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Research Article

Simulating the Impact of Elevated Levels of Interleukin-6 on the Pharmacokinetics of Various CYP450 Substrates in Patients with Neuromyelitis Optica or Neuromyelitis Optica Spectrum Disorders in Different Ethnic Populations

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Abstract. A physiologically based pharmacokinetic (PBPK) model was used to simulate the impact of elevated levels of interleukin (IL)-6 on the exposure of several orally administered cytochrome P450 (CYP) probe substrates (caffeine, S-warfarin, omeprazole, dextromethorphan, midazolam, and simvastatin). The changes in exposure of these substrates in subjects with rheumatoid arthritis (and hence elevated IL-6 levels) compared with healthy subjects were predicted with a reasonable degree of accuracy. The PBPK model was then used to simulate the change in oral exposure of the probe substrates in North European Caucasian, Chinese, and Japanese population of patients with neuromyelitis optica (NMO) or NMO spectrum disorder with elevated plasma IL-6 levels (up to 100 pg/mL). Moderate interactions [mean AUC fold change, ≤ 2.08 (midazolam) or 2.36 (simvastatin)] was predicted for CYP3A4 probe substrates and weak interactions (mean AUC fold change, ≤ 1.29–1.97) were predicted for CYP2C19, CYP2C9, and CYP2D6 substrates. No notable interaction was predicted with CYP1A2. Although ethnic differences led to differences in simulated exposure for some of the probe substrates, there were no marked differences in the predicted magnitude of the change in exposure following IL-6–mediated suppression of CYPs. Decreased levels of serum albumin (as reported in NMO patients) had little impact on the magnitude of the simulated IL-6–mediated drug interactions. This PBPK modeling approach allowed us to leverage knowledge from different disease and ethnic populations to make predictions of cytokine-related DDIs in a rare disease population where actual clinical studies would otherwise be difficult to conduct.

KEY WORDS: CYP450 suppression; drug–drug interactions; interleukin-6 (IL-6); neuromyelitis optica; neuromyelitis spectrum disorder.

INTRODUCTION

Drug development for rare diseases is challenging because conducting a clinical study with the number of patients necessary to obtain sufficient data for robust statistical analysis is not feasible (1). Many rare diseases currently have no indicated treatments, and the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have adopted specific orphan drug legislation to give incentives to develop drugs for these diseases (2,3). One of the challenges in the clinical development of drugs for rare diseases is to estimate the effect of the study drug on the efficacy/safety of concomitant medications since interactions between diseases and drugs cannot be evaluated in healthy volunteers.

With respect to disease–drug interactions, it is well known that the drug disposition processes can be affected by inflammatory conditions including several types of infections, surgical procedures, inflammatory diseases, cancer and autoimmune diseases. One of the mechanisms affecting these interactions is the elevated levels of cytokines such as interleukin-6 (IL-6) in patients compared with healthy volunteers (4). Cytokines such as IL-6 have been shown to suppress the activity of cytochrome P450 (CYP) enzymes *in vitro* and *in vivo* (4–9).

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Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage primarily targeting the optic nerves and spinal cord (10). Similar to results found in other inflammatory disorders, raised serum IL-6 concentrations (up to 80 pg/mL) have been reported in NMO patients (11). Anti–IL-6 therapies are being investigated for the treatment of NMO and NMO spectrum disorders (NMOSD) (12,13). In patients with elevated IL-6 concentrations, upon administration of an anti–IL-6 agent, the exposure of a co-administered CYP-cleared drug may be decreased due to the removal of the cytokine-mediated down-regulation of CYP enzymes (7,14–16).

The down-regulation of CYP enzymes by cytokines at physiologically relevant cytokine concentrations has been studied *in vitro* using hepatocytes (8). CYP3A and CYP2C19 were reported to be the enzymes most sensitive to cytokine-mediated suppression, and IL-6 was the most potent CYP suppressor among the cytokines tested (8,17). *In vitro* CYP suppression data has been successfully utilized in physiologically based pharmacokinetic (PBPK) models to predict the impact that raised IL-6 concentrations in disease have on CYP expression *in vivo* and to study the effect of administration of anti–IL-6 agents in such patients concomitantly exposed to small-molecule drugs (18–20). The predicted changes in the exposure of different CYP substrates (caffeine, S-warfarin, omeprazole, simvastatin, and midazolam) due to IL-6–mediated suppression of different CYP isoforms (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) show good agreement with the observed data (18–20).

Inter-ethnic variability in pharmacokinetics has also been reported (21–23). One of the factors contributing to inter-ethnic variability is differences in enzyme abundance and the frequency of enzyme genetic polymorphisms (21–23). To date, the impact of IL-6–mediated CYP suppression in different ethnicities has not been explored.

Serum albumin concentrations in NMO and NMOSD patients are decreased compared with concentrations in healthy volunteers (24,25). This decrease in serum albumin concentration in patients with NMO and NMOSD may have an impact on the pharmacokinetics of small-molecule drugs, as has been shown in other disease states such as cirrhosis (26–28), and hence may have an impact on their interaction with concomitantly administered anti–IL-6 agents.

The objectives of this study were to use prior *in vitro* and *in vivo* information on IL-6–mediated down-regulation of CYP enzymes to predict the impact of various IL-6 plasma concentrations on the systemic exposure of probe CYP substrates, caffeine (CYP1A2), S-warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), simvastatin, and midazolam (CYP3A) in North European Caucasian, Japanese, and Chinese virtual subjects adjusted for the age and sex demographics of NMO/NMOSD patients. In addition, the effect of decreased plasma albumin levels on the pharmacokinetics of the probe CYP3A substrate simvastatin in North European Caucasian subjects and the level of interaction with IL-6 was also assessed.

METHODS

Physiologically Based Pharmacokinetic Model

The Population-Based Simcyp Simulator (V16.1; Simcyp, Sheffield, UK) was used to simulate the time course of concentrations of the CYP probe substrates caffeine, S-warfarin, omeprazole, dextromethorphan, simvastatin, and midazolam (victim drugs) and IL-6 (perpetrator) in plasma. Details of the PBPK model used in the current study are included in the Supplementary Material.

Modeling of IL-6 Profiles

The model for IL-6 was based on a previously published model (19). To cover the variable exposure of IL-6 (molecular weight 21,000 g/mol) in the NMO population, a number of simulations were run to achieve different steady-state plasma IL-6 concentrations (10, 50, or 100 pg/mL) that span those reported in the literature (11,29). Specific details of the IL-6 model are included in the Supplementary Material. The final parameters used for the IL-6 compound file for simulation of IL-6 pharmacokinetics are shown in Table I.

Table I. Input Parameter Values Used for IL-6 Model

Parameter	Value	Method/reference
Molecular weight (g/mol)	21,000	(30)
Log *P*	0.01	Assumed
Compound type	Neutral	
B/P	1.00	Assumed
f_u	1.00	Assumed
Main plasma binding protein	Human serum albumin	
Distribution model	Minimal PBPK model	
V_{ss} (L/kg)	0.430	(19)
CL_{iv} (L/h)	1.00	(19)
CL_R (L/h)	0	Assumed
Enzyme	CYP1A2	
E_{min}	0.230	(8)
EC_{50} (μM)	5.96×10^{-5}	(8)
Enzyme	CYP2C9	
E_{min}	0.053	(8)
EC_{50} (μM)	5.76×10^{-6}	(8)
Enzyme	CYP2C19	
E_{min}	0.214	(8)
EC_{50} (μM)	3.40×10^{-6}	(8)
Enzyme	CYP2D6	
E_{min}	0.302	(8)
EC_{50} (μM)	7.19×10^{-6}	(8)
Enzyme	CYP3A4	
E_{min}	0.240	(8)
EC_{50} (μM)	3.48×10^{-6}	(8)
Enzyme	CYP3A5	
E_{min}	0.240	Same values as used for CYP3A4; (8)
EC_{50} (μM)	3.48×10^{-6}	Same values as used for CYP3A4; (8)

B/P, ratio of concentration of drug in blood to plasma; f_u, free fraction in plasma; V_{ss}, volume of distribution at steady state; $CL_{i.v.}$, systemic clearance; CL_R, renal clearance; EC_{50}, concentration that supports half E_{min} (i.e., half of the maximal suppressive effect); E_{min}, minimum amount of active enzyme observed in the *in vitro* system (i.e., the maximum amount of suppression) expressed as a fraction of the vehicle control value

Enzyme Dynamics and Suppression of CYPs

A semi-mechanistic dynamic model incorporating the effects of enzyme suppression on the levels of individual CYP proteins in the liver was used to simulate the effects of IL-6 on various CYP isoenzyme-mediated metabolism of probe substrates in the liver (19,31). IL-6–mediated suppression of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A *in vitro* was studied in human hepatocytes (8), and the E_{min} and EC_{50} concentrations from that study were used in the simulations (Table I). Details of the enzyme dynamics and suppression model used in the current study are included in the Supplementary Material.

Population Details

The default Simcyp parameter values for creating virtual North European Caucasian, Japanese, or Chinese populations (population demographics and physiological parameters including liver volume, liver blood flow, and enzyme abundances) have been described previously (21,22,32). For North European Caucasian and Chinese subjects, the default population files in the Simcyp Simulator were used without modification. Some updates were made to the default Japanese population file age–height and height–weight relationships, hepatic and intestinal CYP abundances, serum creatinine, and kidney volume variability. Details of the updates to the Sim-Japanese population used in the current study are included in the Supplementary Material.

Details of the demographic data and key covariates (i.e., serum/plasma albumin and IL-6 levels) collected for NMO or NMOSD subjects are included in the Supplementary Material and discussed in the "Results" section.

Study Design and Simulation Details

Verification of Performance of IL-6 Model

A comparison of observed and predicted plasma concentrations following a single oral dose of caffeine (100 mg), S-warfarin (5 mg), omeprazole (20 mg), dextromethorphan (30 mg), midazolam (0.03 mg/kg), or simvastatin (40 mg) to virtual subjects without IL-6 or with steady-state IL-6 concentrations of 10, 50, or 100 pg/mL was carried out. Ten trials of virtual subjects were simulated to assess likely inter-trial variability. The characteristics of the virtual subjects (i.e., number of participants, age, and sex) and the study design were matched to each clinical study in terms of dose, as well as the time, frequency, duration, and route of administration for victim drugs. The IL-6 levels used in the simulations are relevant *in vivo* concentrations for individuals with rheumatoid arthritis (the target population in the reported clinical studies) (7,18,19). The predicted mean C_{max}, AUC, and their corresponding fold change [= (AUC or C_{max} with IL-6)/(AUC or C_{max} without IL-6)] for these CYP probe substrates in the presence of steady-state concentrations of IL-6 (50 or 100 pg/mL) were compared with the observed data (i.e., fold change of C_{max} or AUC in untreated rheumatoid arthritis patients to C_{max} or AUC after treatment with the anti–IL-6 monoclonal antibodies tocilizumab or sirukumab).

Simulation of IL-6–Mediated Suppression of CYPs in NMO Subjects

To mimic the demographics of subjects with NMO, the following simulations were conducted. Ten virtual trials of 10 subjects aged 30 to 46 years (proportion of females, 0.82) receiving a single oral dose of caffeine (150 mg), S-warfarin (10 mg), omeprazole (20 mg), dextromethorphan (30 mg), simvastatin (40 mg), or midazolam (5 mg) on day 15, co-administered with steady-state IL-6 concentrations of 0, 10, 50, or 100 pg/mL from day 1 to day 18, were generated to assess variability across groups. Simulations were performed using the North European Caucasian, Chinese, and Japanese populations.

To investigate the impact of CYP2C19, CYP2C9, and CYP2D6 polymorphisms on the interactions between the CYP probes and IL-6, additional simulations were performed for 10 virtual trials of 10 subjects aged 30 to 46 years (proportion of females, 0.82) receiving a single oral dose of omeprazole (20 mg), S-warfarin (20 mg), or dextromethorphan (30 mg) on day 15, co-administered with steady-state IL-6 concentrations of 0 or 100 pg/mL from day 1 to day 18, in subjects from the North European Caucasian and Japanese populations categorized as extensive metabolizer (EM) or poor metabolizer (PM) genotypes with respect to these CYPs (or categorized as *1/*1 and *3/*3 for CYP2C9).

The suppressive effect was measured as the fold change of the area under the curve (AUC) or maximum concentration (C_{max}) of the victim drug in the presence *versus* absence of IL-6 levels. The geometric mean values and 95% confidence intervals (CIs) for the whole simulation (based on all individual subjects) were calculated.

Impact of Serum Albumin Levels on IL-6–Mediated Suppression of CYPs in NMO Subjects

To investigate the effect of changes in albumin level on the pharmacokinetics of a CYP probe substrate (simvastatin, 40 mg) and the interaction between the probe substrate and different levels of IL-6, a sensitivity analysis was performed. Simvastatin was chosen as an exemplar probe substrate because it is metabolized by CYP3A, binds to albumin in the plasma, and showed the greatest interaction with IL-6. These simulations were conducted in a single 33-year-old female North European Caucasian subject where the albumin levels were varied between 14.8 and 76.6 g/L. This range covers the range of values reported for NMO and NMOSD subjects (24,25).

RESULTS

Development of a Population with Characteristics of NMO or NMOSD

For most of the covariates searched for among patients with NMO or NMOSD, there was no relevant information identified in the literature; however, information related to the age and sex characteristics of patients with NMO or NMOSD was found. In total, 18 studies describing relevant demographic information of NMO or NMOSD subjects across a range of ethnicities were identified (11,13,25,33–39)

and the data collected is shown in the Supplementary Material (Table S5). The median age of onset of NMO or NMOSD across the studies ranged from 29.5 to 45.7 years of age with no particular relationship with ethnicity being observed. There was insufficient information to perform a formal meta-analysis for the age of subjects, so simulations were conducted with individuals across the age range of 30 to 46 years. The different studies identified comprised a total of 1323 subjects of which 1085 were female. Thus, simulations were performed with a population where the proportion of female subjects was specified to be 82%.

Limited information describing the plasma/serum levels of IL-6 in NMO/NMOSD was identified; the maximum value seen in any of the subjects was 80 pg/mL (11) which is within the range of values reported for subjects with rheumatoid arthritis (19). In addition, serum albumin levels were reported to be lower in NMO subjects than in healthy controls (mean; 45 g/L; range 32.5–61.9 g/L), with a mean value of 41 g/L (range 19.7–67.9 g/L, $n = 89$) in NMO/NMOSD patients (24,25).

Development and Performance Verification of IL-6 Model

The mean predicted plasma concentration–time profiles for IL-6 following administration of intravenous infusion doses of IL-6 (0.00926–0.0926 μg/h) to virtual North European Caucasian subjects (age 30 to 46 years; 82% female) are shown in the Supplementary Material (Fig. S4). The predicted plasma IL-6 steady-state levels (mean and range) in the Chinese and Japanese virtual populations were comparable to those of the North European Caucasian population (shown in the Supplementary Material; Table S6).

The changes in active CYP enzyme levels observed in the virtual North European Caucasian NMO subjects administered with intravenous infusion doses of IL-6 (0.00926–0.0926 μg/h) to achieve mean steady-state concentrations of IL-6 of 10 to 100 pg/mL are shown in the Supplementary Material (Fig. S5). Similar levels of IL-6–mediated enzyme suppression were observed in the virtual NMO subjects of the Chinese and Japanese populations (see details in the Supplementary Material; Table S7).

The simulated pharmacokinetics (C_{max} and AUC) of caffeine, S-warfarin, omeprazole, dextromethorphan, simvastatin, and midazolam in virtual subjects (without IL-6 levels) were comparable with those observed in the healthy Caucasian subjects (40–52). With the exception of dextromethorphan, the fold change of predicted and observed mean AUC or C_{max} values were < 2 for these CYP substrates. Considering the very high variability (41,53), the predicted dextromethorphan exposure in the current study is within the range of clinical data.

A comparison between predicted and observed systemic exposures following single oral administration of caffeine (100 mg), S-warfarin (5 mg), omeprazole (20 mg), dextromethorphan (30 mg), simvastatin (40 mg), or midazolam (0.03 mg/kg) under steady-state IL-6 concentrations of 0, 10, 50, or 100 pg/mL was made in North European Caucasian and Japanese populations with demographics matching those of rheumatoid arthritis subjects reported in the clinical studies (7,15,16) (see Supplementary Material for details; Tables S8–S13). Simulations using IL-6 concentrations of 10 pg/mL (the baseline levels reported in healthy volunteers) showed minimal changes in the pharmacokinetics of CYP substrates. As the simulated steady-state concentration of IL-6 was increased to 50 or 100 pg/mL, there were non-linear, IL-6-concentration-dependent increases in the exposures of orally administered simvastatin, midazolam, omeprazole, S-warfarin, and dextromethorphan (see Supplementary Material for details; Figs. S6–S11).

Although variable, the predicted pharmacokinetic profiles (C_{max} or AUC) of these CYP substrates were broadly comparable with the observed data in rheumatoid arthritis patients apart from dextromethorphan where the predicted values were 4 to 8.5 times the mean values of the observed data (Supplementary Material; Tables S8–S13). However, considering the high variability in dextromethorphan pharmacokinetics, with C_{max} ranging from 0 to 18 ng/mL and AUC ranging from 0 to 260 ng/mL*h (41,53), the predicted dextromethorphan exposure in the current study (Table II) is within the range of reported clinical data. The fold changes in AUC and C_{max} observed in rheumatoid arthritis patients co-administered these CYP substrates with or without tocilizumab or sirukumab (7,15,16,54) were predicted reasonably well when steady-state IL-6 concentrations of 50 or 100 pg/mL were used (Table II). These IL-6 concentrations are within the range of IL-6 concentrations found in rheumatoid arthritis patients (18,19). The predicted and observed mean fold change in AUC values were 1.07 *vs*. 0.89 for caffeine, 1.33 *vs*. 1.22 for S-warfarin, 1.92 *vs*. 1.92 for omeprazole, 1.21 *vs*. 1.03 for dextromethorphan, 2.30 *vs*. 2.36 for simvastatin, and 1.63 *vs*. 1.48 for midazolam (Table II).

Predicting the Impact of IL-6–Mediated Suppression of CYPs in Virtual NMO Subjects

The predicted plasma concentration–time profiles following a single oral dose of S-warfarin (10 mg), omeprazole (20 mg), dextromethorphan (30 mg), simvastatin (40 mg), or midazolam (5 mg) in the absence of IL-6 or in the presence of steady-state IL-6 concentrations of 10 to 100 pg/mL in virtual NMO subjects of North European Caucasian, Chinese, and Japanese populations are shown in Figs. 1, 2, 3, 4 and 5.

The predicted geometric mean C_{max} and AUC fold change (and 95% CIs) in the exposure for caffeine, S-warfarin, omeprazole, dextromethorphan, simvastatin, and midazolam at steady-state 100 pg/mL IL-6 levels in the three ethnic populations are shown Fig. 6, and at various steady-state IL-6 levels (10–100 pg/mL) are shown in Supplementary Material (Table S14).

For each of the CYP substrates tested, with the exception of caffeine, the susceptibility to an interaction with IL-6 increases in NMO patients as the concentration of IL-6 increases; i.e., as the steady-state IL-6 concentration is increased from 10 to 100 pg/mL, the mean predicted AUC fold change increases from 1.18 to 2.36 for simvastatin, 1.15 to 2.08 for midazolam, 1.13 to 1.97 for omeprazole, 1.04 to 1.29 for S-warfarin, and 1.05 to 1.37 for dextromethorphan (Supplementary Material; Table S14).

IL-6 had a negligible impact on the exposure of caffeine (i.e., C_{max} fold change or AUC fold change) in NMO patients in the three ethnic populations (Fig. 6) as the steady-state IL-6 concentration was increased from 10 to 100 pg/mL

Table II. Predicted and Observed C_{max} and AUC Values and Corresponding Fold Changes for Cytochrome P450 Probe Substrates in the Presence of Steady-State IL-6 Concentrations[e] of 50 or 100 pg/mL

	Predicted mean ± SD	[#]Observed mean ± SD	Predicted mean fold change (trial range)	[#]Observed mean fold change
Caffeine (CYP1A2)[b]				
C_{max} (ng/mL)	2380 ± 978	1910 ± 974	1.01 (1.01–1.02)	0.96
AUC (ng.h/mL)	25,000 ± 16,400	15,800 ± 10,000	1.07 (1.04–1.08)	0.89
S-warfarin (CYP2C9)[b]				
C_{max} (ng/mL)	560 ± 215	780 ± 115	1.03 (1.02–1.04)	0.98
AUC (ng.h/mL)	23,100 ± 10,200	24,200 ± 4360	1.33 (1.16–1.37)	1.22
Omeprazole (CYP2C19)[b]				
C_{max} (ng/mL)	493 ± 262	1070 ± 464	1.63 (1.44–1.65)	1.67
AUC (ng.h/mL)	1390 ± 1280	3720 ± 2620	1.92 (1.68–2.02)	1.92
Dextromethorphan (CYP2D6)[c, d]				
C_{max} (ng/mL)	11.1 ± 8.0	2.76 ± 3.17	1.14 (1.11–1.16)	1.27
AUC (ng.h/mL)	186 ± 182	21.9 ± 29.8	1.21 (1.16–1.25)	1.03
Simvastatin (CYP3A)[a]				
C_{max} (ng/mL)	16.4 ± 10.7	36.0 ± 22.0	2.00 (1.82–2.22)	2.57
AUC (ng.h/mL)	70.4 ± 48.3	105 ± 46.0	2.30 (2.07–2.57)	2.36
Midazolam (CYP3A)[b, d]				
C_{max} (ng/mL)	14.0 ± 8.9	17.3 ± 7.8	1.37 (1.28–1.41)	1.34
AUC (ng.h/mL)	52.8 ± 35.0	50.7 ± 24.3	1.63 (1.50–1.72)	1.48

AUC, area under the plasma drug concentration–time curve of 0 to time "*t*"; C_{max}, maximum plasma concentration; AUC or C_{max} fold change = exposure measure (AUC or C_{max}) with IL-6/exposure measure without IL-6

[#] Observed data ($N = 12$) represents data for CYP probe substrate dosed to rheumatoid arthritis patients 1 week before tocilizumab[a,c] *or sirukumab*[b] *treatment (7,15,16).* [d] *Predicted data is based on simulations in the presence of 50 pg/mL steady-state IL-6 concentrations.* [e] *Systemic IL-6 levels span within the range of IL-6 concentrations found in rheumatoid arthritis patients (18,19)*

(Supplementary Material; Table S14). There was no marked difference in the magnitude of interaction with IL-6 for these CYP substrates between the North European Caucasian, Chinese, or Japanese populations (Fig. 6).

Predicted geometric mean (95% CI) C_{max} and AUC values and corresponding fold changes for omeprazole (CYP2C19), S-warfarin (CYP2C9), and dextromethorphan (CYP2D6) in the absence and presence of steady-state IL-6 (100 pg/mL) in polymorphic North European Caucasian and Japanese populations are shown in Fig. 7 and Supplementary Material (Table S15).

With regard to the impact of CYP2C19 polymorphisms on IL-6–mediated DDIs, in the North European Caucasian population of CYP2C19 extensive metabolizers (EM), there was no notable difference in the susceptibility of omeprazole to an IL-6–mediated DDI compared with that of the mixed-phenotype population [mean C_{max} and AUC fold changes were 1.67 *vs*. 1.68 and 1.97 *vs*. 1.97 (mixed 2C19 phenotype *vs*. 2C19 EM) with 100 pg/mL steady-state IL-6 concentrations] (Figs. 6 and 7 and Supplementary Material, Tables S14–S15). In the North European Caucasian population of CYP2C19 poor metabolizers, there was a reduction in the susceptibility of omeprazole to an IL-6–mediated DDI compared with that in the mixed-phenotype or the CYP2C19 extensive metabolizer populations (mean C_{max} and AUC fold changes were 1.27 and 1.81 with 100 pg/mL steady-state IL-6 concentrations) (Figs. 6 and 7 and Supplementary Material, Tables S14–S15). The susceptibilities of omeprazole to an IL-6–mediated DDI in the Japanese populations of CYP2C19 extensive and poor metabolizers were similar to those simulated in the North European Caucasian CYP2C19 extensive and poor metabolizer populations (Figs. 6 and 7). The mean C_{max} and AUC fold changes in Japanese subjects were1.46 and 1.88, respectively, for extensive metabolizers and 1.24 and 1.78 for poor metabolizers with 100 pg/mL steady-state IL-6 concentrations (Fig. 7 and Supplementary Material, Table S15).

With regard to CYP2C9 polymorphisms, in the North European Caucasian CYP2C9*1/*1 population, there was no marked difference in the susceptibility of S-warfarin to an IL-6–mediated DDI compared with that in the mixed-genotype population [mean C_{max} and AUC fold changes were 1.03 *vs*. 1.03 and 1.29 *vs*. 1.32 (mixed 2C9 genotype *vs*. 2C9*1*1) with 100 pg/mL steady-state IL-6 concentrations] (Figs. 6 and 7 and Supplementary Material, Tables S14–S15). In the North European Caucasian CYP2C9*3/*3 population, there was no susceptibility of S-warfarin to an IL-6–mediated DDI. Mean C_{max} and AUC fold changes were, respectively, 1.00 and 0.97 with 100 pg/mL steady-state IL-6 concentrations (Fig. 7 and Supplementary Material, Table S15). The susceptibilities of S-warfarin to an IL-6–mediated DDI in the Japanese populations of CYP2C9*1/*1 and *3/*3 populations were similar to those simulated in the North European Caucasian CYP2C9*1/*1 and *3/*3 populations. The mean C_{max} and AUC fold changes in Japanese subjects were, respectively, 1.01 and 1.29 for CYP2C9*1/*1 population, and 1.0 and 1.0 for CYP2C9*3/*3 population with 100 pg/mL steady-state IL-6 concentrations (Fig. 7 and Supplementary Material, Table S15).

With regard to CYP2D6 polymorphisms, in the North European Caucasian CYP2D6 extensive metabolizer (EM) population, there was no marked difference in the susceptibility of dextromethorphan to an IL-6–mediated DDI compared with that in the mixed-phenotype population [mean

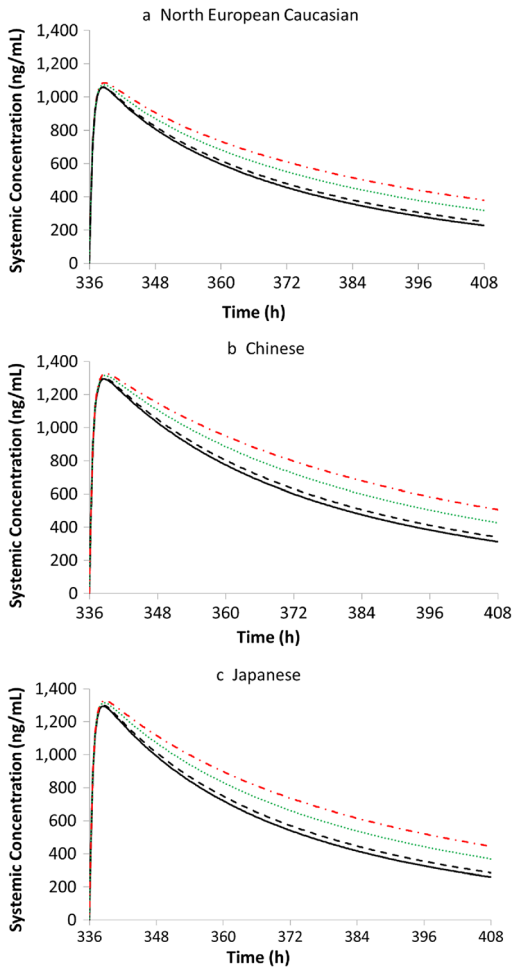

Fig. 1. Mean predicted concentrations of S-warfarin following a single oral dose of 10 mg on day 15 (336 h) in the absence (solid line) and presence of 10 (dashed black line), 50 (dotted green line), and 100 (dash-dotted red line) pg/mL steady state IL-6 in virtual NMO subjects of North European Caucasian (**a**), Chinese (**b**), and Japanese (**c**) populations

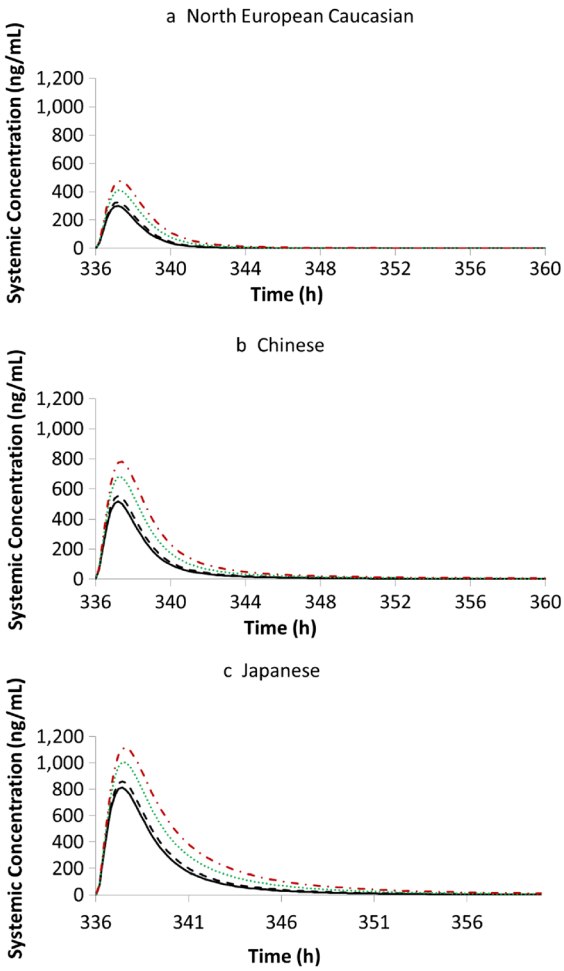

Fig. 2. Mean predicted systemic concentrations of omeprazole following a single oral dose of 20 mg on day 15 (336 h) in the absence (solid black line) and presence of 10 (dashed black line), 50 (dotted green line), and 100 (dash-dotted red line) pg/mL steady-state IL-6 in virtual NMO subjects of North European Caucasian (**a**), Chinese (**b**), and Japanese (**c**) populations

C_{max} and AUC fold changes were 1.28 *vs.* 1.29 and 1.37 *vs.* 1.38 (mixed 2D6 phenotype *vs.* 2D6 EM) with 100 pg/mL steady-state IL-6 concentrations] (Figs. 6 and 7 and Supplementary Material, Tables S14–S15). In the North European Caucasian CYP2D6 poor metabolizer (PM) population, there was a reduction in the susceptibility of dextromethorphan to an IL-6–mediated DDI compared with that in the mixed-phenotype or CYP2D6 extensive metabolizer populations [mean C_{max} and AUC fold changes were, respectively, 1.28 *vs.* 1.04 and 1.37 *vs.* 1.13 (mixed 2D6 phenotype *vs.* 2D6 PM) with 100 pg/mL steady-state IL-6 concentrations] (Figs. 6 and 7 and Supplementary Material, Tables S14–S15). The susceptibilities of dextromethorphan to an IL-6–mediated DDI in the Japanese populations of CYP2D6 extensive and poor metabolizers were similar to those simulated in the North European Caucasian CYP2D6 extensive and poor metabolizers. The mean C_{max} and AUC fold changes in Japanese subjects were, respectively, 1.31 and 1.39 for extensive metabolizers, and 1.06 and 1.14 for poor metabolizers with 100 pg/mL steady-state IL-6 concentrations (Fig. 7 and Supplementary Material, Table S15). Also, the susceptibilities of dextromethorphan to an IL-6–mediated DDI in the North European and Japanese populations of CYP2D6 intermediate (IM) and ultrarapid (UM) metabolizers were similar between these two populations (data not shown).

Effect of Changing Albumin Levels on IL-6–Mediated DDIs

As the human serum albumin concentration was increased from 14.8 to 76.6 g/L in the virtual female subject, the exposure to total simvastatin also increased as judged by the increase in simulated C_{max} and AUC (Fig. 8a). The effect of varying the albumin concentration on the interaction between simvastatin and IL-6 was also investigated at the three different IL-6 steady-state concentrations (10, 50, and 100 pg/mL). As the concentration of albumin in the plasma decreased, there was a trend for the fold change in C_{max} of simvastatin exposure in the presence of IL-6 to increase. This increase in fold change in C_{max} was more pronounced as the IL-6 exposure increased, and at 100 pg/mL IL-6, the fold change in C_{max} changed from 2.33 to 2.71 as the albumin

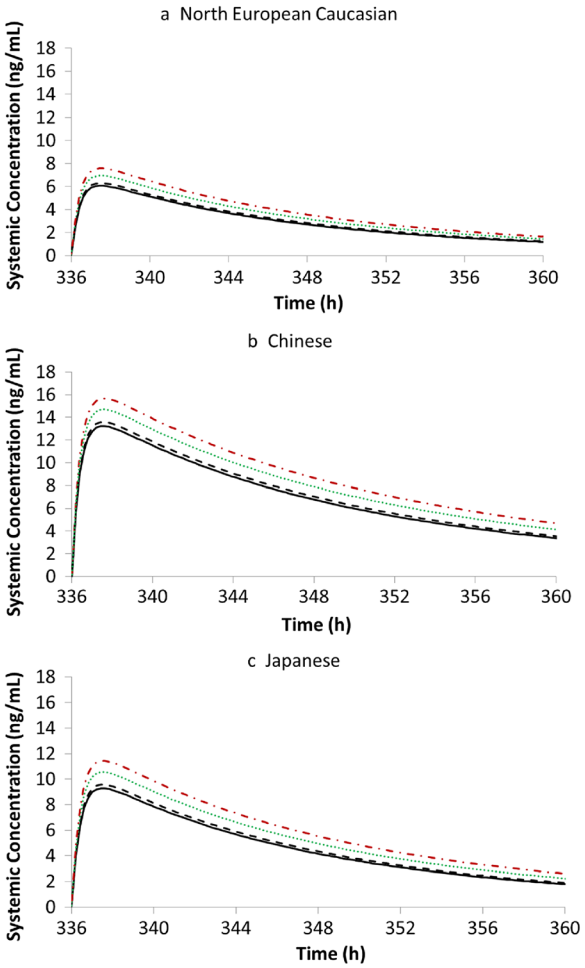

Fig. 3. Mean predicted systemic concentrations of dextromethorphan following a single oral dose of 30 mg on day 15 (336 h) in the absence (solid line) and presence of 10 (dashed black line), 50 (dotted green line), and 100 (dash-dotted red line) pg/mL steady-state IL-6 in virtual NMO subjects of North European Caucasian (**a**), Chinese (**b**), and Japanese (**c**) populations

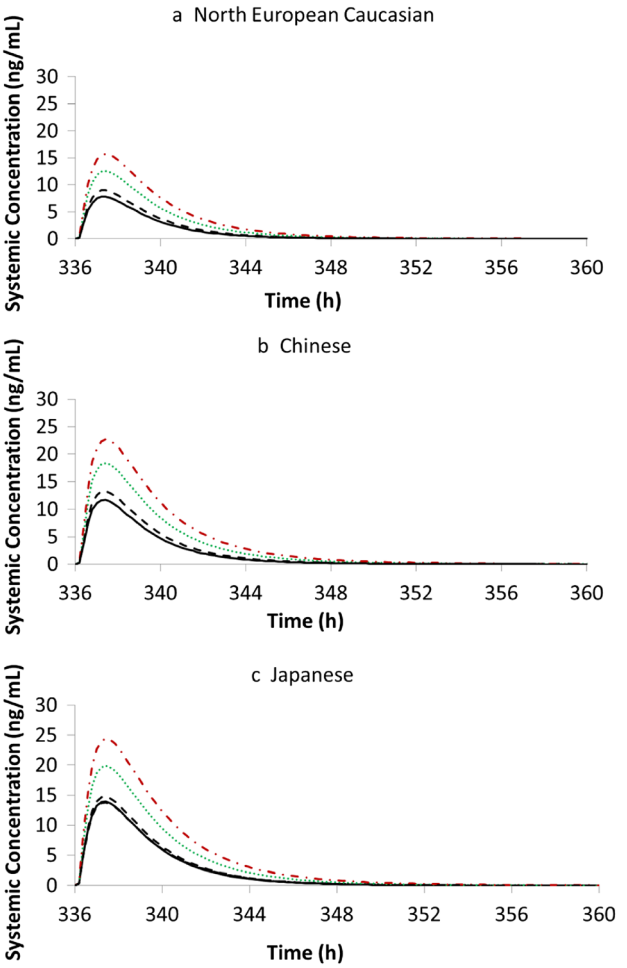

Fig. 4. Mean predicted systemic concentrations of simvastatin following a single oral dose of 40 mg on day 15 (336 h) in the absence (solid black line) and presence of 10 (dashed black line), 50 (dotted green line), and 100 (dash-dotted red line) pg/mL steady-state IL-6 in virtual NMO subjects of North European Caucasian (**a**), Chinese (**b**), and Japanese (**c**) populations

concentration decreased from 76.6 to 14.8 g/L (Fig. 8b). In contrast to the effects on C_{max}, there was minimal alteration in the AUC fold changes as the human serum albumin level in the virtual individual was varied, regardless of the IL-6 concentration in the plasma (Fig. 8c).

DISCUSSION

The application of the current approach for quantitatively predicting the IL-6–mediated DDIs with small molecules in various disease conditions (i.e., rheumatoid arthritis, bone marrow transplantation, post-surgical trauma, leukemia) had been outlined previously (19,20). The predicted degree of interaction with 50 or 100 pg/mL steady-state IL-6 using the PBPK model herein were similar to the reported values in rheumatoid arthritis patients receiving anti-IL-6 therapies (16,19).

The largest changes in exposure were predicted for the CYP 3A4 substrate simvastatin and the CYP 2C19 substrate omeprazole, but even here the mean change in AUC fold change was predicted to be < 2.5-fold in line with the clinical observations. Although the data was variable, the change in exposure for caffeine in subjects with elevated IL-6 levels was minimal with the reported 90% confidence intervals including an AUC fold change of 1 (16). This is in line with *in vitro* IL-6–mediated suppression data (based on both enzyme activity as well as on mRNA expression) (8), in which CYP1A2 was the enzyme least sensitive to IL-6, likewise the current PBPK model predicted that IL-6 would have minimal impact on caffeine exposure in rheumatoid arthritis subjects [predicted mean AUC ratio (trial range) = 1.07 (1.04–1.08)].

Dextromethorphan AUC was not changed significantly in rheumatoid arthritis patients following treatment with tocilizumab (15,54). The current model, however, predicted a slight increase in the exposure for dextromethorphan with steady-state IL-6 concentrations of 50 and 100 pg/mL (AUC fold change, 1.21 and 1.37, respectively). The exact reason for this over-prediction in the dextromethorphan exposure is not clear at this stage. However, one of the reasons could be that the *in vitro* CYP2D6 suppression data used in the current model is based on the incubations from only a single hepatocyte donor (8); hence, potential inter-donor variability

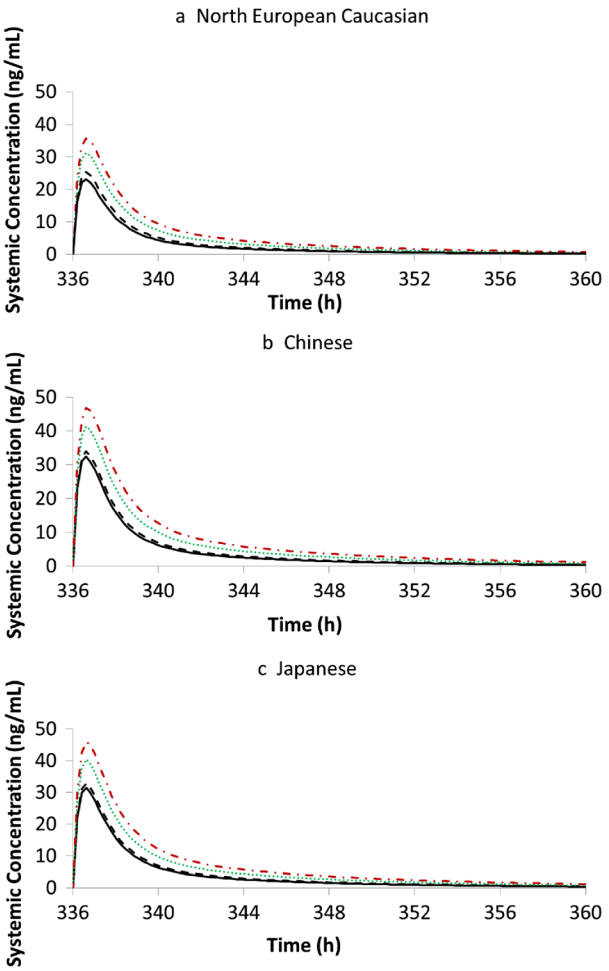

Fig. 5. Mean predicted systemic concentrations of midazolam following a single oral dose of 5 mg on day 15 (336 h) in the absence (solid black line) and presence of 10 (dashed black line), 50 (dotted green line), and 100 (dash-dotted red line) pg/mL steady-state IL-6 in virtual NMO subjects of North European Caucasian (**a**), Chinese (**b**), and Japanese (**c**) populations

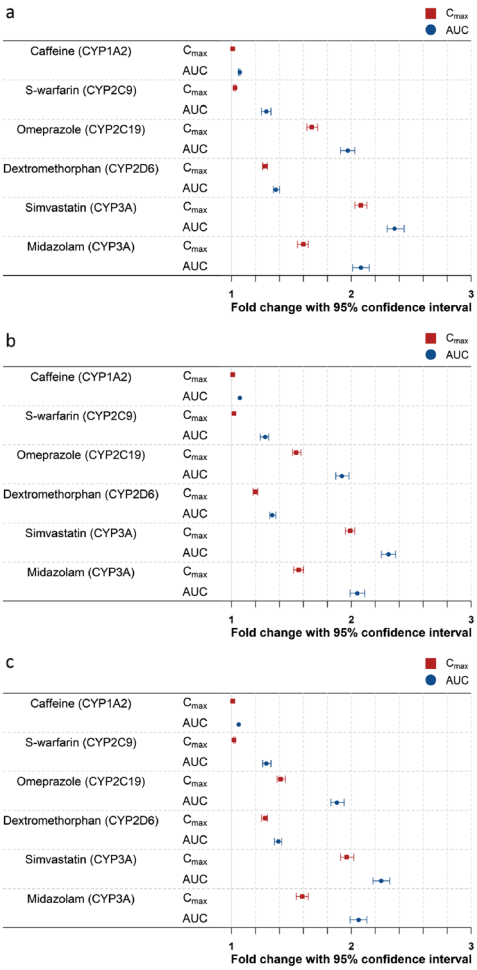

Fig. 6. Predicted geometric mean C_{max} and AUC fold changes (and 95% CIs) for cytochrome P450 probe substrates in the presence of steady-state IL-6 (100 pg/mL) in virtual NMO subjects of North European Caucasian (**a**), Chinese (**b**), and Japanese (**c**) populations

could be contributing to the predicted over-prediction of dextromethorphan exposure in the current study. Further *in vitro* studies using additional donors would be useful for better understanding the variability in IL-6–mediated suppression for CYP2D6.

Similar to other inflammatory disorders/conditions (i.e., in rheumatoid arthritis, after surgery, and during infection) (19), serum IL-6 concentrations are elevated in NMO patients (≤ 80 pg/mL) (11). Recruiting enough subjects with NMO to conduct a dedicated DDI study is however challenging; therefore, a PBPK modeling approach was used to investigate the likelihood of IL-6–mediated DDIs in NMO patients treated with anti-IL-6 therapies.

Although there were differences between the North European Caucasian, Chinese, and Japanese populations in the simulated pharmacokinetics of some of the CYP probe substrates, the simulated effect of IL-6–mediated suppression was similar in all three populations and similar to those simulated in the rheumatoid arthritis subjects. These findings are in alignment with data reported by Terao *et al.* and Zhuang *et al.* (16,54).

As some of the CYP isozymes are known to be polymorphically expressed, simulations were conducted in populations of extensive and poor metabolizers of each of the polymorphic enzymes. Both North European Caucasian and Japanese populations containing only extensive metabolizers for CYP2C19, CYP2C9 (*1/*1 for CYP2C9) or CYP2D6 each showed similar susceptibility to IL-6–mediated DDIs when compared with populations with mixed CYP phenotypes (taking into account the reported phenotype frequencies) (32). This is unsurprising because the frequency of extensive metabolizers for these CYPs is high (> 85%) in the North European Caucasian population (32). In populations of poor metabolizers (*3/*3 for CYP2C9), the susceptibility to IL-6–mediated DDIs was vastly reduced due to low levels of or absence of active CYP enzymes. For omeprazole and dextromethorphan in the CYP2C19 and CYP2D6 poor metabolizer populations, a reduced level of IL-6–CYP interaction was predicted compared with that in the extensive metabolizer populations. This is due to suppression of other clearance pathways that contribute to the elimination of omeprazole (CYP3A4) and dextromethorphan (CYP2C9, CYP2C19, and CYP3A4) and that are still acting in poor metabolizers of CYP2C19 or CYP2D6, respectively. For S-warfarin, elimination in CYP2C9 *3/*3 subjects is primarily

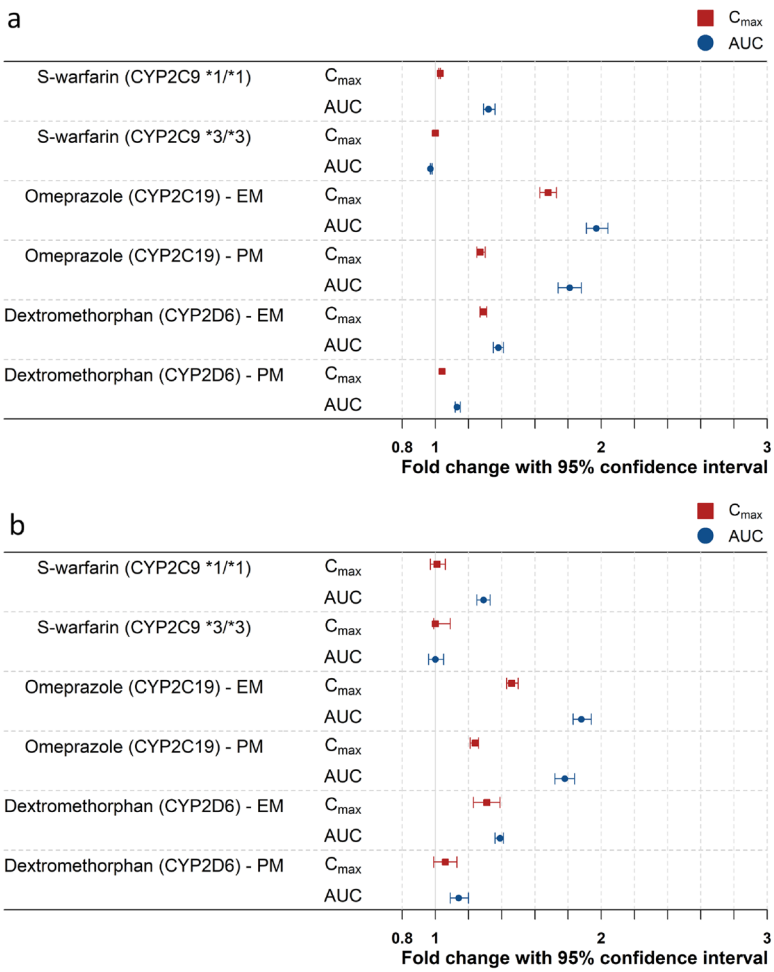

Fig. 7. Predicted geometric mean (95% CI) C_{max} and AUC fold changes for S-warfarin (CYP2C9), omeprazole (CYP2C19), and dextromethorphan (CYP2D6) in the presence of steady-state IL-6 (100 pg/mL) in polymorphic North European Caucasian (**a**) and Japanese (**b**) populations

via renal elimination and hence is not affected by raised IL-6 levels. Although the simulations conducted in this study were primarily focused on the effects of anti-IL-6 mAb treatment, other therapeutic modalities could also change the serum levels of IL-6. For instance, *in vitro* data indicated that small molecule drug JAK1/2 (Janus Kinase) inhibitors (i.e., ruxolitinib, tofacitinib) markedly reverse IL-6–mediated suppression of hepatic CYPs and drug transporters (55). Treatment of patients suffering from myeloproliferative neoplasms or rheumatoid arthritis with ruxolitinib or tofacitinib leads to a reduction in the elevated plasma IL-6 levels of these patients (56,57). To the best of our knowledge, no formal studies to investigate the clinical DDI data between JAK inhibitors and CYP substrates due to changes in IL-6 levels have been reported in the literature. However, considering the common driving factor (i.e., elevated IL-6 levels) for these potential DDIs (due to treatment with anti-IL-6 mAb *versus* small molecule drug JAK inhibitors), the current PBPK approach could be used for predicting IL-6–mediated DDIs for JAK inhibitors as well.

Varying the serum albumin concentration from 14.8 to 76.6 g/L led to an increase in the total simvastatin exposure (C_{max} and AUC). The C_{max} fold change with steady-state IL-6 of 100 pg/mL was decreased (2.71 to 2.33) as the serum albumin concentration increased from 14.8 to 76.6 g/L. In contrast, there was little impact on the AUC fold change as the human serum albumin level in the virtual individual was varied, regardless of the IL-6 concentration in the plasma. Therefore, a decrease in serum albumin concentrations in NMO patients is not expected to have any significant impact on the change in CYP substrate exposure due to increased IL-6 concentrations in these patients. In contrast for a low extraction compound, alprazolam (CYP3A substrate), the AUC fold change with steady-state IL-6 of 100 pg/mL was decreased (1.94 to 1.50) as the serum albumin concentration increased from 14.8 to 76.6 g/L (data not shown). However, there was negligible impact on the C_{max} fold change as the human serum albumin level in the virtual individual was altered, regardless of the IL-6 concentration in the plasma. This suggests that a decrease in serum albumin concentrations in NMO patients can potentially have an impact on the change in exposure of a low extraction compound due to increased IL-6 concentrations in these patients.

Some limitations of the current study are that the *in vitro* IL-6 suppression data used to inform the PBPK model are only taken from one study. It would be good in the future to revise the model if more *in vitro* data becomes available. In addition, the study only considers the effect of IL-6 and not other cytokines as a suppressor of the CYP isozymes. Although other cytokines are also elevated in inflammatory conditions such as

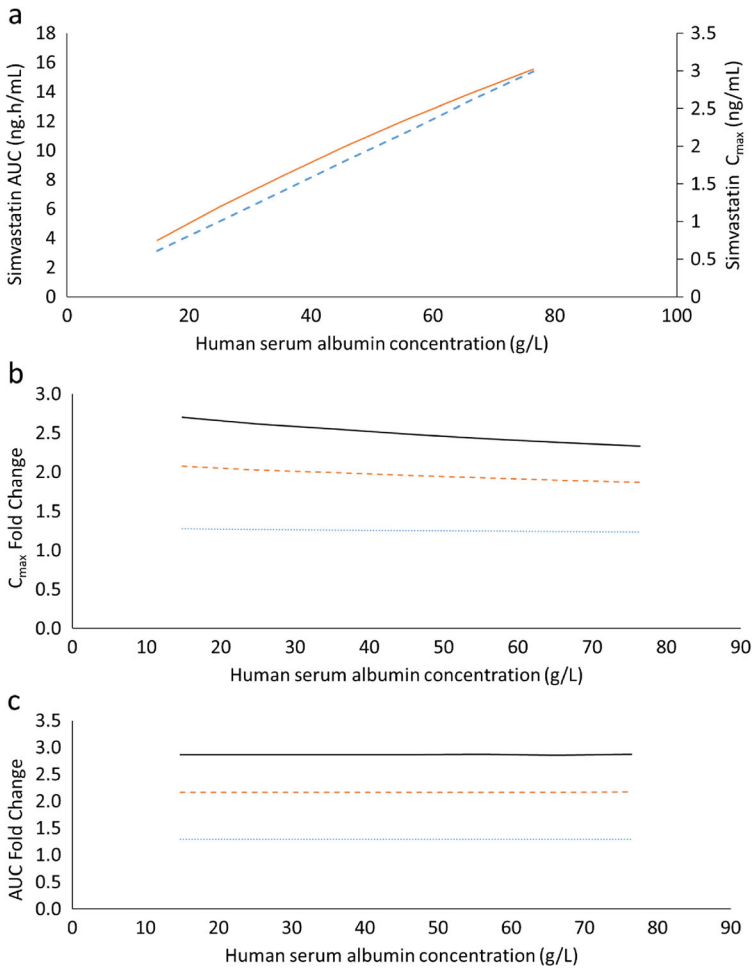

Fig. 8. Simulated relationship between simvastatin C_{max} (solid orange line) and AUC (blue dashed line) as the human serum albumin concentration in the virtual female subject used for sensitivity analysis was varied between 14.8 and 76.6 g/L (**a**). Effect of changing human serum albumin concentrations on the C_{max} fold change (**b**) or AUC fold change (**c**) for simvastatin in the presence of IL-6 at a steady-state concentration of 10 (dotted blue line), 50 (dashed orange line), and 100 (solid gray line) pg/mL

rheumatoid arthritis, it is reported that compared with other cytokines such as IL-10 and interferons, IL-6 is the key cytokine that has the most significant suppressive effects on CYPs *in vitro* and *in vivo* (8,17,20,58–60). This suggests that the role of other cytokines on the overall disposition of these CYP substrates in the NMO population may be small.

As well as changing the levels of CYP isozymes, it has been shown that elevations in cytokines can also modulate the levels of transporters and other proteins *in vitro* (e.g., P-glycoprotein, organic anion transporting polypeptides) that play a role in the disposition of some drugs (55). However, to the best of our knowledge, clinically relevant DDIs involving inflammatory cytokine-mediated suppression of transporter activity have not been reported. The role of transporters could not be considered in the current model due to the lack of concentration-dependent IL-6 suppression data on transporters and information on turnover rates for these transporter proteins.

In this study, we evaluated the impact of a constant elevated IL-6 concentration on CYP enzymes. However, NMO is a relapsing disease with recurring attacks of optic neuritis and myelitis, or both (24), and IL-6 levels in the relapse phase are probably higher than IL-6 levels in the stable phase. Xu *et al.* (20) reported that the effect of cytokines on CYPs depends primarily on the duration of cytokine elevation and that transient cytokine elevation has a low DDI potential; however, no consensus has been reached on this point. The precise relationship between DDI and a patient's inflammatory status remains to be clarified.

CONCLUSION

The findings of this study indicated that increasing levels of IL-6 led to predicted increases in exposure to the CYP probe substrates tested, with the exception of caffeine (CYP1A2). The CYP3A substrates (simvastatin and midazolam) were the most sensitive to IL-6–mediated suppression, with mean AUC fold changes >2. CYP2C19 (omeprazole) was the next most sensitive to IL-6–mediated suppression (mean AUC fold change of up to 1.97), and CYP2C9 (S-warfarin) and CYP2D6 (dextromethorphan) had moderate sensitivity to IL-6–mediated suppression with mean AUC fold change of up to 1.29 and up to 1.37, respectively. There were no notable ethnic differences between the North European Caucasian, Japanese, and Chinese populations in the sensitivity of the change in pharmacokinetics of CYP probe substrates following IL-6–mediated suppression. Reduced susceptibility to IL-6–mediated suppression of CYPs was observed in populations containing only poor metabolizers of CYP2C9, CYP2C19 or CYP2D6 enzymes. Also, decreased

serum albumin concentrations (as has been reported in NMO patients) had only a limited effect on the simulated IL-6–mediated DDIs with simvastatin in NMO patients.

Overall, these findings show the utility of PBPK model-based approaches for predicting IL-6–mediated DDIs due to suppression of CYPs in a rare disease population like that of NMO or NMOSD. Conducting disease–drug interaction trials involving patients with rare diseases is challenging because of the limited patient population and accompanying ethical and operational difficulties, as well as the issue of polypharmacy. Leveraging prior knowledge on the particular characteristics of the disease population *via* PBPK models can provide an effective and efficient way to explore the interaction risk.

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AUTHOR CONTRIBUTIONS

K.K.M., C.E.-T., K.T., K.L.G., O.J.H., I.G., N.P., and P.S.D. wrote the manuscript.

K.K.M., C.E.-T., K.L.G., I.G., N.P., and P.S.D. designed the research.

K.K.M., K.L.G., O.J.H., and I.G. performed the research.

K.K.M., K.L.G., and I.G. analyzed the research.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest K.K.M., K.L.G., and I.G. are employees of Certara UK Limited, Simcyp Division, Sheffield, United Kingdom.

C.E.-T. and K.T. are employees of Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.

N.P. and P.S.D. are employees of F. Hoffmann–La Roche Ltd., Basel, Switzerland.

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