other inflammatory diseases requires further investigation, including the effect of inflammation on tofacitinib PK, this study successfully demonstrated an experimental application of PBPK modeling in evaluating ethnic sensitivity in PK at early stages of development, presenting the potential usefulness of PBPK modeling as an efficient and scientific method for optimal dose setting in the Japanese population. In combination with population PK analyses, the application of the PBPK modeling approach has the potential to expand to provide even more valuable input to impact drug development strategies and regulatory decision making.

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