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Individualized regimen of Posaconazole oral suspension in Chinese HSCT patients based on population pharmacokinetic model

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To establish a population pharmacokinetic (PopPK) model of posaconazole suspension in Chinese hematopoietic stem cell transplantation (HSCT) patients and to recommend an optimal dosing regimen. A single-center, retrospective, model-based study was conducted in 62 Chinese patients, including 103 with posaconazole plasma concentrations. PopPK analysis using NONMEM software. A one-compartment model of first-order elimination and absorption was in good agreement with the experimental data. Analysis of covariance showed that body weight (WT), creatinine clearance (CCR), and proton pump inhibitor (PPI) had a significant effect on the pharmacokinetics of posaconazole. The dose simulation results show that patients with CCR ≥ 90 mL/min require at least 3 mg/kg TID and 7 mg/kg BID dosing regimens for prevention and treatment, respectively. However, when combined with PPI, at least 5 mg/kg BID and 5 mg/kg TID dosing regimens are required for prevention and treatment, respectively. Regardless of whether it is used in combination with PPI or not, patients with a CCR of 60–90 mL/min can achieve PTA goals by using a 4 mg/kg BID and 4 mg/kg TID regimen for prevention and treatment, respectively. A dosing regimen of 3 mg/kg BID in patients with a CCR of 30–60 mL/min is sufficient to meet the PTA goal of prophylaxis, and the dose needs to be elevated to 4 mg/kg BID for the treatment of fungal infections, and there is no need to change the dose according to the coadministration of PPI. When the patient's CCR is less than 30 mL/min, whether or not combined with PPI, the administration regimen of 2 mg/kg BID and 3 mg/kg BID can meet the PTA goals for prevention and treatment, respectively.

Keywords Posaconazole, Pharmacokinetics, Hematopoietic stem cell transplantation, Dosage, Invasive fungal infections

Patients undergoing hematopoietic stem cell transplantation (HSCT) are at high risk for fungal infections, and invasive fungal disease (IFD) is a significant cause of morbidity and mortality in HSCT patients[1]. Although the epidemiology of IFD has changed dramatically with improvements in medical technology and prevention strategies, the mortality rate of infected patients remains high, mainly because of delays in treatment due to difficulties in diagnosis[2]. Antifungal therapy is therefore necessary for HSCT patients. The use of antifungal drugs during patient treatment is effective in reducing morbidity and mortality[3]. Posaconazole is a systemic triazole broad-spectrum antifungal drug with a structure derived from itraconazole and an antifungal mechanism of action like that of other triazoles[4]. Compared to echinocandins and other triazoles, posaconazole offers a wider antibacterial range, higher antibacterial activity, and superior economic advantages. Posaconazole has a wide variety of uses in the prevention and treatment of IFD and is advised as a first-line medication in several guidelines and studies[5].

The U.S. Food and Drug Administration (FDA) initially authorized posaconazole as an oral suspension in 2006, and its delayed-release tablet and intravenous injection were additionally authorized there in 2013 and

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2014, correspondingly[6]. The pharmacokinetic profile of posaconazole is highly variable, and for posaconazole oral suspension, higher gastric pH and gastric motility may reduce the bioavailability of posaconazole by decreasing its solubility and shortening its gastric emptying time, whereas concomitant administration with food may increase its bioavailability by increasing its gastric emptying time. Posaconazole is highly lipid-soluble and tissue-permeable, crossing the blood–brain and placental barriers. Posaconazole can be widely distributed in different tissues and body fluids in the body and accumulates in peripheral tissues. In addition, about 17% of the metabolism of posaconazole is glucuronidated by uridine diphosphate-glucuronosyltransferase (UGT), and the rest of the metabolism is not biotransformed and is excreted in its original form[4]. The efficacy of posaconazole is correlated with its blood concentration, and the target trough concentration (C_{min}) of posaconazole should be maintained above 0.7 μg/mL for the prevention of IFD and above 1.0 μg/mL as the C_{min} for the treatment of IFD[7]. Some studies have shown that a high percentage of patients failed to attain target concentrations because of the high inter- and intra-patient variability in posaconazole concentrations[8]. Although delayed-release tablets and intravenous injection of posaconazole have been shown to have higher and more stable exposure profiles, its oral suspension is still widely used in China[9]. A mathematical modeling technique called population pharmacokinetic (PopPK) is used to quantitatively evaluate the pharmacokinetic properties of medication absorption, distribution, metabolism, and excretion as well as to explain inter-individual variability[10]. With PopPK modeling and simulation, patients taking posaconazole suspension can receive sufficient effective exposure during treatment[11]. Huang S et al.[10] conducted a systematic external validation of posaconazole PopPK models published since 2022, which showed that the currently published PopPK models have poor predictive performance for posaconazole concentrations and indicated the need to establish a PopPK model for posaconazole for the Chinese population. In addition, there is still a lack of PopPK studies on posaconazole suspension in patients with HSCT. Therefore, we conducted a retrospective, single-center, PopPK study to evaluate the pharmacokinetic profile of posaconazole suspension in Chinese patients with HSCT.

Materials and methods

Ethics

The study was designed to comply with legal requirements and the Declaration of Helsinki and was approved by the Ethics Committee of Shandong First Medical University (approval number R202312200209). All methods were performed in accordance with the relevant guidelines.

Study design and patients

This retrospective, single-center, study was conducted at the First Affiliated Hospital of Shandong First Medical University, China. The study was conducted between October 2021 and April 2023. Inclusion criteria: (1) Patients undergoing HSCT; (2) Administration of posaconazole suspension for at least > 7 days; (3) Therapeutic drug monitoring was performed during treatment and at least 1 posaconazole concentration was obtained. Exclusion criteria: (1) Inadequate demographic or medication use information; (2) Blood collection and detection is not compliant; (3) Patients who have participated in clinical trials of other antifungal drug interventions during hospitalization.

Enrolled patients received posaconazole oral suspension (Noxafil®) at a dose of 150–600 mg/d twice a day (bid) or three times a day (tid), usually with meals at around 08:00, 11:30 and 18:30. Collect age, gender, height, weight, medication administration information and coadministration information for each patient. Collection of biochemical laboratory values biochemical tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), gamma-glutamyltransferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), creatinine clearance (Ccr) and estimated glomerular filtration rate (eGFR) for each patient. Body mass index (BMI) calculated as weight(kg) /height^2(cm) and eGFR calculated with CKE-EPI in ml/min[12]. Ccr was calculated using the Cockcroft–Gault equation[13].

Sample collection and bioanalysis

When the patient had taken a continuous dosage of posaconazole suspension for at least 7 consecutive days, blood sample collection began. Pharmacokinetic samples were collected 0.5 h before the first dose on that day and 2 or 4 h after the dose. The concentration of the sample collected before the first dose of that day was defined as the C_{min}. 1–3 concentration samples were collected per patient, and at least one C_{min} was collected. Blood samples were collected in tubes with EDTA. Separation of plasma by centrifugation (4000 rpm, 10 min) and immediate analysis of separated plasma.

The plasma concentration of posaconazole was measured by high performance liquid chromatography (HPLC) using an inert sustain C18 column (5 μm; 4.5 mm × 250 mm, Shimadzu Corporation). The mobile phase consisted of ultrapure water and acetonitrile. The flow rate was set to 0.8 ml/min and the ultraviolet (UV) detector wavelength was set to 261 nm. Prior to HPLC injection, protein precipitation was performed with acetonitrile and the supernatant was injected after centrifugation at 12,000 rpm for 10 min.

According to FDA Guidance (2018) on Bioanalytical technique Validation, the technique was satisfactorily validated for specificity, linearity, precision, accuracy, and stability. The linear calibration curve is 0.1–10 μg/mL. The lower limit of quantification (LLOQ) is 0.1 μg/mL.

Population pharmacokinetic modeling

PopPK modeling was performed using NONMEM version 7.3.0. The absorption rate constant (Ka)was fixed to 0.4 /h and then tested and analyzed for the one-compartment model and the two-compartment model, respectively[11,14,15]. Comparative analysis of models through criteria such as objective function value (OFV) and diagnostic plots of the model's goodness-of-fit to determine the best structural model. A power exponential

error model was used to describe the inter-individual variability of the subjects, the expression of which is given in Eq. (1).

$$\theta_i = \theta_{pop} \times e^{\eta i} \tag{1}$$

In Eqs. (a), θ_i denotes the value of the PK parameter for the i-th subject, θ_{pop} denotes the population-typical value of this PK parameter, and η_i denotes the inter-individual variability among subjects obeying a normal distribution with a mean of 0 and variance of ω^2. Four residual models, summation, proportional, power exponential, and mixed, were run on the one- and two-compartment models, respectively, and the OFV from the runs, as well as the model diagnostic plots, were compared to find a residual model that is more suitable for describing the variability of the residuals. The residual model is formulated as Eq. (2), Eq. (3), Eq. (4) and Eq. (5). Where ERR denotes the residual error, which follows a normal distribution with mean 0 and variance σ^2.

$$\text{Summation error model} : Y = F(x) + ERR(1) \tag{2}$$

$$\text{Proportional error model} : Y = F(x) \times (1 + ERR(1)) \tag{3}$$

$$\text{Power exponential error model} : Y = F(x) \times e^{ERR(1)} \tag{4}$$

$$\text{Mixederror model} : Y = F(x) \times (1 + ERR(1) + ERR(2)) \tag{5}$$

Each covariate will be substituted into the population model in turn, and a covariate will be considered significant ($P < 0.05$) if its OFV decreases by more than 3.84 after it is substituted into the model. Covariates were included using a round-by-round screening approach, where the covariates with the largest declines in OFV were selected in each round to remain in the model and continued to be screened using this model as the baseline until all covariates had declines in OFV of less than 3.84 to stop screening. All significant covariates were substituted together into the model and then eliminated sequentially using backward elimination, at which point a more stringent p-value test ($P < 0.001$) was used, i.e., if the OFV increased by more than 10.83 after the elimination of a covariate, the factor was significant. The backward elimination process also uses the round-by-round screening method, eliminating the covariates with the smallest elevated OFV in each round until all covariates have elevated OFV greater than 10.83, and finally obtaining the final model.

Pharmacokinetic model evaluation

The accuracy of the parameters and their respective standard errors were used to gauge the model's goodness-of-fit (GOF). The stability of the final model is assessed by the nonparametric bootstrapping method. The percentage of successful model bootstrap and the median and 5th and 95th quartiles of the bootstrap parameters were calculated by sampling the original data with put-back 1000 times to get 1000 new datasets. Evaluate the predictability of the final model using the normalized prediction distribution errors (NPDE) test in terms of data and graphs. The NPDE is expected to follow a (0, 1) normal distribution based on 1000 simulations of the dataset with the final model parameters. Graphical summary of NPDE results using R (version 4.2.2). Prediction-corrected visual prediction checks were performed on the final model through 1000 simulations, and the visual predictive check plot were plotted by Pirana (version 23.1.1).

Simulations

Based on the final PopPK model, the optimal dosing regimen was evaluated using Monte Carlo simulation (n = 100). Twelve dosing regimens of 2,3,4,5,6, and 7 mg/kg at BID or TID were simulated, respectively. Steady-state $C_{min} \geq 0.7$ μg/mL were used as target concentrations for prevention of IFD, $C_{min} \geq 1.0$ μg/mL was used as a target concentration for treatment of IFD[4,9]. The number of times the steady-state C_{min} surpassed the goal concentration divided by the total number of simulations, then multiplied by 100%, was used to compute the percentage of target attainment (PTA). More than 70% of PTA is considered an acceptable dosing regimen[9].

Ethics statement

Due to the retrospective nature of the study, Medical Ethics Committee of the First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital) waived the need of obtaining informed consent.

Results

Demographic characteristics

A total of 103 concentration points from 62 HSCT patients were included for PopPK modeling. Patient demographics and study indicators are detailed in Table 1. The 98 concentration points collected were primarily C_{min}. Posaconazole concentrations ranged from 0.1–4.03 μg/mL with a median of 0.706 μg/mL.

Model building

A one-compartment pharmacokinetic model with first-order absorption and elimination best characterized the pharmacokinetics of posaconazole. The model follows the Residual unknown variability (RUV) of the proportional error model. The pharmacokinetic parameters of this model include apparent clearance (CL/F), apparent volume of distribution (V/F) and Ka. The covariates examined were age, gender, bodyweight (WT), BMI, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin (ALB), gamma-glutamyltransferase,

Items	Median (Range)
Demographics	
Age(year)	20.5(3–65)
Gender(male)	30
Bodyweight (kg)	45.85(13.65–80)
BMI(kg/m^2)	19.17 (10.74–28.34)
Biochemical parameters	
ALT(U/L)	27.15(2.7–188.3)
AST(U/L)	19.2(2.5–234.1)
ALP(U/L)	107 (45–243)
ALB(g/L)	40.1 (5.1–49.3)
GGT(U/L)	32.2 (9–327)
TBIL(umol/L)	11 (4.00–134.7)
DBIL(umol/L)	4.9 (1.37–114.9)
CCR(mL/min)	103.81 (14.44–240.64)
eGFR(mL/min)	129.98 (33.38–282.08)
Combined use of medications	
Proton pump inhibitor (No. of patients)	11
Phenytoin sodium (No. of patients)	12
Metoclopramide (No. of patients)	7

Table 1. Patient characteristics and study indicators.

total bilirubin, direct bilirubin, CCR, eGFR, proton pump inhibitor (PPI), phenytoin sodium, and metoclopramide. The final covariate retained is WT, CCR, and PPI. CCR have a significant effect on CL/F, and WT and PPI have a significant effect on V/F. Table 2 lists the estimated PK parameters for the final model as well as the outcomes of the internal validation. All PK parameters were calculated with adequate accuracy and without any bias. Indicating that the final model was stable, bootstraps had a success rate of 83.7%.

Model evaluation

The model diagnostic plot of the final model is shown in Fig. 1. The real-world concentrations compared (DV) to the population predicted concentrations (PRED) and the individual predicted concentrations (IPRED) revealed an appropriate degree of agreement with the observed values (Fig. 1A,B). However, there are still some PRED and IPRED that are over-predicted. No apparent trends in the projected concentrations or over time were shown by the conditional weighted residuals (CWRES). The Majority of the CWRES are in the range of -2 to 2 and are symmetrically distributed around the x-axis (Fig. 1C,D).

Parameters	Final Model Estimates	RSE (%)	Shrinkage (%)	Median by 1000 bootstraps	95% CI by 1000 bootstraps
Ka (1/h)	0.4 FIX	–	–	–	–
CLpop (L/h)	11.5	22.3	–	10.63	4.55–17.2
CLccr (L/h)	0.68	32.1	–	0.88	0.4–3.21
Vpop (L)	829	5.2	–	763	123.55–1520
Vwt (L)	1.78	16.2	–	1.58	0.82–2.39
Vppi(L)					
Ppi = 0	3.34	8.7	–	4.05	0.99–16.53
Ppi = 1	12.8	20.0	–	14.8	3.31–66.94
IIVCL (%)	111.8	17.3	25.2	97.5	3–147.6
IIVV (%)	82.6	12.7	32.1	78.5	2.9–117.5
Proportional error (%)	13.7	13.6	35.2	14.2	10.0–21.9

Table 2. Population pharmacokinetic parameter estimation of posaconazole in patients with HSCT. CL/F (L/h) = $11.5 \times e^{1.12} \times (CCR/103.81)^{0.68}$; V/F (L) = $829 \times e^{0.826} \times (WT/45.85)^{1.78} \times Vppi$. *RSE* residual standard error, *CI* confidence interval, *Ka* absorption rate constant, *CLpop*, clearance of the typical subject, *CCR* creatinine clearance, *CLccr*, magnitude of the effect of creatinine clearance on CL, *Vpop*, volume of distribution of the typical subject, *WT* bodyweight, *Vwt* magnitude of the effect of bodyweight on V, *PPI* proton pump inhibitor, 0 for no combined use, 1 for combined use, *Vppi* magnitude of the effect of proton pump inhibitor on V, *IIVCL* interindividual variability on clearance, *IIVV* interindividual variability on apparent volume of distribution.

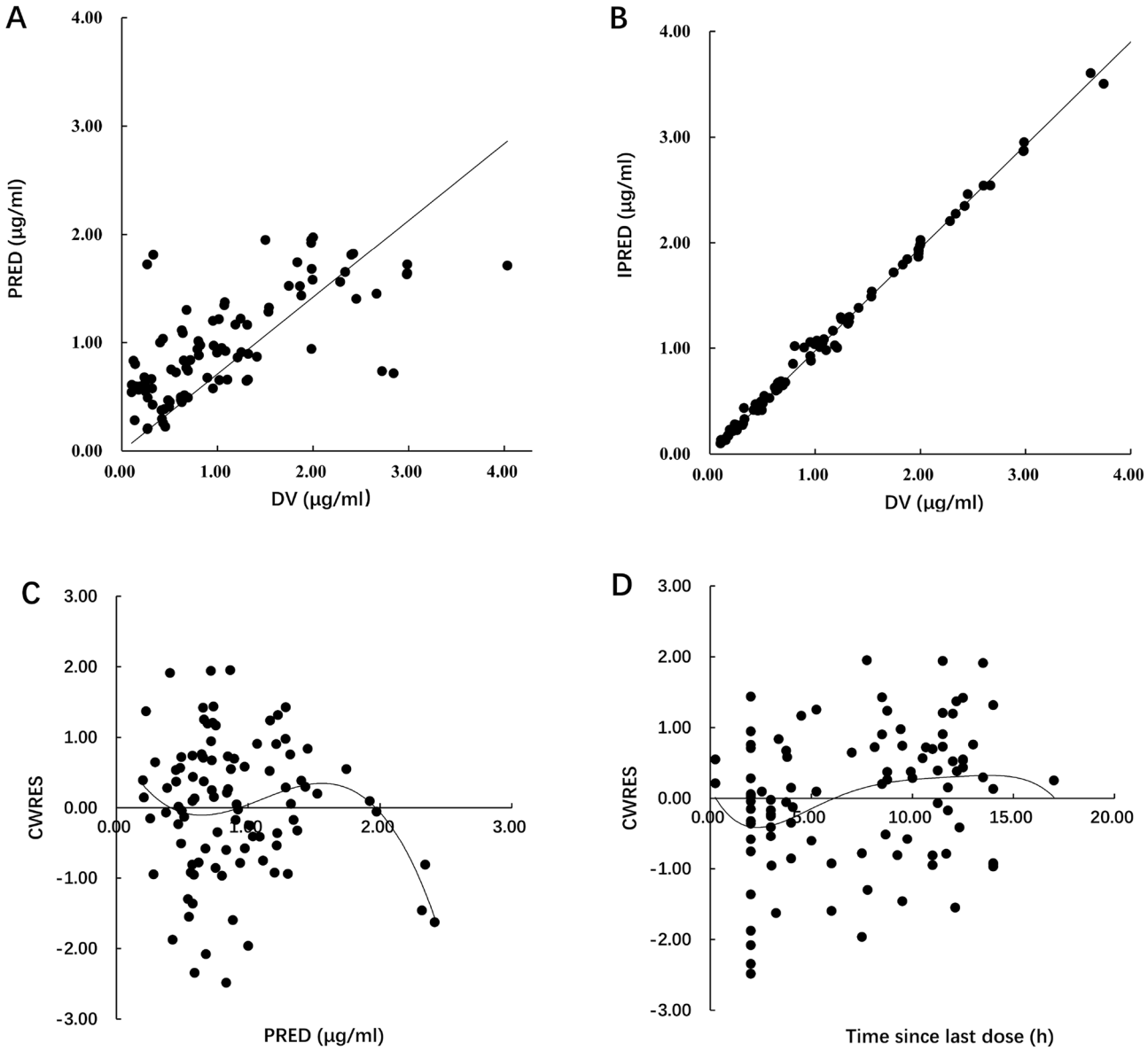

Fig. 1. The model diagnostic Plot for the final PopPK model of posaconazole.

The results of the validation of the NPDE method on the predictive performance of the final model are shown in Fig. 2. The mean and variance of NPDE were 0.034 and 0.924, respectively. The statistical results were Wilcoxon signed rank test P = 0.774 and Shapiro-Wilks normal distribution test P = 0.773, with *P*-values greater than 0.05, suggesting that the NPDE obeys a normal distribution, and the final model is predictable. The quantile–quantile plot (Q-Q plot) shows that the data points are tightly packed around the trend line and evenly distributed on both sides (Fig. 2A). The NPDE histogram (Fig. 2B) is close to a normal distribution, and the data points in the NPDE vs. PRED (Fig. 2C) and NPDE vs. TIME (Fig. 2D) scatter plots show no significant trend changes. Combining the statistical and graphical results, it can be determined that the final model is somewhat predictable.

Figure 3 shows the visual predictive check plot of the model. The trend of the fold lines in the graph indicates that the final model has a good predictive ability, but the large shaded area in the graph indicates a high degree of variability.

Simulations

The results of the dose simulation showed that the CCR of the patient had a more pronounced effect on the PTA value of the dosing regimen, whereas the coadministration of PPI had less of an effect on the PTA value. Patients with a low CCR were more likely to have a higher PTA value due to a slower excretion rate of posaconazole.

The results of the dose simulation showed that patients with a CCR ≥ 90.00 mL/min required at least 3 mg/kg TID and 7 mg/kg BID dosing regimens for prophylaxis and treatment, respectively, but in the case of co-administration of PPI, at least 5 mg/kg BID and 5 mg/kg TID dosing regimens were required for prophylaxis and treatment, respectively. The administration regimen of 4 mg/kg BID and 4 mg/kg TID can meet the PTA

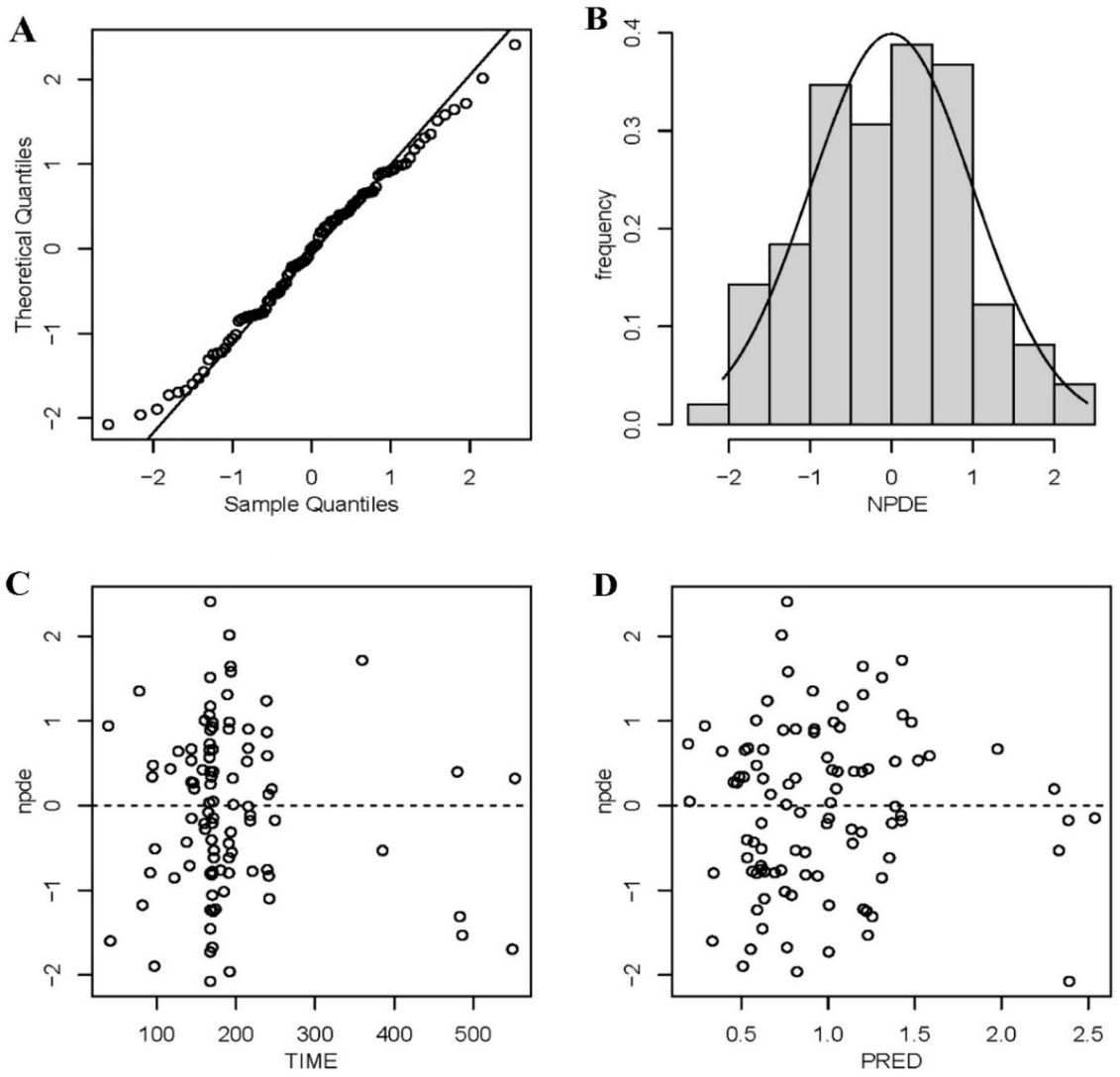

Fig. 2. The normalized prediction distribution error (NPDE) of the final population pharmacokinetic model of posaconazole.

goals for both prevention and treatment in patients with a CCR of 60.00–90.00 mL/min, whether or not combined with PPI. A dosing regimen of 3 mg/kg BID in patients with a CCR of 30.00–60.00 mL/min is sufficient to meet the PTA goal for prophylaxis, and the dose needs to be elevated to 4 mg/kg BID for the treatment of fungal infections without the need for a change in dosage based on the coadministration of PPI. The dosing regimens of 2 mg/kg BID and 3 mg/kg BID met the prophylactic and therapeutic PTA goals, respectively, when the patient's CCR was < 30.00 mL/min, regardless of whether or not the patient was co-administered with PPI. The results of the dose simulation for prophylaxis are shown in Fig. 4, and the results of the dose simulation for therapeutic use are shown in Fig. 5.

Discussion

A one-compartment pharmacokinetic model of first-order absorption and elimination was successfully used in this study to characterize the posaconazole pharmacokinetics, which is consistent with the results of earlier PopPK studies of posaconazole suspensions in other patient populations[11]. Posaconazole suspension taken with a meal, or a high-fat meal promotes the absorption of posaconazole resulting in an increase in the concentration of the medication[4]. We included 62 patients with HSCT who followed a light diet and took posaconazole suspension with meals as prescribed. Therefore, food was not included as a covariate in this study. Due to the small sample size of the absorption phase collected in this study, it was not possible to robustly estimate the value of the absorption rate constant Ka. Therefore, fixing the Ka value in the PopPK modelling process can effectively improve the stability and prediction performance of the model. Early in the model construction, we did not choose to fix the Ka value, but the final model data obtained were unsatisfactory and did not pass the internal validation of the model. According to other similar posaconazole suspension PopPK research literature and after many attempts,

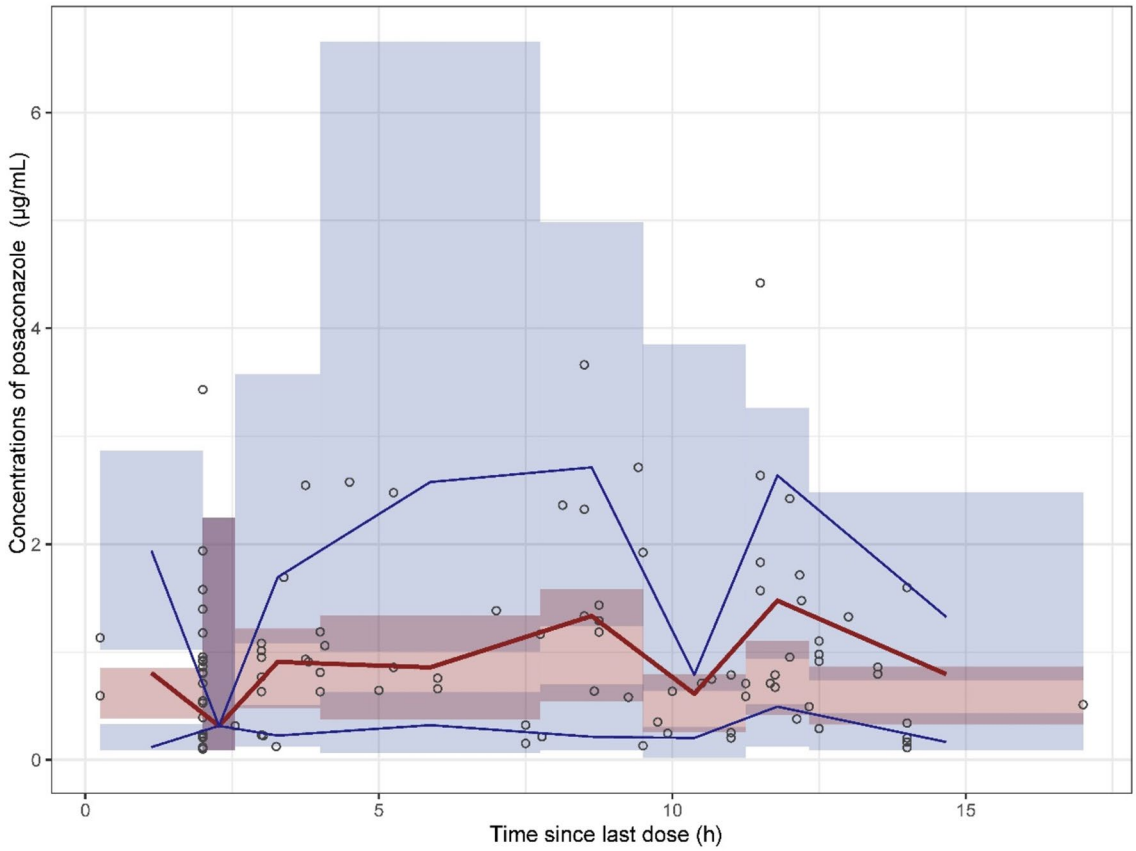

Fig. 3. The visual predictive check plot.

we finally chose to fix the Ka to 0.4/h[14,15]. The absence of external validation is the main limitation of this study. Subsequent external validation of the model is also worth investigating when we collect more patient samples.

The typical value of the V/F population of HSCT patients evaluated was 829 L. High individual variability in the apparent volume of distribution (V) of posaconazole among HSCT patients[4]. A PopPK study of posaconazole tablet formulation in an adult HSCT patient population assessed a typical V/F population value of 548 L[12]. The V/F of posaconazole tablets is lower than that of the suspension, which may be related to a difference in bioavailability (F) rather than a real difference in V, according to earlier PopPK research[16,17]. In the final model, WT and PPI were included as covariates of V/F. Posaconazole is a lipophilic drug with high tissue affinity and can be widely distributed in adipose tissue, with a greater apparent volume of distribution in large body weight populations[11]. The results of PopPK studies by Lin D et al[9] and Elkayal O et al[18] also showed that WT was a significant covariate affecting V/F of posaconazole, which is in line with the findings of the present study. Therefore, patients with large body weights should require higher doses to achieve effective exposure. Elevated gastric pH decreases the solubility of posaconazole, leading to a decrease in posaconazole F[4,5]. PPI have a potent inhibitory effect on gastric acid secretion, which can reduce the absorption of posaconazole suspensions, and the results of the present study also showed that PPI were a significant covariate in reducing posaconazole exposure. Combinations with PPI should be avoided in patients using posaconazole suspension. The population typical value of CL/F assessed in this study was 11.5 L/h. The CL values in this study were similar to those in the PPK study prior to posaconazole, which were around 10[11]. It is noteworthy that the study by AbuTarif MA et al[19] found that liver function indicators such as GGT and bilirubin were significant covariates affecting the pharmacokinetic parameters of posaconazole, and the findings of our study also suggest that liver function affects the pharmacokinetics of posaconazole. Posaconazole is barely metabolized by the cytochrome P450 pathway in humans, a small portion (approximately 17%) is glucuronidated by UGT1A4, and the remainder is not biotransformed. After oral administration of posaconazole suspension, about 77% of the dose is excreted in the feces and only about 13% of the dose is excreted in the urine through the kidneys[4,5]. Distinguishing from previous posaconazole PopPK studies, our findings suggest that CCR is a significant covariate influencing posaconazole CL/F. Patients with abnormal renal function who have low CCR values will have a smaller CL/F than those with normal renal function. The instructions for Posaconazole Suspension indicate that appropriate dose adjustments are not required for patients with mild to severe renal impairment, but close monitoring of patients with severe renal insufficiency is required. Therefore, it is necessary to monitor the drug concentration of posaconazole in HSCT patients with impaired renal function, especially severe renal insufficiency.

The recommended dosage for administration of posaconazole suspension is 200 mg TID in the instruction manual, but a more detailed dosing regimen is not given based on different individual patients or groups. In order

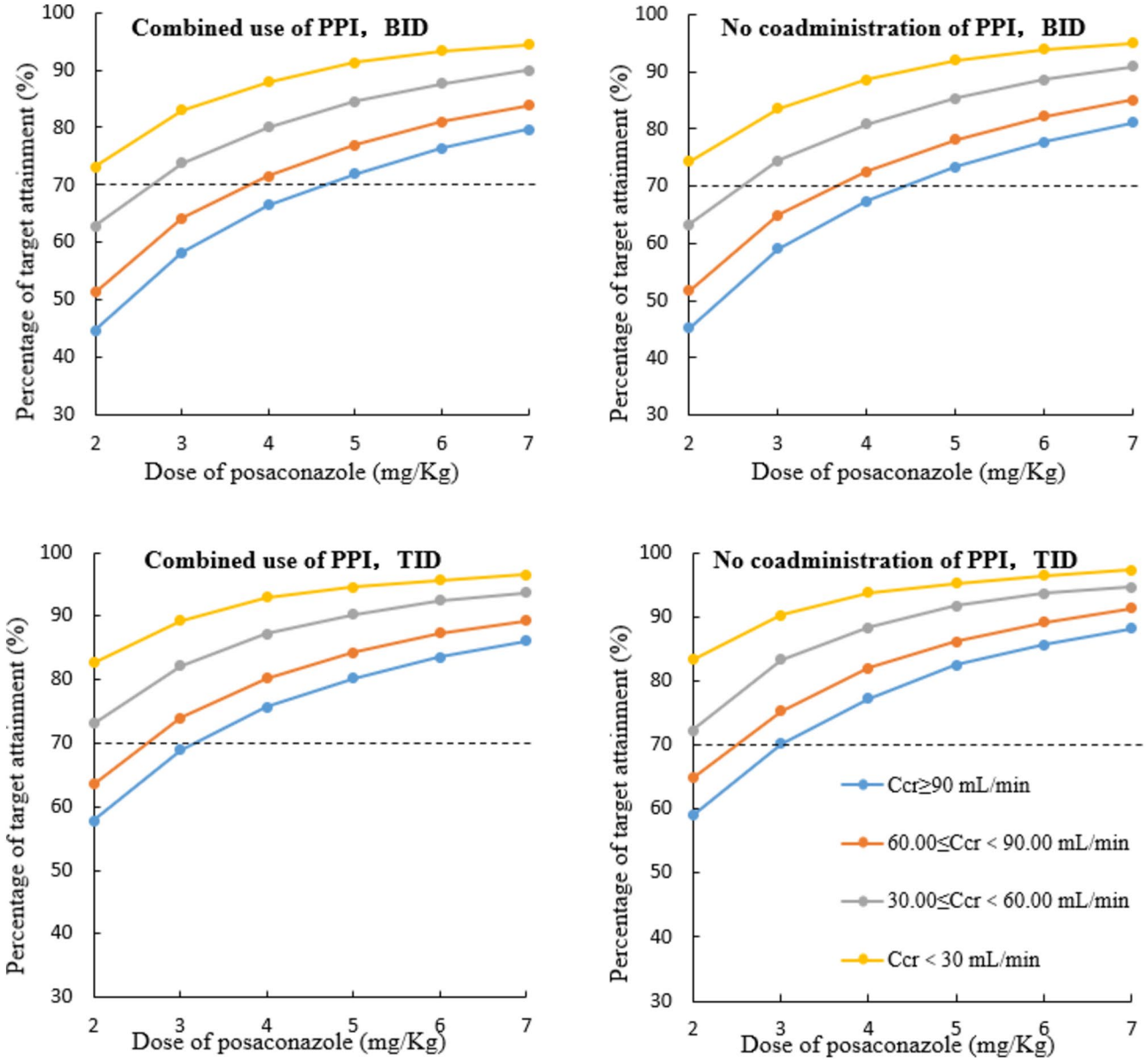

Fig. 4. Graphical results of dose simulation for prophylactic medication.

to advance the individualised treatment of HSCT patients when using posaconazole suspension, we analysed a more detailed dosing regimen using Monte Carlo simulation based on the established posaconazole PopPK model. The PTA value was used as an evaluation index for the dosing regimen, and a dosing regimen was considered feasible when the simulated PTA value of a given dosing regimen was greater than 70%[9]. Slower excretion of posaconazole in patients with low CCR values increases the blood concentration of posaconazole and therefore results in higher PTA values. Co-administration of PPI inhibits the secretion of gastric acid, which inhibits the absorption of posaconazole suspension, and therefore the PTA values of patients co-administered with PPI will be lower. The results of the dose simulation showed that the CCR of the patients had a more pronounced effect on the PTA values of the dosing regimen, whereas the effect of co-administration of PPI was relatively small. This may be due to the fact that the rate of excretion of posaconazole by the patient is the major factor affecting the concentration of this drug when the CCR value is abnormal, whereas co-administration of PPI is a secondary factor affecting the concentration of the drug. The effect of co-administered PPI on posaconazole blood concentrations is only greater when the patient's CCR value is normal. The results of the dose simulation in this study suggest that dose adjustments need to be made accordingly to the CCR values of HSCT patients. Dosing regimens also need to be adjusted when patients have co-administered PPI, especially for patients with CCR ≥ 90 mL/min. Notably, absorption of posaconazole suspensions is saturable, and posaconazole exposure does not increase further when the maximum daily dose exceeds 800 mg[20,21]. Therefore, when a patient's daily dose calculated from the recommended dosing regimen exceeds 800 mg, the use of posaconazole suspension will not be recommended for the patient and may be replaced with a tablet or intravenous injection of posaconazole.

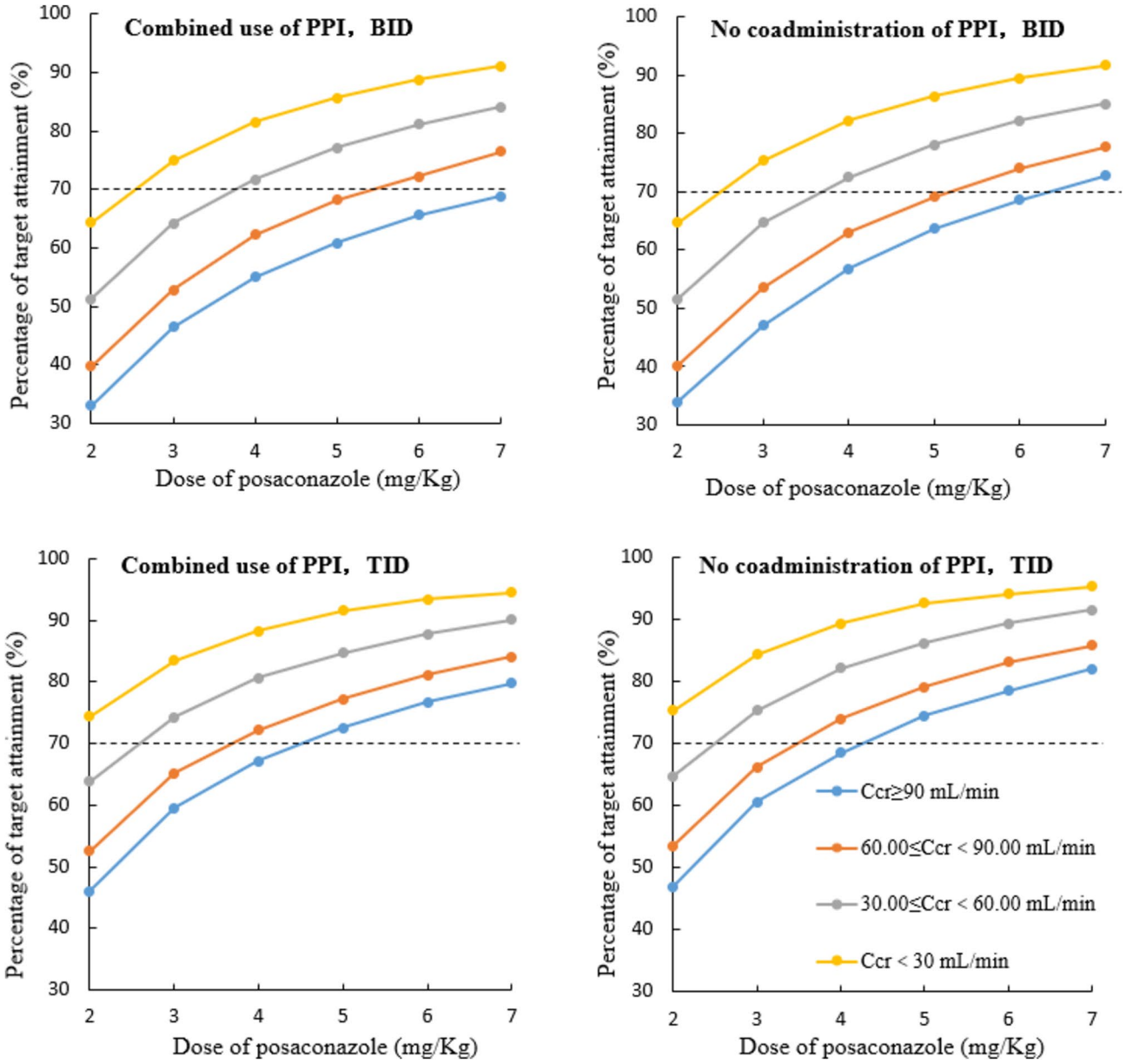

Fig. 5. Graphical results of dose simulation for therapeutic medication.

Conclusions

In summary, we developed the first PopPK model for posaconazole suspension in Chinese HSCT patients. The final model showed that WT, CCR and PPI were covariates affecting the pharmacokinetics of posaconazole. The results of dose simulation in this study suggest that corresponding dose adjustments need to be made based on the CCR values of HSCT patients. When patients use PPI in combination, the dosing regimen also needs to be adjusted, especially for patients with CCR ≥ 90 mL/min. Based on the dose simulation results mentioned above, data support can be provided for the individualized administration of posaconazole in HSCT patients.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

S.H.Y conceived and designed the study. Z.H.D and Y.S.S conducted the experiment. Y.L.Y, S.W.L and Q.Y.Y collected clinical data and contributed to manuscript preparation. P.W, Y.P.S and Y.Y.Z analysed the data. Y.S.S.

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Competing interests

The authors declare no competing interests.

Additional information

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