Drug Design, Development and Therapy

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ORIGINAL RESEARCH

A Population Pharmacokinetics Study of Venetoclax Concomitant with Voriconazole in Patients with Hematologic Malignancies

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Background: Venetoclax is a selective small-molecule BCL-2 inhibitor that has been approved for treating hematologic malignancies. Co-administration with CYP3A inhibitors, such as voriconazole, poses a high risk of drug–drug interactions (DDIs) that can increase venetoclax exposure. This study aimed to develop a population pharmacokinetics (PopPK) model to characterize the PK properties of venetoclax when co-administered with voriconazole.

Methods: Patients (≥18 years of age) treated with venetoclax for hematologic malignancies and concomitant with voriconazole were enrolled. A PopPK model of venetoclax was developed, and Monte Carlo simulations were performed to optimize dosing regimens.

Results: A total of 261 samples from 30 patients were collected as the development dataset, and 55 samples from 43 patients as the external validation dataset. Venetoclax concentrations were adequately described by a two-compartment linear model with first-order absorption and elimination and absorption lag-time. Albumin was identified as a significant covariate influencing the clearance, with a typical value of 1.31 ± 0.08 L/h. Simulation indicated that the exposure to venetoclax (75 mg/day and 100 mg/day) concomitant with voriconazole was higher than that to venetoclax (400 mg/day) alone and tended to accumulate over two weeks.

Conclusion: Co-administration of voriconazole contributed to elevated venetoclax exposure. These potential DDIs suggest the need for therapeutic drug monitoring of venetoclax.

Keywords: venetoclax, voriconazole, population pharmacokinetics model, hematologic malignancies

Introduction

Venetoclax is a first-in-class, orally bioavailable selective B cell lymphoma 2 (BCL-2) inhibitor that induces apoptosis in malignant cells.[1] Currently, it has been approved in several countries for treating chronic lymphocytic leukemia (CLL), small lymphocytic leukemia, and acute myeloid leukemia (AML) in elderly or adults with significant comorbidities.[2] Additionally, it is an effective treatment option in relapsed patients or other hematological malignancies, including indolent non-Hodgkin lymphoma, diffuse large B-cell lymphoma, and multiple myeloma, demonstrating its clinical utility beyond first-line settings.[3–7]

According to the package insert, venetoclax is predominantly metabolized by cytochrome P450 3A (CYP3A), primarily via CYP3A4/5. Consequently, co-administration with moderate or strong CYP3A inhibitors (eg, certain azole antifungals) could increase venetoclax exposure and thus require dose adjustment.[8] In clinical practice, patients with hematological malignancies are at high risk for fungal infections due to chemotherapy and neutropenia, making voriconazole or posaconazole a common choice for antifungal prophylaxis against invasive fungal infections.[9] As strong

Received: 24 December 2024
Accepted: 17 April 2025
Published: 5 May 2025

CYP3A4 inhibitors, voriconazole or posaconazole-mediated drug–drug interactions (DDIs) with venetoclax are a concern for clinicians.[10–12]

Currently, several population PK (PopPK) studies have shown that CYP3A inhibitors (not specifically referring to which drug) can reduce apparent oral clearance (CL/F) of venetoclax by 82–86% across various patient populations and healthy subjects.[13–17] However, the triazole antifungals inhibit CYP3A4, the enzyme responsible for venetoclax metabolism, to varying degrees.[18] There is a lack of studies specifically examining the effects of voriconazole on venetoclax PK parameters and the dose schedule for co-administration.

This study aims to develop a PopPK model to characterize the impact of voriconazole on venetoclax PK parameters. Our findings will contribute to the dose optimization of venetoclax concomitant with voriconazole in patients with hematologic malignancies.

Materials and Methods

Patients and Setting

This prospective observational study was conducted in the Department of Hematology of the First Affiliated Hospital of Zhengzhou University from September 2022 to May 2023 in accordance with the principles of the Declaration of Helsinki Patients (≥18 years) diagnosed with hematologic malignancies and receiving venetoclax and voriconazole were eligible for inclusion. Exclusion criteria were as follows: (1) <18 years old, (2) lack of demographic, clinical, or laboratory information at baseline, and (3) less than 7 days of treatment with venetoclax and voriconazole. This study was approved by the ethics committee of the hospital (KY-2022-0388), and written informed consent was obtained from all patients.

Venetoclax (100 mg per tablet) was orally 100 mg once daily. For patients not taking voriconazole prior to venetoclax, voriconazole (200 mg per tablet) was initiated at 400 mg twice daily (bid) on the first day, then 200 mg bid for the following days. For patients taking voriconazole prior to venetoclax, voriconazole at 200 mg bid was continued. During treatment, dose adjustments and adjuvant chemotherapy were dependent on the clinician based on the patient's response, adverse drug reactions, and/or tolerability.

Sample Collection and Bioanalytical Methods

The dataset was divided into development and validation datasets. For the development dataset, intensive blood samples were collected from patients at 0–1 h before venetoclax dosing and 2, 4, 5, 6, 7, 8, 12, and 24 h after dosing on day 5–11 (2 mL in EDTA tubes). For the validation dataset, sparse samples were collected from patients 0–1 h prior to venetoclax dosing on day 2–22.

Plasma concentrations of venetoclax and voriconazole were determined using a validated high-performance liquid chromatography system (LC-20A, Shimadzu, Japan) equipped with API 3200 triple-quadrupole tandem mass spectrometer (AB Sciex, USA) method. The method was operated in the multiple-reaction monitoring mode to detect venetoclax, voriconazole, venetoclax-d8, and voriconazole-*d*3 at *m/z* transition 869.5→321.5, 350.2→281.0, 877.4→329.7, and 353.2→284.0, respectively. The calibration standards covered venetoclax and voriconazole concentrations ranging from 0.05 to 10.0 μg/mL. This method was accurate with acceptable precision as shown in Supplementary Methods.

PopPK Modeling

PopPK parameters of venetoclax were estimated by the first-order conditional estimation method (FOCE ELS) using Phoenix® NLME software (v8.3, Pharsight, Mountain View, CA, USA). For base modeling, one- and two-compartment models with first-order absorption kinetics and with or without absorption lag-time (Tlag) were tested to fit the raw data. Additive, proportional, and mixed (additive + proportional) residual error models were assessed. An exponential error model was used to measure between-subject variability. Model parameters included central clearance (CL/F), central compartment volume of distribution (V), inter-compartmental clearance (Q/F), peripheral compartment volume of distribution (V2), and absorption rate constant (ka). Initial values of CL/F and V/F were derived from non-

compartmental analysis. PK model was selected on the basis of the precision (standard error) of parameter estimates, goodness-of-fit (GOF) plots, and likelihood ratio tests (−2LL).

For covariate modeling, gender (male = 0, female = 1), age, weight, serum creatinine, creatinine clearance (CrCL), serum proteins, albumin (ALB), alanine aminotransferase, aspartate aminotransferase, and voriconazole concentration were evaluated as covariates using an exponential model. Continuous covariates were normalized by the median (of observed values), and categorical covariates were reflected as index variables. By comparing with the initial model, a drop of >6.63 ($P < 0.01$) in objective function value (OFV; −2LL) by forward addition and an increase of >10.83 ($P < 0.001$) by backward elimination were inclusion criteria for covariates.

Model Evaluation and Validation

The final model was internally validated by GOF plots. The prediction-corrected visual predictive check (pc-VPC) was performed with 1000 replicates, and the 5th, 50th, and 95th percentiles of the observed and simulated data were graphically compared. Model stability was assessed using the bootstrap analysis on 1000 individuals.

The validation dataset was used for external evaluation. The degree of visual agreement related to the model fitting of the data was considered by GOF plots. Mean prediction error (MPE) and mean absolute prediction error (MAPE) as a measure of bias and precision, respectively, were calculated as follows:

$$\mathrm{MPE}\ (\%) = \frac{1}{\mathrm{N}} \sum_{\mathrm{i}=1}^{\mathrm{N}} \left(\frac{\mathrm{Cpred} - \mathrm{Cobs}}{\mathrm{Cobs}} \right) \times 100$$

$$\mathrm{MAPE}\ (\%) = \frac{1}{\mathrm{N}} \sum_{\mathrm{i}=1}^{\mathrm{N}} \left| \frac{\mathrm{Cpred} - \mathrm{Cobs}}{\mathrm{Cobs}} \right| \times 100$$

where *C*pred indicates the predicted concentration, *C*obs indicates the observed concentration, and N denotes the number of observations. A PopPK model was deemed acceptable when MPE was within ± 20% and MAPE was less than or equal to 30%.[19]

Simulations

Based on the final model, Monte Carlo simulations were performed on 1000 subjects taking venetoclax 100 mg, 75 mg, or 50 mg per day and concomitant with voriconazole for 14 days. Covariates were chosen as 10th, 50th, and 90th values of patients. The area under the concentration–time curve across 24 hours (AUC_{24h}) was calculated by the linear trapezoidal linear interpolation method.

Results

Patients Characteristics

A total of 73 patients were enrolled, of whom 30 contributed to 261 blood samples and were grouped into the development dataset, and the remaining 43 contributed to 55 samples and were grouped into the external validation dataset. Baseline demographics and covariates were shown in Table 1. All patients received venetoclax with 100 mg/day without ramp-up, except for one patient who reduced the dose to 50 mg/day due to severe nausea and neutropenia on day 3.

Plasma Concentrations of Venetoclax

In the development dataset, AUC and trough concentrations (C_{min}) of venetoclax were 52.4 μg h/mL (range 19.2 to 121.9 μg h/mL) and 1.89 μg/mL (range 0.74 to 5.30 μg/mL), respectively. In the external validation dataset, the median C_{min} was 1.99 μg/mL (range 0.46 to 5.41 μg/mL). Both datasets indicated a large individual variability of venetoclax concomitant with voriconazole.

Table 1 Demographic and Clinical Characteristics of the Study Population

Characteristic	Development Dataset (n = 30)	Validation Dataset (n = 43)
Age, years, median (range)	57.0 (18.0–74.0)	58.0 (18.0–81.0)
Weight, kg, median (range)	60.0 (40.0–100.0)	65.0 (42.0–95.0)
Sex, n (%)		
Male	17 (56.7)	22 (51.2)
Female	13 (43.3)	21 (48.8)
Hematologic malignancies type, n (%)		
Acute myeloid leukemia	22 (73.3)	31 (72.1)
Chronic myelomonocytic leukemia	2 (6.7)	1 (2.3)
Acute lymphoblastic leukemia	2 (6.7)	4 (9.3)
Chronic lymphocytic leukemia	1 (3.3)	0 (0)
Mantle cell lymphoma	1 (3.3)	0 (0)
Myelodysplastic syndrome	1 (3.3)	7 (16.3)
Mixed phenotype acute leukemia	1 (3.3)	0 (0)
ECOG performance status, n (%)		
1	25 (83.3)	29 (67.4)
2	3 (10.0)	10 (23.3)
3	2 (6.7)	4 (9.3)
Concomitant drugs, n (%)		
Azacitidine	18 (60.0)	38 (88.4)
Decitabine	9 (30.0)	4 (9.3)
Zanubrutinib	1 (3.3)	0 (0)
None	2 (6.7)	1 (2.3)
Laboratory test, median (range)		
White cell counts, 10^9/L	3.6 (0.7–65.5)	2.9 (0.6–63.7)
Hemoglobin, g/L	82.5 (53.0–138.0)	80.0 (54.0–128.0)
Platelet, 10^9/L	39.0 (6.0–470.0)	60 (6.0–505.0)
Neutrophil count, 10^9/L	1.6 (0–9.7)	1.6 (0–57.2)
Serum creatinine, μmol/L	58.5 (35.0–99.0)	55.0 (30.0–206.0)
Creatinine clearance, mL/min	104.5 (54.6–250.7)	100.4 (39.1–221.2)
Alanine aminotransferase, U/L	18.0 (5.0–141.0)	14.0 (5.0–81.0)
Aspartate aminotransferase, U/L	17.0 (8.0–112.0)	17.0 (5.0–92.0)
Serum proteins, g/L	61.3 (41.7–80.1)	66.6 (52.0–80.8)
Albumin, g/L	38.4 (27.2–48.5)	38.3 (24.0–47.1)

Notes: Data were n (%) or median (range).
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

PopPK Analysis

All venetoclax concentration–time data were best described by a two-compartment linear model with first-order absorption and elimination and Tlag (Table S1). The residual variability was well described by the proportional residual error model. Random effect of Q/F was not taken into the model because of shrinkage factor >0.5.

In the covariate screening step, a significant association between ALB and CL/F (ΔOFV = 11.4, $P < 0.001$) was found and incorporated into the final model. ALB was optimal exponentially as follows:

$$CL/F = tvCL/F \times [ALB/38.4]^{ALB\ on\ CL/F}$$

where tvCL/F was the typical value of CL/F, ALB on CL/F represented fixed parameter coefficient of ALB on CL/F, and 38.4 was the median ALB of patients. Other covariates, including gender, age, weight, serum creatinine, CrCL, serum proteins, alanine aminotransferase, aspartate aminotransferase, and voriconazole concentration, had no significant effect on PK parameters. The final PopPK parameters were presented in Table 2.

Table 2 Population PK Parameter Estimates in the Final Model and Bootstrap

Parameter	Final Model				Bootstrap	
	Estimate ± SE	RSE (%)	95% CI	Shrinkage (%)	Median (RSE %)	95% CI
tvka (1/h)	0.11 ± 0.04	32.48	0.04 to 0.18	NA	0.11 (27.57)	0.06 to 0.18
tvV/F (L)	28.02 ± 8.39	29.96	11.48 to 44.55	NA	27.13 (31.06)	11.48 to 44.55
tvV2/F (L)	87.26 ± 27.69	31.73	32.72 to 141.80	NA	88.60 (32.33)	32.72 to 141.80
tvCL/F (L/h)	1.31 ± 0.08	6.03	1.15 to 1.46	NA	1.31 (9.83)	1.15 to 1.46
ALB on CL/F	−1.49 ± 0.33	−22.19	−2.15 to −0.84	NA	−1.49 (−41.18)	−2.15 to −0.84
tvQ/F (L/h)	5.29 ± 1.46	27.57	2.42 to 8.16	NA	5.21 (22.62)	2.42 to 8.16
tvTlag (h)	3.36 ± 0.01	0.39	3.33 to 3.38	NA	3.48 (9.37)	3.33 to 3.38
Inter-individual variability						
ω^2ka	0.09 ± 0.04	44.44	0.01 to 0.17	36.55	0.11 (45.45)	0.01 to 0.21
ω^2V/F	0.26 ± 0.12	46.15	0.02 to 0.50	36.18	0.31 (38.71)	0.07 to 0.55
ω^2V2/F	2.35 ± 0.72	30.64	0.94 to 3.76	14.34	2.59 (46.33)	0.24 to 4.94
ω^2CL/F	0.82 ± 0.40	48.78	0.04 to 1.60	28.68	0.11 (45.45)	0.01 to 0.21
ω^2Tlag	0.09 ± 0.04	44.44	0.01 to 0.17	24.03	0.08 (50.0)	0.0 to 0.16
Residual variability (σ)						
stdev0	0.13 ± 0.01	5.99	0.12 to 0.15	14.55	0.13 ± 0.01	0.11 to 0.15

Abbreviations: SE, standard error; RSE, relative standard error; CI, confidence interval; ALB, albumin; tvV/F, typical value of central compartment distribution volume (V/F); V2, peripheral compartment distribution volume; CL, central compartment clearance; Q, inter-compartmental clearance; ALB on CL/F, fixed parameter coefficient of albumin on CL/F; ωka, variance of inter-individual variability for ka; stdev0, standard deviation; NA, not applicable.

Model Evaluation and Validation

For internal validation, GOF plots (Figure 1a–d) of the final model showed good agreement between observed and predicted values. Pc-VPC (Figure 2) presented the central tendency of observed and predicted data and captured most of the observed data within 90% prediction intervals. Bootstrap results (Table 2) were consistent with the PK parameters, indicating the stability and robustness of the final model.

For external validation, GOF plots were displayed in Figure S1. There was a good agreement between observations with both population and individual predictions. The population MPE was 7.0%, and MAPE was 35.3%, which slightly exceeded acceptable criteria. The individual MPE of 5.5% and MAPE of 9.1% were considered acceptable.

Dosing Simulation

Based on the final PopPK model, subjects administered venetoclax at doses of 50 mg/day, 75 mg/day, and 100 mg/day with voriconazole for 14 days were simulated with a median ALB level (38.4 g/L, Figure 3). Simulation indicated that venetoclax exposure consistently increased for 14 days. Comparing AUC_{24h} at day 14 to day 7, the median accumulation ratios were 1.2 (range 1.1–1.3, Figure 4).

In addition, subjects with different ALB levels (32.5 g/L, 38.4 g/L, and 45.7 g/L were simulated to take venetoclax 100 mg/day concomitant with voriconazole for 14 days (Figure S2). The results showed that the AUC_{24h} on day 14 was 53.1 ± 18.2 μg h/mL, 56.8 ± 24.4 μg h/mL, and 80.1 ± 30.1 μg h/mL, respectively, indicating that the covariates did not cause a 2-fold change in AUC_{24h}, and therefore no dose adjustment needed to be considered.

Discussion

To the best of our knowledge, this is the first PopPK study of venetoclax administered concomitantly with voriconazole in patients with hematologic malignancies. As a result, venetoclax exhibited large inter-individual variability in drug exposure. A two-compartment PK model with first-order absorption and elimination adequately described the plasma concentration–time data for venetoclax.[13–17]

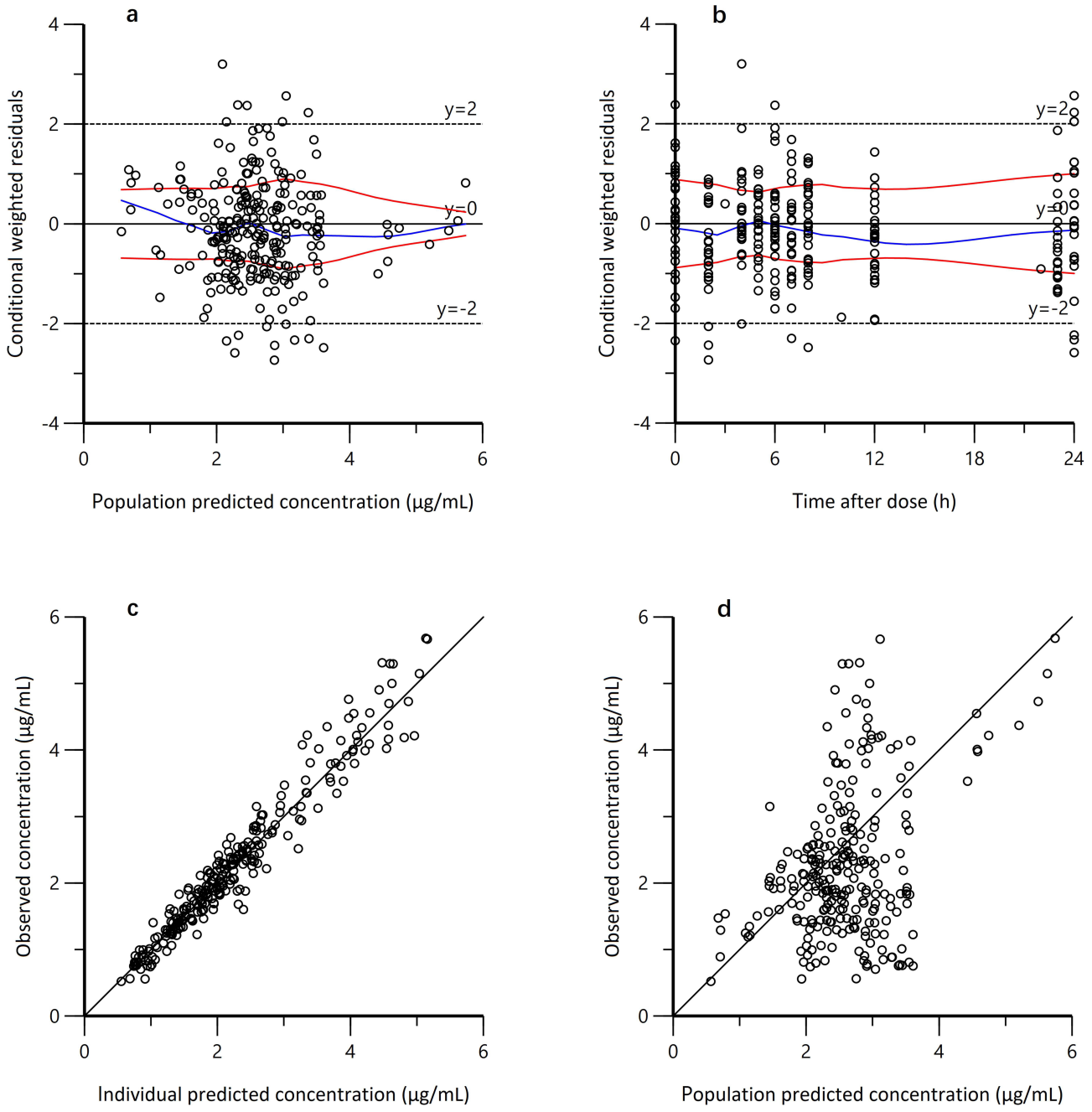

Figure 1 Goodness-of-fit plots for the final population pharmacokinetic model. (**a**) conditional weighted residuals versus population predicted concentrations; (**b**) conditional weighted residuals versus time after dose; (**c**) observed versus individual predicted concentrations; (**d**) observed versus population predicted concentrations. The blue lines represent smoothed regression lines; the red lines represent computed absolute regression lines (with negative reflection).

Concomitant use of voriconazole, the typical CL/F value for venetoclax was 1.31 ± 0.08 L/h (Table 2), which was much lower than that of 15.0–19.5 L/h for venetoclax alone and also lower than that of 2.2–3.6 L/h in other PopPK models that considered strong CYP3A inhibitors as covariates.[13–17] Of note, this value was comparable to 1.1–1.4 L/h reported by two PK studies, in which venetoclax was co-administered with posaconazole in patients with AML.[20,21] This discrepancy could be attributed to two reasons. On the one hand, other PopPK models incorporated different CYP3A inhibitors as a covariate. However, the magnitude of CYP3A inhibition varies widely among strong CYP3A inhibitors.[22] For instance, ritonavir or ketoconazole was reported to increase the mean maximum plasma concentration (C_{max}) and AUC of venetoclax by 2.3- to 2.4-fold and 6.1- to 8.1-fold, respectively.[22,23] Nonetheless, posaconazole was estimated to

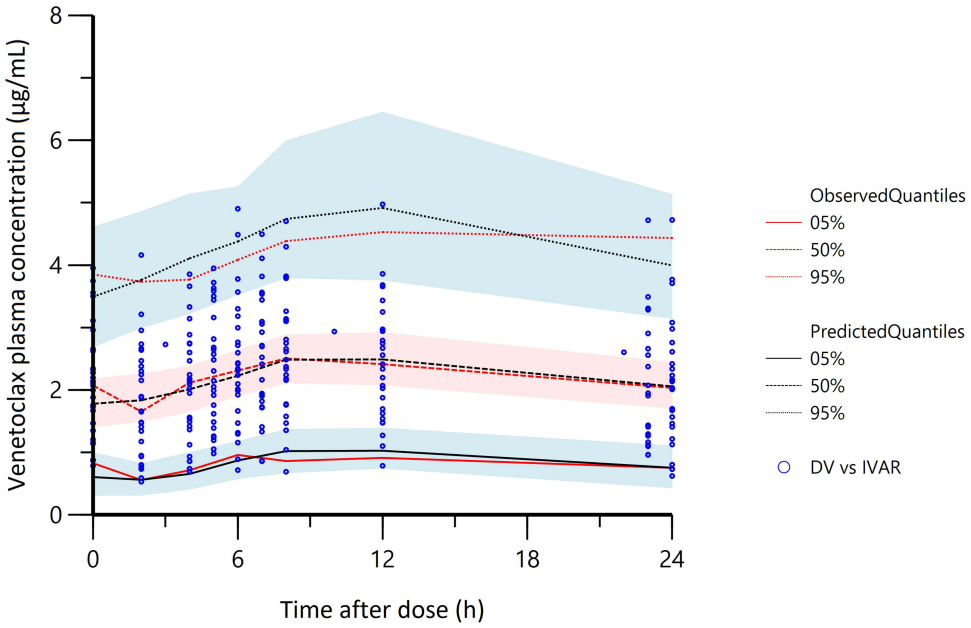

Figure 2 The prediction corrected-visual predictive check of the population pharmacokinetic model. The blue dots represent the observed data.
Abbreviations: DV, observed data; IVAR, time.

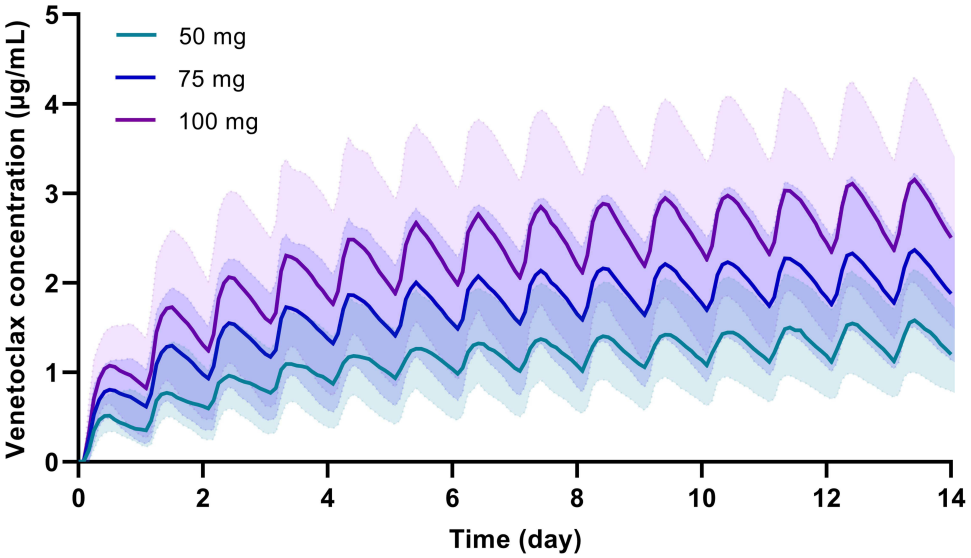

Figure 3 Simulated PK profiles of venetoclax in patients with co-administered voriconazole based on the population pharmacokinetics model. The black line represents the median concentration; the gray shadow represents a 90% confidence interval.

increase venetoclax C_{max} and AUC by 7.1- and 8.8-fold, respectively.[21] A recent study showed that the average venetoclax AUC (100 mg) with posaconazole was 103% higher than that of venetoclax (400 mg) with caspofungin. While, when with voriconazole, venetoclax AUC was increased by 77%.[18] Therefore, different CYP3A4 strong inhibitors may lead to different CL/F values. On the other hand, other PopPK models incorporated a large number of healthy subjects. Previous studies have indicated that CL/F values were approximately 35% (95% CI, 25–45%) higher in healthy subjects or patients with non-hematologic diseases compared to those with hematologic malignancies.[16]

In addition to CYP3A inhibitors, previous PopPK models included race, gender, liver function, food, and disease as covariates.[12–16] In this study, food effect was not incorporated due to the inability to obtain dietary conditions. Instead, Tlag was introduced, as a previous PopPK model for healthy subjects.[24] At last, gender, age, weight, serum creatinine,

https://doi.org/10.2147/DDDT.S514173

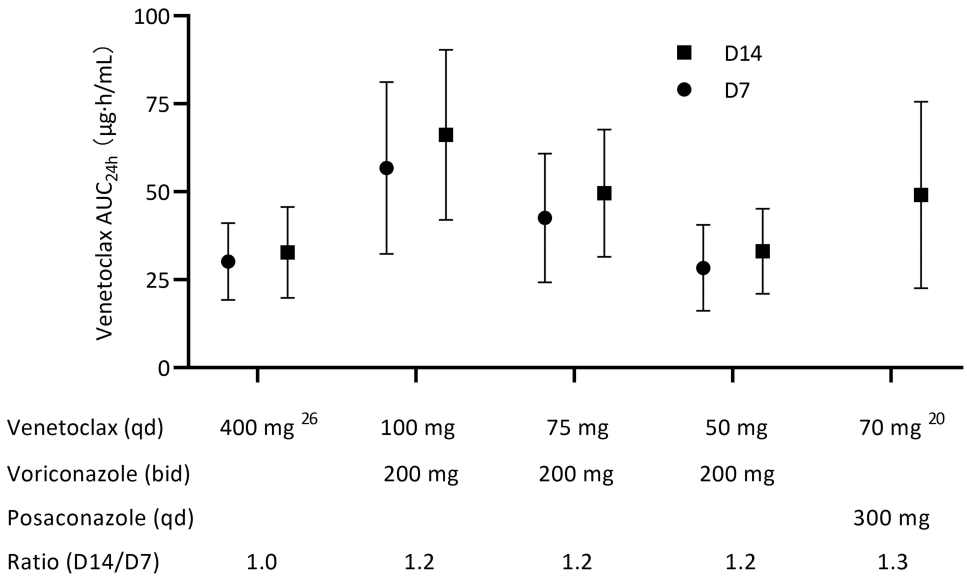

Figure 4 Comparing the simulated and observed AUC_{24h} of venetoclax with different dosage. AUC24h, area under the concentration–time curve across 24 hours; qd, once daily; Bid, twice daily; 26 or 20, the reference 26 or 20.

CrCL, serum proteins, alanine aminotransferase, and aspartate aminotransferase had no significant effect on PK parameters of venetoclax, and only the effect of ALB on CL/F was identified. Generally, a decrease in ALB level can increase the free fraction of highly protein-bound drugs.[25] Venetoclax is highly bound to plasma protein (fu < 0.01), regardless of concentration, according to the prescribing information. Consequently, as ALB concentration increased, the CL/F of total venetoclax declined (Table 2).

During external validation, the predictive performance of the final model exhibited a small imprecision of 35.3%. One possible reason is that the validation dataset consisted only of trough concentrations, with low values leading to large biases.

Based on the final PopPK model, simulations showed venetoclax AUC_{24h} (mean ± SD) on day 7 at doses of 50 mg and 100 mg, when co-administered with voriconazole, were 28.4 ± 12.2 μg h/mL and 56.8 ± 24.4 μg h/mL, respectively. These values were lower than those at the same doses with posaconazole (47.2 ± 27.4 μg h/mL and 76.2 ± 13.7 μg h/mL).[21] On day 14, the simulated AUC_{24h} at 75 mg was 49.6 ± 18.1 μg h/mL, comparable with 49.1 ± 26.5 μg h/mL (CV: 54%) observed at 70 mg with posaconazole on day 12.[20] These suggested that the inhibitory effect of voriconazole on venetoclax metabolism was slightly weaker than that of posaconazole, consistent with a previous study.[18] Additionally, the AUC_{24h} at 50 mg was close to that of venetoclax at 400 mg administered alone (32.8 ± 16.9 μg h/mL, Figure 4).[26] Accordingly, when administered with voriconazole, 50 mg of venetoclax may be appropriate.

Notably, comparing AUC_{24h} on day 14 to day 7, the median (range) accumulation ratio of three dosages was 1.2 (range 1.1–1.3), which was different from that of 1.0 (range 0.5–2.1) for venetoclax at 400 mg alone and consistent with that of 1.3 (range 1.0–2.9) for venetoclax at 70 mg with posaconazole.[20] These findings suggested that venetoclax concentrations did not reach a steady state and continued to accumulate over two weeks. Recent studies indicated that overexposure to venetoclax was associated with prolonged-duration neutropenia in patients with AML or high-risk myelodysplastic syndrome.[27,28] Furthermore, a 5-week venetoclax dose ramp-up schedule for CLL and a 3-day dose ramp-up schedule for AML are recommended to mitigate tumor lysis syndrome risk.[1] When combined with CYP3A4 inhibitors, venetoclax exposures increase substantially even with a dose reduction of at least 50%.[18] Whether this will increase the incidence of adverse reactions and how venetoclax dose ramp-up remains unknown. Given the inter-individual variability of PK characteristics, DDIs, accumulation with CYP3A4 inhibitors, and exposure–response relationship, therapeutic drug monitoring (TDM) may be useful for venetoclax dosage adjustment.[11] At present, there is no study reporting the therapeutic window of venetoclax, so further investigation is necessary.

This study has several limitations. First, only patients treated with venetoclax and voriconazole were recruited. Without a control group receiving venetoclax alone, it is difficult to isolate voriconazole's specific impact compared to other CYP3A inhibitors. Second, food effect was not incorporated into the PopPK model, despite evidence that a meal significantly increases venetoclax exposure. Third, the external validation dataset only contains trough concentrations, which leads to MAPE exceeding the 30% threshold and may raise concerns about model reliability. Finally, since the present study provides PK insights into venetoclax and voriconazole co-administration, further research is needed to explore the exposure–response relationship or present clinical outcomes that would support TDM-guided dose adjustment.

Conclusions

In conclusion, the PopPK model demonstrated that ALB was a significant covariate affecting venetoclax CL/F when co-administrated with voriconazole. Due to the strong inhibitory effect of voriconazole on venetoclax metabolism, the CL/F of venetoclax was much lower than that of venetoclax alone. Simulation indicated that venetoclax exposure at doses of 75 mg and 100 mg with voriconazole was higher than that of 400 mg alone and tended to accumulate over two weeks. A dose of 50 mg could be appropriate. Further investigations into a goal therapeutic range to optimize efficacy and safety are warranted.

Data Sharing Statement

The data are contained within the article or Supplementary Material. Further requirements can be requested from the corresponding author.

Funding

This work was supported by the Science and Technology Research Project of Henan Province (Grant No. 252102310438) and the Key Project of the Medical Science and Technology Research Program of Henan Province (Grant No. SBGJ202302070).

Disclosure

The authors declared no competing interests in this work.

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