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REVIEW

Population Pharmacokinetic Models of Venetoclax in Hematologic Malignancies: A Systematic Review

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Abstract: Several population pharmacokinetic (PPK) models of B cell lymphoma-2 (BCL-2) venetoclax (VEN) have been developed and published to characterize the influencing factors of pharmacokinetics in hematologic malignancies. This review described PPK models of VEN examining the magnitude and types of covariate effects in PK parameters, as well as identified areas that require further investigation in order to facilitate their use. Currently, there are six analyses on PPK models of VEN summarized in this review. Most analyses described the pharmacokinetics of VEN with a two-compartment model and all covariates are categorical. The median estimated apparent clearance (CL/F) was 446 L/Day and apparent volume of distribution of the central compartment (V_2/F) was 114.5 L. The median IIV of CL/F reported was 39.5% and V_2/F was 46.7%. Most commonly, CYP3A inhibitors, OATP1B3 inhibitors and rituximab co-administration were found to be significant covariates on CL/F. In addition, sex and population were influential covariates on V_2/F. A detailed description of the characteristics of PPK models of VEN is provided in this review, as well as the effects of covariates on the PK parameters. For future development of the VEN PPK model, CYP3A inhibitors, rituximab co-administration, OATP1B1 transporter inhibitors, sex, population, and food might be considered. Further research and comprehensive investigations should be undertaken to explore reference ranges for therapeutic drug monitoring, define the potential role of patients with cerebrospinal fluid complications, and assess new or potential covariates. These endeavors will facilitate the development of personalized VEN therapy.

Keywords: venetoclax, BCL-2 inhibitor, population pharmacokinetics, PPK model, systematic review

Introduction

Direct stimulation of the mitochondrial apoptotic pathway is a new therapeutic strategy in the current targeted therapy of hematologic malignancies. B cell lymphoma-2 (BCL-2) family is a key apoptotic factor in the endogenous apoptotic signaling pathway, which inhibits apoptosis and plays an important role in tumorigenesis and development.[1] Many hematological tumors show the overexpression of the anti-apoptotic protein BCL-2,[2–4] such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM), so BCL-2 inhibitors have a broad application prospect in hematological malignancies. Venetoclax (VEN) is the world's first approved oral BCL-2 inhibitor targeting the apoptotic pathway in tumors. By binding directly to BCL-2, VEN displaces and releases pro-apoptotic proteins, ultimately leading to apoptosis of malignant cells.[5–7] This mechanism of action targets BCL-2 protein and is innovative and unique. The Food and Drug Administration (FDA) granted an accelerated approval to it.[8] Currently, FDA has approved the use of VEN in primary and relapsed or refractory (R/R) CLL/small lymphocytic leukemia (SLL), as well as newly diagnosed AML in patients who are age 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. VEN has been approved for marketing in China by the end of 2020 and entered the national health insurance catalog in early 2023. However, due to the short period of

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time since its approval, there is little experience in clinical application. Despite its widespread use, consensus on its standardized clinical application and patient management has not been reached.

The pharmacokinetic (PK) characteristics of VEN are established.[9–11] A peak plasma concentration (Cmax) is achieved in 5 to 8 hours following oral administration.[12] However, the safe range of blood concentrations and monitoring protocols are currently inconclusive. Based on available studies, several factors affect the pharmacokinetics of VEN, including body weight, age, and ethnicity.[13] After low- and high-fat meals, VEN exposure was higher than when fasting.[14] In addition, VEN, which is highly bound to plasma proteins, is primarily metabolized by cytochrome P450 (CYP) 3A4.[15] VEN is a substrate for CYP3A4 and P-gp, so it may be affected by P-gp inhibitors such as rifampicin. In clinical studies involving patients with AML, an observed relationship between VEN exposure and a higher probability of response, as well as certain safety events, was identified through an analysis of efficacy and safety using exposure-response methodology. Freise et al[10] indicated that a daily dosage of 400 mg of VEN is associated with a high (>80%) probability of achieving an objective response in R/R CLL/ SLL patients and with a minimal chance of increasing neutropenia as well as infection.

A variety of VEN population pharmacokinetic (PPK) models[11,15–19] have been developed for patients with different types of hematological malignancies. However, there is no study that has summarized and evaluated these PPK models yet. Selecting an appropriate PK model and identifying important covariates which affect VEN has becoming very challenging. Consequently, existing models' strategies should be better used, and new models' development should take additional considerations. It is the first systematic investigation of the PPK models of VEN that has been conducted to our knowledge. The purpose of our study was to provide a comprehensive analysis of the published studies on PPK, investigate clinical determinants influencing the PK of VEN, and identify areas that require further investigation.

Method

Search Strategy

Using PubMed and Embase, an electronic literature search was conducted to identify PPK analyses of VEN for the entire period from the beginning to September 2023. Search terms used to identify the relevant PPK analyses on VEN are as follows: venetoclax, Venclyxto, BCL-2 inhibitor, ABT-199, population pharmacokinetic, PPK, nonlinear mixed effect, NONMEM, etc. Further, additional relevant materials were identified by conducting a thorough examination of all relevant lists of references.

Inclusion Criteria and Exclusion Criteria

Those studies included in this systematic review were (1) conducted on humans, (2) based on the use of VEN as the treatment, (3) providing PPK analyses of VEN, and (4) using at least one type of PPK analysis method. In contrast, the publications that (1) were reviews or methodology studies or (2) excluded the model development process were excluded.

Data Extraction

To interpret the results, a reviewer extracted information about the study design, baseline characteristics of the population, and PPK analyses. A reviewer-extracted information related to the study design, population baseline characteristics, and PPK analyses, which were critical to interpretation of the results. To minimize errors, the second reviewer independently verified the data extraction. Standard data collection forms were used to extract the following information from eligible studies: study design (eg, number of patients and samples, data source, dosage range, methods of concentrations determination), patient population characteristics (eg, sex, age, weight, race), and PPK analyses (eg, pharmacokinetic model, sample collection, tested covariates, methods of screening covariates, covariates of the final model and their relationship with pharmacokinetic parameters and model evaluation).

Quality Analysis

In each included study, two authors independently assessed its methodological quality using the National Institutes of Health (NIH) Study Quality Assessment Tool for Case Series Studies.[20] Methodologists and the NIH developed this tool based on quality assessment methods and concepts that can be applied to nonrandomized studies and case series, which are commonly used in systemic reviews including observational studies.[21]

Covariate Effects

Using R software (version 4.3.1), forest plots were used to summarize the effects of significant covariates on CL/F and V_2/F in each study. Due to the fact that most published PPK analyses used only the final model, results from this manuscript are based on the covariate effects estimated from the final PPK models.

Results

Study Characteristics

Among 380 unique titles screened, in total, six analyses were selected for further analysis (Figure 1). Six of the analyses had a good quality rating according to the NIH study quality assessment tool (Table S1). A summary of the included analyses is shown in Table 1. Among the six analyses included, a median (range) of 274 (73–3016) patients were used for the development of the PPK model, with five analyses[11,16,18,19,22] involving more than 200 subjects. All analyses were based on clinical trials, and three analyses did not state NCT numbers.[11,16,22] Among the analyses that evaluated the model, three used three different evaluation methods.[15,18,19] Quantification of VEN concentrations in serum was performed using liquid chromatography methods with tandem mass spectrometric detection (LC-MS).[11,15,17–19]

A summary of the gender, age, and body weight of the patients can be found in Table 2. In the included analyses, a wide range of races (White, Black, Asian, Hispanic, etc.) and multiple disease types (CLL, ALL, AML, NHL, SLE, DLBC, etc.) were represented. There is one analysis that female subjects with SLE were only analyzed in terms of VEN pharmacokinetics.[17] The study populations received variable VEN dosing regimens (10–1200mg, po), and it is commonly necessary to ramp up the VEN dose to 400 mg per day over a five-week period.

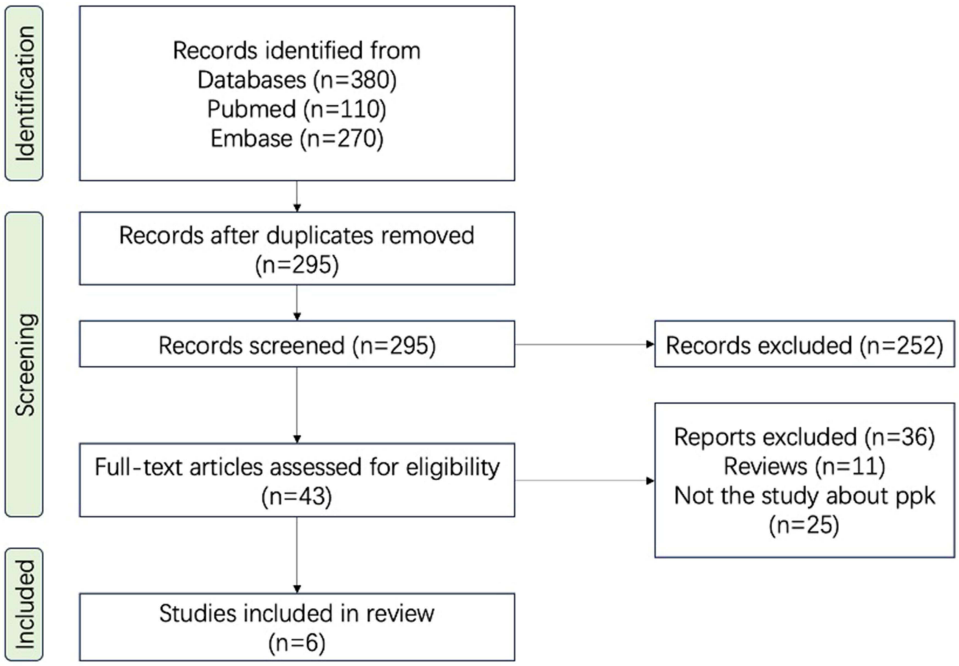

Figure 1 Study selection process.

Table 1 Characteristics of the Included Analyses [n = 6]

Characteristics	No. of Analyses [n (%)]
Number of patients	Median 253 (range 73–3016)
Number of samples	Median 1332 (range 600–26,346)
Data source: Clinical trials	6 (100%)
Methods of concentrations determination	
LC-MS	5 (71.43%)
NA	1 (28.57%)
Best structural pharmacokinetic model	
Two-compartment	6 (100%)
Residual error models	
Proportional	2 (33.33%)
Combined proportional and additive	1 (16.67%)
NA	3 (50.00%)
Numbers of model evaluation methods used (VPC, NPDE, bootstrap analysis, diagnostic plots)	
3 methods	3 (50.00%)
2 methods	3 (50.00%)

LC-MS, liquid chromatography methods with tandem mass spectrometric detection; NA, not available; VPC, visual predictive check; NPDE, normalized prediction distribution errors.

Population Pharmacokinetic Analyses

For each analysis, Table 3 summarizes selected structural models, pharmacokinetic parameters, IIV, residual error, and evaluation of PPK models. An industry-standard software program, NONMEM, was used to develop all PPK models.

All the publications described VEN's pharmacokinetics using a two-compartment model. The median (range) estimated apparent clearance (CL/F), inter-compartmental clearance (Q/F), apparent volume of distribution of the central compartment (V_2/F) and apparent volume of distribution of the peripheral compartment (V_3/F) were 446 L/Day (360–469 L/day), 98.8 L/Day (94.5–158 L/day), 114.5 L (37–118 L), and 121 L (116–217 L). In the final model, five analyses were used to describe the IIV of CL/F and V_2/F. The median (range) IIV of CL/F reported was 39.5% (37.3–45.7%) and V_2/F was 46.7% (42.3–507.2%). There were five analyses[11,15–17,19] that used the proportional residual error model to explain random residual variability. The additive error was applied in three analyses,[11,15,19] which were $3.05*10^{-7}$ $3.03*10^{-7}$ and $3.07*10^{-7}$. Two analyses[18,22] lacked information about residual error. An internal evaluation was almost conducted on the final models of the included analyses, and only one analysis was not known. A number of methods were commonly used, including visual predictive checks (VPC),[11,15–19] bootstrapping,[11,17] normalized prediction distribution errors (NPDE)[15,18,19] and diagnostic plots.[15,16,18,19]

Information about the pharmacokinetic sampling is summarized in Table 4. Five analyses showed the schedule of pharmacokinetic sampling,[11,15,17–19] which are subtly different according to single-dose, multiple-dose, and multiple-drug administration. Most samples of analyses were collected at 2, 4, 6, and 8h post-dose. Only one analysis[17] mentioned non-blood samples, it described that urine samples were collected on the 7th post-dose study day of cycle 1 in the multiple-dose part of the study over intervals of 0–4, 4–8 and 8–24 h. Besides, none of these analyses has reported cerebrospinal fluid (CSF) samples.

Covariate Modeling

The main purpose of most PPK analyses was to identify the potential covariates that affect VEN's PK. Table 5 summarizes the covariate screening process and the covariates incorporated into the final models.

In all the publications, among the covariates assessed for inclusion were demographic factors (body weight, sex, age, race and region), laboratory values [renal and hepatic function, creatinine clearance (CrCL), bilirubin (BIL), aspartate aminotransferase (AST), albumin (ALB) and alanine aminotransferase (ALT)], disease characteristics [population, Binet stage, Eastern Cooperative Oncology Group performance status (ECOG PS), Cumulative illness rating scale score, serum ß2-microglobulin levels, B symptoms, mutational status, cytogenetic factors and so on], co-administrations (with

Table 2 Studies Design and Characteristics of the Population

Analyses	Patients(n)	Samples (n)	Male (%)	Female (%)	Age(Year) Mean ± SD; Median [Range]	Body weight (kg)Mean ±SD; Median [Range]	Race (%)	Disease Type(%)	Drug Dose	Data Source	Sample Assay
Jones 2016[11]	505	7483	306 (60.59%)	199 (39.41%)	63.5±11.80; 65 [25–88]	79.5±16.89; 78.6 [36.9–143.0]	White (91.9%) Black(4.5%) Hispanic(0.2%) Asian(1.2%) Other(2.2%)	CLL/SLL (66.53%) NHL (23.37%)	10–1200mg, qd, po	8 clinical studies	LC-MS
Minocha 2018[17]	73	708	0	73 (100%)	Single-dose (Placebo 44±15, VEN 44±11) Multiple-dose (Placebo42±11, VEN 46±10)	Single-dose (Placebo76±20, VEN 73±16) Multiple-dose (Placebo70±14, VEN 78±17)	Single-dose [Placebo White (83%), Black(17%) VEN White(78%), Black(22%)] Multiple-dose: [Placebo White (85%), Black(15%) VEN White(81%), Black(19%)]	SLE	Single ascending oral doses of VEN 10, 30, 90, 180, 300 or 500 mg or matching placebo; multiple ascending oral doses of VEN 30, 60, 120, 240, 400, or 600 mg or matching placebo.	NCT01686555	HPLC-MS /MS
Deng 2019[15]	182	600	126 (69.23%)	56 (30.77%)	63.9±10.6; 65[28–83]	78.4±14.1; 77[41–115]	White (96.7%) Asian(3.3%)	Relapsed/ refractory CLL	5-week VEN dose ramp-up was administered to reach a target dose of 400 mg,	MURANO study (NCT02005471)	LC-MS
Samineni 2022a[18]	274	1563	183 (66.79%)	91 (33.21%)	70[42–89]	76.0[40–138]	White (84.3%) Black(1.1%) Hispanic(6.6%) Asian(0.4%) Other(7.7%)	CLL	400mg, qd, po	The Phase 3 CLL14 trial (BO25323; NCT02242942), GP28331 (NCT02339181)	LC-MS

(*Continued*)

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Table 2 (Continued).

Analyses	Patients(n)	Samples (n)	Male (%)	Female (%)	Age(Year) Mean ± SD; Median [Range]	Body weight (kg)Mean ±SD; Median [Range]	Race (%)	Disease Type(%)	Drug Dose	Data Source	Sample Assay
Samineni 2022b[19]	232	1100	129 (55.60%)	103 (44.40%)	61.2±12.6; 64[18–85]	77.8±16.8; 77.0 [46–182]	White (71.1%) Asian(2.2%) Black/African American (1.7%) Native Hawaiian or Pacific Islander (1.3%) Unknown(23.7%)	DLBCL	200–800mg, po, once daily (21 days per cycle) or 10/ 21-day dosing	NCT02055820	LC-MS
Gong 2023[16]	3016(No Information:10)	26,346	1689 (56.19%)	1317 (43.81%)	NA	76.0±18.8; 75.2 [7.4–174.0]	White (81.0%) Asian(9.3%) Black(6.7%) Native Hawaiian Or Pacific Islander (0.2%) American Indian/ Alaska Native (0.1%) Multiple(0.6%) Other(0.9%) Missing(1.1%)	Healthy (8.59%) CLL/SLL (35.64%) NHL (6.66%) AML (26.46%) MM (14.49%) MDS (3.08%) ALL (2.19%) Solid (0.23%) Lupus (2.42%) Other (0.23%)	10–1200 mg	41 clinical studies	NA

Abbreviations: CLL, Chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; NHL, Non-Hodgkin's lymphoma; LC-MS, liquid chromatography methods with tandem mass spectrometric detection; SLE, Systemic Lupus Erythematosus; HPLC-MS/MS, high- performance liquid chromatography-tandem mass spectroscopy; DLBCL, diffuse large B cell lymphoma; AML, acute myeloid leukemia; NA, not available.

Table 3 Modeling Strategies and PK Parameters of Published PPK Analyses of VEN

Analyses	PK Model	CL/F (L/Day)	Q/F (L/ Day)	V_2/F (L)	V_3/F (L)	IIV	Residual error	PPK model evaluation
Jones 2016[11]	Two-compartment PK model with first-order absorption and elimination	413	94.5	113	116	CL/F 39.9%; V_2/F 48.1%	σ^2_{prop} 0.244; $\sigma^2_{add}3.05*10^{-7}$	Bootstrap, prediction-corrected VPC
Minocha 2018[17]	Two-compartment model with first-order absorption, absorption lag time, and linear elimination	391.2	88.8	Apparent central volume of distribution in females, L 37	122	CL 38%, central volume of distribution 68%, absorption rate constant 19%	Proportional residual error (40%)	Bootstrap, VPC
Deng 2019[15]	NA	469	100	118	123	CL/F 37.3%; V_2/F 42.3%	$\sigma^2_{prop}0.219$, $\sigma^2_{add}3.03*10^{-7}$	Standard diagnostic plots, VPC, and NPDE
Samineni 2022a[18]	Two-compartment PK model with first-order absorption and elimination	446	98.8	116	121	NA	NA	diagnostic plots, VPCs and NPDE.
Samineni 2022b[19]	Two-compartment PK model with first-order absorption and elimination	447	97.2	118	119	CL/F 39.1%; V_2/F 45.3%;	$\sigma^2_{prop}0.22$, $\sigma^2_{add}3.07*10^{-7}$	Diagnostic plots, VPC and NPDE
Gong 2023[16]	A two-compartment PK model with transit compartments for absorption and first-order elimination	360	158	107	217	CL/F 45.7%; V_2/F 57.2%,	σ^2_{prop} 0.189	Diagnostic plots and visual VPC

Abbreviations: PK, model pharmacokinetic model; CL/F, apparent clearance; Q/F, inter-compartmental clearance; V_2/F, apparent volume of distribution of the central compartment; V_3/F, apparent volume of distribution of the peripheral compartment; IIV, interindividual variability; σ^2, residual variances; PPK, population pharmacokinetics; VPC, visual predictive check; NA, not available; NPDE, normalized prediction distribution errors.

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Table 4 Pharmacokinetic Sampling of Published PPK Analyses of VEN

Analyses	Pharmacokinetic Sampling [a]
Jones 2016[11]	Study 1: 0, 2, 3, 4, 6, 8, 24, 48, 72 h post-dose and sparse PK sampling Study 2: 0, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96 h Study 3: 0, 2, 4, 6, 8 h post-dose and sparse PK sampling Study 4: 8 h post-dose and sparse PK sampling Study 5: 8 h post-dose and sparse PK sampling Study 6: 0, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, and 72 h post-dose Study 7: 0, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72 h post-dose Study 8: 0, 2, 4, 6, 8.10, 12, 16, 24, 48, 72, 96 h post-dose
Minocha 2018[17]	Single-dose: VEN 10, 30, 90, 180, 300, 500 mg or matching placebo orally in single ascending doses; pre-dose and at 2, 4, 6, 8, 24, 48, and 72 h post-dose. Multiple-dose: VEN 30, 60, 120, 240, 400, or 600 mg or matching placebo orally in multiple ascending doses. On study days 1 and 7 of cycle 1 at pre-dose and at 2, 4, 6, 8 and 24 h post-dose. Additional pre-dose samples were collected on study days 4, 29, 32 and 35. Urine samples: in the multiple-dose part of the study over the 0–4, 4–8 and 8–24 h intervals on study day 7 post-dose in cycle 1.
Deng 2019[15]	Plasma samples were taken from the VEN–rituximab arm for PK analysis before and 4h after VEN dosing on C1D1 (after completion of the dose ramp-up) and C4D1.
Samineni 2022a[18]	CLL14: pre-dose on cycle 4 day 1 and at 4 h post-dose for patients enrolled into the VEN-obinutuzumab arm only. GP28331: In arm A, VEN plasma samples were collected on ramp-up day 1 (pre-dose, and 2, 4, 6, 8, and 10 h post-dose) , day 8, and day 15 (pre- dose and 8 h post-dose) for all cohorts, and also on day 22 and day 29 (pre-dose and 8 h post-dose) for selected cohorts. After that, for all patients in arm A, samples were collected on cycle 1 day 1 (pre-obinutuzumab infusion) and cycle 1 day 3 (pre-dose, and 2, 4, 6, 8, and 10 h post-dose), and on day1 (pre-dose) for all remaining cycles. In arm B, VEN plasma samples were collected on cycle 1 day 22 (pre-dose, and 2, 4, 6, 8, and 10 h post-dose) and cycle 3 day 1 (pre-dose and 8 h post-dose) for all cohorts, and on cycle 2 day 1, day 8, day 15, and day 22 (pre-dose and 8 h post-dose) for selected cohorts.
Samineni 2022b[19]	On cycle 1 day 4 and cycle 2 day 1 at pre- and up to 8h post-dose and at pre-dose on cycle 1 day 8 and cycle 2 day 10.
Gong 2023[16]	NA

Notes: [a]Blood samples unless otherwise specified.
Abbreviation: NA, not available.

moderate and strong CYP3A inhibitors, OATP1B1 transporter inhibitors, bortezomib, navitoclax, daratumumab, dexamethasone, carfilzomib, bendamustine, azacitidine, decitabine, rituximab and obinutuzumab), dose and food.

In the above covariates, the stepwise covariate method including forward addition and backward elimination is usually used to identify the covariates. As significant covariates on CL/F, the effects of moderate and strong CYP3A inhibitors (5/5),[11,15,18,19,22] rituximab co-administrations (2/4)[11,15] and OATP1B1 transporter inhibitors (4/5)[15,16,18,19] were frequently reported. In addition, covariates associated with CL/F, such as population,[16] bortezomib co-administration,[16] carfilzomib co-administration[16] and bendamustine co-administration,[16] have been reported in a limited amount of studies. The effect on V_2/F were commonly described by population (4/5)[11,16,18,19] and sex (5/5)[11,15,16,18,19] as the covariates. Covariates affecting F_1 have rarely been investigated, only food (3/3),[15,18,19] dose (2/3)[18,19] and Asian race[16] (1/4).

Covariate Effects

A quantitative analysis was performed on the effects of all covariates that were included in the final model (Figures 2 and 3). It is interesting that all covariates are categorical. The most studied covariates that significantly influenced CL/F were CYP3A inhibitors, OATP1B3 inhibitors and rituximab co-administration. Three analyses[11,15,16] showed that moderate and strong CY3A inhibitors were estimated to decrease the CL/F, with the latter to a greater extent. Two analyses[19,22] only provided estimated value, 95% Confidence Interval is missing. A minimal increase (7% and 21%) in the CL/F of VEN was observed after rituximab co-administration. An investigation of other covariates, such as OATP inhibitor co-administration, was conducted only in one study, and CL/F was also considered to be significantly affected by co-administration of bendamustine, carfilzomib, and bortezomib. The combined administration of OATP inhibitors would result in a 17%

Table 5 List of Tested and Included Covariates in the PPK Models of VEN

Analyses	Tested covariates	Covariate selection	Included Covariates		
			CL /F	V_2/F	F_1
Jones2016[11]	BW, SEX, AGE, CrCL, BIL, AST, ALT, ALB, RENAL, HEPATIC, RACE, POPULATION, OATP1B1 transporter inhibitors, rituximab co-administration, acid-reducing agents co-administration	Forward inclusion, backward elimination	CYP3A modulators, rituximab co-administration	SEX, POPULATION	-
Minocha2018[17]	BW, AGE, CrCL, RACE	forward addition	-	-	-
Deng2019[15]	Moderate and strong CYP3A inhibitors, rituximab co-administration, OATP1B1 transporter inhibitors, SEX, POPULATION, DOSE, FOOD	Forward addition, backward elimination	Rituximab coadministration, Strong CYP3A inhibitors, moderate CYP3A inhibitors, OATP1B3 hepatic uptake transporter inhibitors	SEX	FOOD
Samineni2022a[18]	Moderate and strong CYP3A inhibitors, rituximab co-administration, OATP1B3 transporter inhibitors, SEX, POPULATION, DOSE, FOOD, RENAL, HEPATIC, AST, BIL, ALB, CrCL, obinutuzumab administration, Binet stage, Cumulative Illness Rating Scale score, ECOG PS, B symptoms, serum ß2-microglobulin levels, mutational status, cytogenetic factors	Forward addition	Strong and moderate CYP3A inhibitors, OATP1B3 hepatic uptake transporter inhibitors	POPULATION, SEX	FOOD, DOSE
Samineni2022b[19]	AGE, BW, SEX, POPULATION, RACE, DOSE, ECOG PS, IPI, SATGE, COO, BCL-2 IHC, MYC IHC, DP, DH, C3AHIB, OATP3HIB, REGION	Previous model[11] was used as the base model.	Strong CYP3A inhibitor, moderate CYP3A inhibitor, OATP1B3 inhibitor,	POPULATION, SEX,	FOOD, DOSE
Gong2023[16]	BW, SEX, Asian RACE, POPULATION, HEPATIC, BIL, AST, RENAL, CrCL, OATPIB, P-gpIB, rituximab/ bortezomib/ dexamethasone/carfilzomib/daratumumab/azacitidine/ navitoclax/bendamustine/decitabine co-administration	Backward elimination	POPULATION, HEPATIC, OATPIB, bortezomib co-administration, carfilzomib co-administration, bendamustine co-administration	POPULATION, SEX	Asian RACE

Abbreviations: F_1, relative bioavailability; BW, body weight; CrCL, creatinine clearance; BIL, bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; OATP1B1, organic anion transporting polypeptide 1B1 transporter phenotype; BCL-2, B cell lymphoma 2 protein; C3AHIB, CYP3A inhibitor flag; COO, cell-of-origin; DH, doubt hit; DLBCL, diffuse large B cell lymphoma; DP, double positive; ECOG PS, Eastern Cooperative Oncology Group performance status, IPI, International Prognostic Index; FL, follicular lymphoma, IHC, immunohistochemistry, OATP3HIB, OATP1B3 inhibitor flag, P-gpIB, P-g inhibitor flag.

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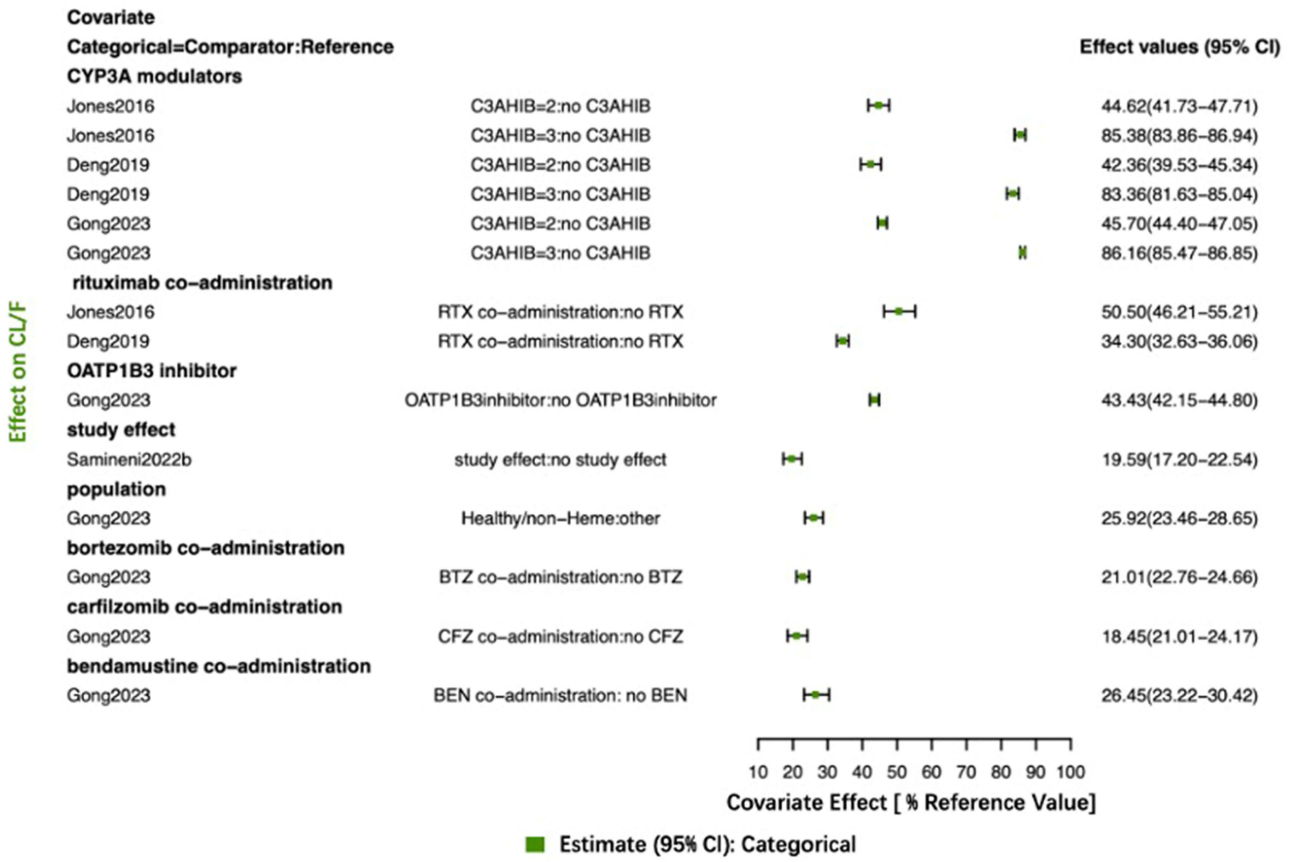

Figure 2 The effects of included categorical covariates on CL/F of VEN. The horizontal lines indicate categorical covariate effects (with 95% confidence intervals [CI]). The typical value of clearance in each study was considered to be 1. The effect of each covariate for CL/F is displayed by the ratio of CL/F in the range of each covariate to the typical CL/Fvalue (Data from Jones2016[11], Deng2019[15], Gong2023[16], Samineni2022b[19]).
Abbreviations: C3AHIB, CYP3A inhibitor indicator variable (2 = moderate, 3 = strong); RTX, rituximab; BTZ, bortezomib; CFZ, carfilzomib; BEN, bendamustine.

decrease in CL/F. It was estimated that co-administration of carfilzomib, bortezomib and bendamustine increased CL/F by 56%, 48%, and 33%, respectively.

Three analyses[11,15,16] found that the V_2/F of VEN has a decrease in SEX, female subjects were estimated to have 28–32% lower V_2/F. Population was also an influential covariate with an increase in V_2/F. In Gong et al's study, patients with non-hematological conditions or healthy subjects had 46% lower V_2/F than subjects with hematological malignancies.[16] And compared to healthy subjects, CLL/SLL and NHL subjects have larger V_2/F.

Discussion

nOver the past few years, there has been growing interest in exploring the PK of VEN, and plenty of studies have sought to identify the sources of variability in VEN through PPK and apply the model's predictive ability to clinical situations. This is the first review which summarizes on the PPK modeling of VEN, which is a potent and selective inhibitor of BCL-2. According to date, there have been six analyses of VEN's PPK model published so far in patients with healthy or non-hematological conditions, and hematological conditions. All analyses described the PK of VEN using the two-compartment PK model with first-order absorption and elimination. The most commonly used covariates in the final PPK models were moderate and strong CYP3A inhibitors, OATP1B3 inhibitors, and rituximab co-administration for CL/F, and population and sex for V_2/F. Typically, models are evaluated using two or three evaluation methods, such as VPC, NPDE, bootstrap analysis, and diagnostic plots. This analysis may provide a uniform platform for selection of covariates for PPK analyses across studies.

In most of these publications, pharmacokinetic samplings were blood samples. Most samples of analyses were collected at 2, 4, 6, and 8h post-dose. For the real-world analyses, it is too difficult to obtain dense blood samples.

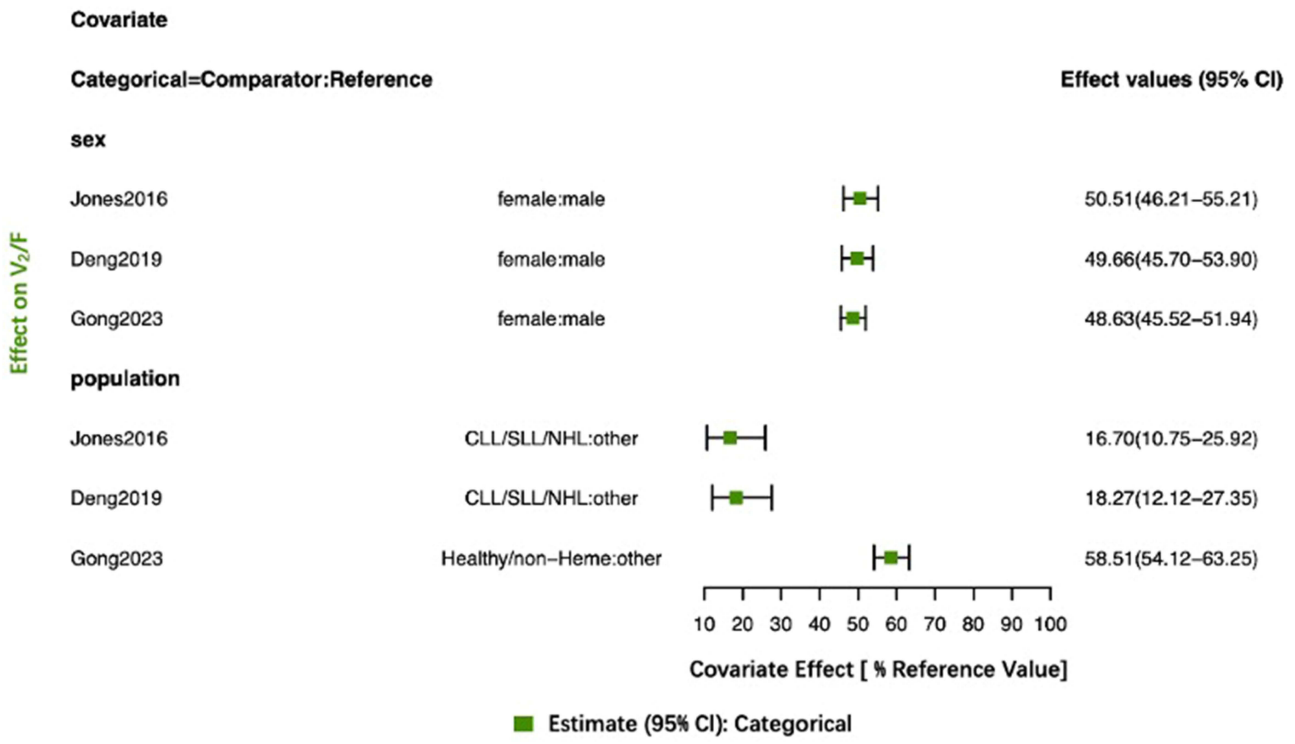

Figure 3 The effects of included categorical covariates on V_2/F of VEN. Categorical covariate effects (95% confidence interval [CI]) are represented by open symbols (horizontal lines). The typical value of V_2/F in each study was considered to be 1. The effect of each covariate for V_2/F is displayed by the ratio of V_2/F in the range of each covariate to the typical V_2/F valuee (Data from Jones2016[11], Deng2019[15], Gong2023[16]).
Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; NHL, non-Hodgkin's lymphoma; Heme, hematological malignancies.

Gradually increase the dose of VEN to 400 mg per day over 5 weeks according to a weekly ramp-up schedule.[23] Before administering VEN, Kobayashi et al collected blood samples and evaluated the minimum plasma concentration (Cmin).[24] The first-in-human study including 116 R/R CLL/SLL patients evaluated the pharmacokinetic profile of VEN and reported that the peak VEN level was reached six to eight hours after the first dose of VEN monotherapy.[25] In accordance with its pharmacokinetics, peak plasma concentrations of VEN are reached 5–8 hours after oral administration.[26] In previous study, it took the median time of 6 hours for VEN to reach plasma concentration, while the approximate $t_{1/2}$ was 18 hours.[27] From the existing research, we proposed to collect steady state trough concentration (C0, after 5 days of regular dosing at a constant dose, 0–0.5 hours before the next dose, as close as possible to 0 hour before dosing.) and steady state peak concentration (C6, 6 hours after the next dose after 5 days of regular dosing at a constant dose.) for therapeutic drug monitoring (TDM) in clinical work. However, there is no clinically referable range for TDM, which needs to be further explored in follow-up study.

Among these analyses, only Minocha et al mentioned urine samples that would be collected over the 0–4, 4–8 and 8–24 h intervals on study day 7 post-dose in cycle 1 in the multiple-dose part of the study.[17] None of analyses mentioned CSF samples. There is little evidence that VEN is effective for patients with hematological malignancies and central nervous system (CNS) involvement, although some observations have been made in cases of a CLL patient,[28] an AML patient[29] and an acute promyelocytic leukemia (APL) patient[30] suggest that blood-brain barrier is crossed by VEN, which reaches potential therapeutic concentrations. In addition, Badawi et al reported the pharmacokinetics of VEN in plasma and CSF samples from pediatric patients with R/R malignancies from a Phase 1 study, which demonstrates VEN's ability to cross into the central nervous system.[31] In light of these findings, VEN may have a role to play for patients with CNS complications. However, there is a need for further research in order to determine its utility in improving clinical outcomes.

In all PPK studies of VEN, CYP3A inhibitors were tested as covariates in five analyses, and all included them in the final model. Inhibitors of CYP3A4 may affect the levels of VEN, as it is a substrate for to CYP3A4. In terms of clinical

consideration, PPK studies could be conducted on concomitant administration of CYP3A inhibitors of moderate and strong potency. In their study, Gong et al[16] found that multiple moderate CYP3A inhibitors used in combination cause a greater decrease in clearance than a single moderate inhibitor. In a study using the PBPK approach,[32] the results were as follows: C_{max} or AUC_{∞} was not affected by weak CYP3A inhibitors or inducers, but VEN exposure was decreased by moderate and strong CYP3A inducers. Moderate and strong CYP3A inhibitors were estimated to increase VEN AUC_{∞}. If potential VEN dose adjustments are required, this should be considered. Brüggemann et al suggested that the use of strong CYP3A4 inhibitors on the ramp-up phase of VEN is contraindicated, thereafter, reduce the dose by at least 75%.[33] When used in the ramp-up phase, moderate CYP3A4 inhibitors should be reduced by 50%, after that, VEN dose should be reduced by at least 50%.[33]

The concomitant use of rituximab has a negligible effect on VEN PK and is not anticipated to have any clinical significance. Moreover, the co-administration of carfilzomib, bendamustine, and bortezomib was estimated to increase CL/F in one model,[16] which is new findings. This interaction may help patients in multiple myeloma who use VEN plus carfilzomib and bortezomib.[34] Since venetoclax disposition pathways are not expected to be impacted by bortezomib and carfilzomib, the mechanism for the effect of these drugs is unclear.

Among the five publications in the VEN PPK, the factor population was also frequently tested. However, only one analysis reported that population had a significant influence on CL/F, and three analyses reported it had an influence on V_2/F. In addition to AML and CLL/SLL, clinical studies of VEN are currently underway in a number of areas, such as myelodysplastic syndrome,[35] multiple myeloma,[36,37] and large B-cell lymphoma.[38] This is a problem that needs to be paid attention in the follow-up research.

Three analyses[15,18,19] tested the effect of food on F_1, and as a categorical covariate, it was included in all three final models. Among adult females in good health, VEN achieved C_{max} 4h after administration and had a half-life of 16.4–17.2h.[14] Food administration resulted in a significantly higher Cmax than fasting administration, approximately 2h later.[13] Patients should be recommended to take VEN with food based on the results of these studies. When dissolution limited absorption occurs, food consumption can increase bioavailability because fat content of food and bile secretion may increase solubility. When administered with low-, moderate-, and high-fat meals, VEN was 2.99-, 3.77-, and 4.25-fold more bioavailable than when administered fasting state,[11] respectively. Therefore, it is advised to administer VEN with food, regardless of fat content, in order to ensure adequate and consistent bioavailability. The instructions recommend taking it within 30min after a meal.[23] Four analyses investigated the effect of race on the PK of VEN, only one[16] of which included it in the final model. It showed that Asian was estimated to have 61% higher F_1. Future research is needed to determine whether VEN requires dose adjustment for Asian population, especially Chinese.

There have been developed and validated sensitive LC-MS/MS methods for the determination of VEN in human plasma and CSF.[39] We could determine its effective therapeutic concentration range, study the blood–brain barrier permeability of VEN and develop PPK models to determine optimal VEN dosing regimens required to achieve targeted CSF exposures. Although VEN is approved for adult patients, it is also used for pediatric patients in practical clinical applications. Currently, it is being investigated to expand its use to pediatric patients, but more robust data are required. According to recent researches, it appears that VEN is well tolerated by pediatric patients and is safe.[40,41] There is still a need for further studies to determine the optimal dose, duration of treatment, and proper combination as well as to assess its long-term safety. We could develope PPK models to estimate the use of VEN in Chinese children.

Our analyses were limited. Firstly, it is important to note that this review was not able to include all model information due to a lack of details in some publications. Then, clinical trial data were used for PPK analyses of VEN, and the study population was mostly representative of the target population. There is a need for some real-world data-based studies. Thirdly, because of the publications included were all in English, relevant studies published in other language might have been missed out.

Conclusion

VEN is becoming more and more widely used in the clinical practice. We proposed to explore reference ranges for TDM in clinical work and highlighted the potential role of VEN for patients with CNS complications, which need further investigate. One hand this review provides a detailed description of the parameters for the construction of VEN models,

their key features, and the established covariate relationships. The covariates CYP3A inhibitors, OATP1B1 transporter inhibitors, sex, population, and food might always be included in the development of a PPK model. This can also allow for a deeper understanding of the pharmacokinetics of VEN, inform the construction of other PPK models for VEN, and identify areas where additional research is needed to facilitate the application of PPK models. On the other hand, doctors and pharmacists could use the summarized information, such as inhibitors of CYP3A4 may affect the levels of VEN, the co-administration of carfilzomib, bendamustine, and bortezomib was estimated to increase CL/F and food administration resulted in a higher Cmax than fasting administration, to make clinical recommendations for the patients.

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Disclosure

The authors report no conflicts of interest in this work.

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