



Effects of Letemovir and/or Methylprednisolone Coadministration on Voriconazole Pharmacokinetics in Hematopoietic Stem Cell Transplantation: A Population Pharmacokinetic Study

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Accepted: 20 September 2021 / Published online: 15 October 2021

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Abstract

Objective The aim of this study was to identify factors affecting blood concentrations of voriconazole following letemovir coadministration using population pharmacokinetic (PPK) analysis in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients.

Methods The following data were retrospectively collected: voriconazole trough levels, patient characteristics, concomitant drugs, and laboratory information. PPK analysis was performed with NONMEM[®] version 7.4.3, using the first-order conditional estimation method with interaction. We collected data on plasma voriconazole steady-state trough concentrations at 216 timepoints for 47 patients. A nonlinear pharmacokinetic model with the Michaelis–Menten equation was applied to describe the relationship between steady-state trough concentration and daily maintenance dose of voriconazole. After stepwise covariate modeling, the final model was evaluated using a goodness-of-fit plot, case deletion diagnostics, and bootstrap methods.

Results The maximum elimination rate (V_{\max}) of voriconazole in patients coadministered letemovir and methylprednisolone was 1.72 and 1.30 times larger than that in patients not coadministered these drugs, respectively, resulting in decreased voriconazole trough concentrations. The developed PPK model adequately described the voriconazole trough concentration profiles in allo-HSCT recipients. Simulations clearly showed that increased daily doses of voriconazole were required to achieve an optimal trough voriconazole concentration (1–5 mg/L) when patients received voriconazole with letemovir and/or methylprednisolone.

Conclusions The development of individualized dose adjustment is critical to achieve optimal voriconazole concentration, especially among allo-HSCT recipients receiving concomitant letemovir and/or methylprednisolone.

1 Introduction

Voriconazole, a triazole antifungal agent, inhibits enzymes involved in the synthesis of ergosterol, a primary component of fungal cell membranes. Voriconazole is used as a first-line agent for the prevention and treatment of invasive fungal infection (IFI) in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients [1–5]. However, the *in vivo* pharmacokinetics of voriconazole are complex and exhibit remarkable inter- and intra-individual variability [6]. Furthermore, the blood concentrations of voriconazole show a nonlinear response to dose adjustments, and excessive voriconazole concentration is reportedly associated with an increased risk of liver dysfunction [7, 8] and neurological adverse effects [9]. Thus, therapeutic drug monitoring is generally recommended for patients receiving voriconazole [10–12].

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Key points

We sought to assess the effects of letermovir coadministration on voriconazole trough concentrations in allogeneic hematopoietic stem cell transplant recipients using a robust population pharmacokinetic analysis.

Coadministration of letermovir or methylprednisolone was related to a larger maximum elimination rate of voriconazole and consequently decreased the voriconazole plasma trough concentrations.

The simulations clearly showed that increased daily doses of voriconazole were required to obtain an optimal trough voriconazole concentration (1–5 mg/L) when letermovir and/or methylprednisolone were coadministered.

Cytomegalovirus reactivation was a common complication after allo-HSCT until the approval of letermovir in Japan in March 2018 [13]. This novel anti-cytomegalovirus drug, used for prophylaxis of cytomegalovirus reactivation until approximately 100 days after transplantation, effectively reduced the risk of clinically significant cytomegalovirus infection [13, 14]. Given the substantial efficacy of letermovir and voriconazole against microorganisms, their coadministration is widely used after allo-HSCT. However, letermovir is a well-known inducer of cytochrome P450 (CYP)-2C19, the major metabolic enzyme for voriconazole [15–18], as well as CYP2C9 enzymes [19]. This drug–drug interaction is estimated to reduce the blood concentrations of voriconazole [20], leading to an increased risk of IFI in allo-HSCT recipients. Various factors have been identified as affecting the in vivo pharmacokinetics of voriconazole, including age and *CYP2C19* polymorphisms [21–24], C-reactive protein (CRP) [25–27], serum albumin levels [28], concomitant drugs (e.g., proton pump inhibitors [PPIs] [29–32] or steroids [33, 34]), among others [35–37].

Population pharmacokinetic (PPK) analysis with non-linear mixed effect modeling is a conventional method for the development of an appropriate pharmacokinetic model with limited sampling data; it aids in the assessment of the potential impact of covariates on the pharmacokinetics of certain drugs. In PPK analysis, fixed and random effects can be obtained, including the population-averaged pharmacokinetic parameters and interindividual and residual variabilities. Given that frequent collection of blood samples is not feasible in clinical practice, PPK analysis is useful for the assessment of clinical data [38].

Although the drug–drug interaction clinical trial between voriconazole and letermovir has been reported previously

[20], to the best of our knowledge, no PPK studies have been undertaken regarding the coadministration of letermovir and voriconazole using real-world clinical data. Therefore, in this study, we used PPK analysis to investigate the effects of concomitant letermovir use and other covariates on the blood concentrations of voriconazole.

2 Methods

2.1 Patients

We retrospectively analyzed 47 patients who underwent allo-HSCT for hematological disorders between April 2016 and March 2020 at the Kyushu University Hospital. Patients who received tacrolimus as prophylaxis for graft-versus-host disease and voriconazole as prophylaxis or treatment for IFI with therapeutic drug monitoring were included. Letermovir 480 mg/day was generally initiated intravenously or orally from the day of stem cell infusion. The exclusion criteria were as follows: (1) voriconazole initiated over 100 days after HSCT, (2) age < 20 years, and (3) liver dysfunction (aspartate aminotransferase and/or alanine aminotransferase level more than fivefold the upper normal range or total bilirubin level > 2.0 mg/dL). This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval no. 652-03).

2.2 Plasma Voriconazole Concentration

The plasma voriconazole concentration was measured using ultra-performance liquid chromatography or ultra-performance liquid chromatography-tandem mass spectrometry method, which was outsourced to SRL, Inc. (Tokyo, Japan) or LSI Medience Corporation (Tokyo, Japan). The limits of quantification of voriconazole were 0.1 mg/L for SRL and 0.3 mg/L for LSI. The calibration ranged between 0.1 and 40.0 mg/L for SRL and between 0.3 and 15.0 mg/L for LSI. The coefficients of variation were always < 15%. The voriconazole concentrations obtained within 5 days of voriconazole initiation were excluded from this analysis because the concentrations did not reach steady state [39].

2.3 Data Collection and Statistical Analysis

The following data were collected from patients' electronic medical records: plasma voriconazole concentrations, daily voriconazole dose, liver function test values (aspartate aminotransferase, alanine aminotransferase, and total bilirubin), stem cell sources, conditioning regimens, and underlying diseases. Information about putative covariates,

including age, sex, body weight, laboratory findings (CRP and albumin), and concomitant drugs (letermovir, PPI, and steroids), was also collected. Comparisons of voriconazole concentrations with or without letemovir coadministration were examined using the Mann–Whitney U test. Statistical analyses were performed using GraphPad Prism version 9 (GraphPad Software; San Diego, CA, USA).

2.4 Population Pharmacokinetic (PPK) Analysis

Nonlinear mixed effect modeling was used to construct the PPK model. The data were analyzed using the NONMEM® version 7.4.3 software package, and the first-order conditional estimation method with η – ε interaction was used as the estimation algorithm.

2.5 Base Model

A nonlinear pharmacokinetic model based on the Michaelis–Menten equation was applied to describe the relationship between the steady-state trough concentration and the daily maintenance dose of voriconazole. The base model is expressed as per Eq. 1. Because the bioavailability of voriconazole is known to be essentially 100% [19], the F -value was set to 1.

$$C_{\text{SS trough}} = \frac{K_m \times F \times \text{Daily dose}}{V_{\text{max}} - (F \times \text{Daily dose})}, \quad (1)$$

where daily dose is the amount of voriconazole administered daily, F is bioavailability, K_m is Michaelis–Menten constant, V_{max} is the maximum elimination rate, and $C_{\text{SS trough}}$ is the steady-state trough concentration.

The V_{max} and K_m correspond to the capacity and affinity for the metabolic enzymes of voriconazole, respectively. The interindividual variability was modeled using an exponential error model, and residual variability was modeled using an additional error model.

2.6 Final Model

The following variables were selected as putative covariates potentially affecting the steady-state trough concentration of voriconazole: sex, age, body weight, albumin, CRP, and coadministration of letemovir, PPIs (rabeprazole, esomeprazole, lansoprazole, omeprazole, and vonoprazan), and steroids (prednisolone, methylprednisolone, and dexamethasone).

The covariate model was constructed based on differences in objective function values (OFVs) estimated by NONMEM between hierarchical models. The final model was established using a stepwise approach with forward inclusion followed by backward elimination. The significance

levels in the likelihood ratio test using OFVs were set at 5% and 1% for forward inclusion and backward elimination, respectively.

An exponential model was used to evaluate the effects of continuous covariates on the parameters (Eq. 2).

$$P_{ij} = P_{i\text{pop}} \times \left(\frac{\text{COV}_j}{\text{COV}_{\text{med}}} \right)^\theta, \quad (2)$$

where P_{ij} is the parameter i scaled for subject j , $P_{i\text{pop}}$ is the typical value for population parameter i , COV_j is the value of the covariate for subject j , COV_{med} is the median value of the covariate in the study population, and θ is the exponential coefficients of the covariate.

The effect of categorical covariates was evaluated as shown in Eq. 3.

$$P_{ij} = P_{i\text{pop}} \times \theta^X, \quad (3)$$

where θ is the effect of the covariate on the parameter and X is an indicator variable of each factor (e.g., male = 0, female = 1).

2.7 Model Evaluation

During model development, the validity of the model was assessed using goodness-of-fit (GOF) plots. Once the final model was constructed, the validity and robustness of the model were evaluated using GOF plots, case deletion diagnostics (CDD), and the bootstrap method. GOF plots were used to evaluate the following relationships: observations versus population prediction (PRED) and individual prediction (IPRED), conditional weighted residuals [40] versus PRED, and absolute values of individual weighted residuals versus IPRED.

CDD was used to investigate the impact of each patient in the study population. Each patient was removed individually from the dataset, and the model parameters were re-estimated. In the bootstrap method, 1000 bootstrap replicates were generated by random sampling with replacement. The final model was fitted to these replicate datasets, and parameter estimates were obtained. The median and 95% confidence intervals (calculated using the percentile method) were compared with the parameter estimates obtained from the original dataset. GOF plots, CDD, and the bootstrap method were performed using R version 3.6.1, Xpose4 version 4.6.1, and Perl-speaks-NONMEM version 4.9.0 [41, 42].

2.8 Simulation

Dosing simulations were conducted using the final PPK model. The influence of significant covariates in the final

model on the voriconazole trough concentrations was investigated. Dosing schedules were set at 300, 400, 500, and 600 mg/day as maintenance doses. In total, 1000 voriconazole steady-state trough concentrations were simulated in each scenario using a Monte Carlo simulation with the estimated final model parameters. The target therapeutic range for the steady-state trough concentration of voriconazole was set to 1–5 mg/L [11]. Simulations and data processing were performed using the R version 3.6.1.

3 Results

3.1 Patient Characteristics

The patient characteristics are shown in Table 1. A total of 216 voriconazole trough concentration samples were collected from the data on 47 allo-HSCT recipients. The median age and body weight were 51 years (range 22–69) and 55.0 kg (range 31.3–90.3), respectively, without sex-related bias. The median albumin and CRP levels were 3.8 g/dL (range 2.5–5.7) and 0.32 mg/dL (range 0.01–19.60), respectively. Letermovir was concomitantly administered to 19 patients. PPIs were initiated as follows: rabeprazole in 16, esomeprazole in 13, lansoprazole in seven, omeprazole in six, and vonoprazan in five patients.

In addition, prednisolone ($n = 19$), methylprednisolone ($n = 18$), and dexamethasone ($n = 2$) were used at the median daily doses of 17.5 mg (range 2.5–50.0), 40.0 mg (range 25.0–80.0), and 16.5 mg (range 13.2–19.8) at the first time of voriconazole plasma concentration measurement, respectively.

3.2 Effect of Letermovir Coadministration on Trough Concentration and Concentration Per Dose Ratio of Voriconazole

We examined the effect of letermovir coadministration on the trough concentration and concentration per dose (C/D) ratio of voriconazole. The median trough concentration in the letermovir (+) group was significantly lower than that in the letermovir (–) group (1.03 vs. 1.85 mg/L; $P < 0.0001$) (Fig. 1a). Similarly, the median C/D ratio in the letermovir (+) group was significantly lower than that in the letermovir (–) group (2.50 vs. 4.84 mg/L; $P < 0.0001$) (Fig. 1b).

3.3 PPK Analysis in Final Model

The relationships among tested covariates are shown in electronic supplementary material (ESM)-1. After stepwise

Table 1 Patient characteristics

Characteristics	Value
Patient	47
VRCZ trough concentration samples	216
Purpose of VRCZ	
Treatment	33
Prophylaxis	14
Administration of VRCZ	
Oral	38
Intravenous	1
Oral and intravenous	8
Age, year	51 (22–69)
Sex, male/female	
Male	23
Female	24
Body weight, kg	55.0 (31.3–90.3)
AST, U/L	22 (7–55)
ALT, U/L	20 (5–93)
T-Bil, mg/dL	0.5 (0.2–1.0)
ALB, g/dL	3.8 (2.5–5.7)
CRP, mg/dL	0.32 (0.01–19.60)
Diagnosis	
AML or MDS	23
ALL	12
Lymphoma	6
Other	6
Source	
BM	22
PB	12
CB	13
Conditioning regimen	
MAC	10
RIC	37
Coadministration of LMV	19
Coadministration of PPI	
Rabeprazole	16
Esomeprazole	13
Lansoprazole	7
Omeprazole	6
Vonoprazan	5

Data are presented as n or median (range) unless otherwise indicated and are from before the conditioning regimen

ALB albumin, ALL acute lymphocytic leukemia, ALT alanine aminotransferase, AML acute myelogenous leukemia, AST aspartate aminotransferase, BM bone marrow, CB core blood, CRP C-reactive protein, LMV letermovir, MAC myeloablative conditioning, MDS myelodysplastic syndromes, PB peripheral blood, PPI proton pump inhibitor, RIC reduced-intensity conditioning, T-Bil total bilirubin, VRCZ voriconazole

covariate modeling, coadministration of letemovir (change in OFV [Δ OFV] = 74.349; $P < 0.01$) and methylprednisolone (Δ OFV = 22.528; $P < 0.01$) were significant covariates for V_{max} , suggesting that the coadministration of these drugs may affect the capacity of the metabolic enzymes of voriconazole. The estimated V_{max} was 72% larger in patients with than without letemovir coadministration and was 30% larger in patients with than without methylprednisolone coadministration. The parameter estimates of the final model are presented in Table 2. The relative standard errors of the estimated parameters were acceptable (relative standard errors < 30%), suggesting that all parameters were precisely estimated. The regression equation for V_{max} in the final model was as follows:

$$V_{max,i} = 670 \times (1.72)^{LMV_i} \times (1.30)^{mPSL_i}, \tag{4}$$

where $V_{max,i}$ is the V_{max} in subject i , LMV_i is concomitant letemovir use in subject i (used = 1, not used = 0), and $mPSL_i$ is concomitant methylprednisolone use in subject i (used = 1, not used = 0). The plots of individual ETAs versus continuous and categorical covariates in the final PPK model are shown in ESM 2 and 3, respectively.

3.4 Model Evaluation

The GOF plot for the final model (Fig. 2) exhibited a high predictive performance, and no systemic deviations were observed. However, a slight overprediction was observed

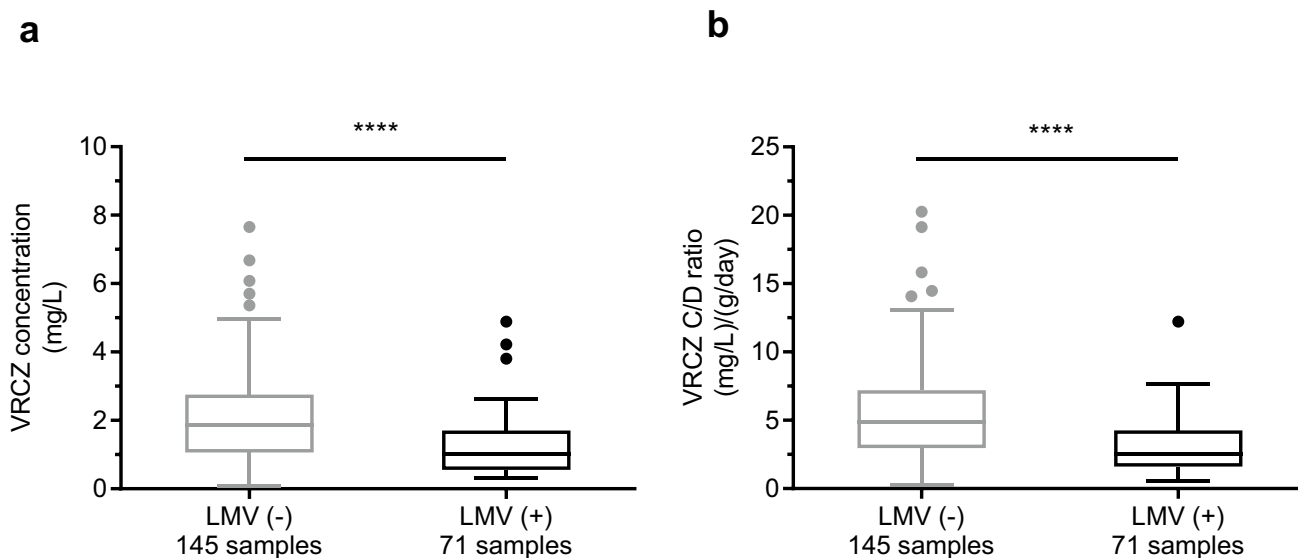


Fig. 1 Comparison of (a) VRCZ concentration and (b) C/D ratio between patients without LMV (LMV(-); 145 samples) and those with LMV (LMV(+); 71 samples). The bars show the median values;

boxes represent the 25th and 75th percentiles of the data. C/D ratio concentration per dose ratio, LMV letemovir, VRCZ voriconazole. **** $P < 0.0001$

Table 2 Parameter estimates from final model and bootstrap evaluation

Parameter	Estimate	RSE (%)	Shrinkage (%)	1000 bootstrap samples Median (95% CI)
Population mean				
K_m (μ g/mL)	1.97	23.5	NA	1.96 (1.35–4.89)
V_{max} (mg/day)	670	10.2	NA	669 (579–1090)
Effect of LMV on V_{max}	1.72	2.3	NA	1.72 (1.51–1.99)
Effect of mPSL on V_{max}	1.30	7.5	NA	1.30 (1.12–1.56)
IIV				
V_{max} (CV%)	23.6	13.9	11.2	23.4 (16.5–32.1)
Residual variability				
Additive error (μ g/mL)	0.77	10.8	8.9	0.75 (0.60–0.92)

CI confidence interval, CV coefficient of variation, IIV interindividual variability, K_m Michaelis–Menten constant, LMV letemovir, mPSL methylprednisolone, NA not applicable, RSE relative standard error, V_{max} maximum elimination rate

in the PRED versus observations plot. The CDD results are shown in Fig. 3. CDD did not reveal any patients with a significant influence on the estimation of covariate effects. The results of the bootstrap method are listed in Table 2. The median value of each estimated parameter from bootstrapping matched the original population estimates in the final model, and the significance of the covariates was further verified because the confidence intervals of their estimates did not include 1.

3.5 Simulation

Figure 4 shows the simulation results of the steady-state trough concentrations of voriconazole. Coadministration of letermovir and methylprednisolone was associated with large and moderate reductions in voriconazole exposure, respectively. The appropriate voriconazole trough concentrations were obtained at doses of 300 or 400 mg/day in patients without coadministration of letermovir and methylprednisolone. In contrast, appropriate voriconazole concentrations were achieved at higher doses in patients treated with letermovir (voriconazole 500 or 600 mg/day) or methylprednisolone (voriconazole 400 or 500 mg/day).

4 Discussion

In the current study, we sought to assess the effects of letermovir coadministration on voriconazole trough concentrations in allo-HSCT recipients using a robust PPK analysis. Coadministration of letermovir or methylprednisolone was related to a larger V_{\max} of voriconazole and consequently decreased the plasma voriconazole trough concentrations. The simulations clearly showed that increased daily doses of voriconazole were required to obtain an optimal voriconazole trough concentration (1–5 mg/L) when letermovir and/or methylprednisolone were coadministered.

We observed that the median voriconazole trough concentration with letermovir coadministration was 44% lower than that without letermovir coadministration because of the 1.7-fold increase in the V_{\max} of voriconazole. Our simulation indicated that, when treated with letermovir, a voriconazole dose of 500 or 600 mg/day was optimal to obtain an appropriate voriconazole trough concentration. Our findings were consistent with those of some previous studies. In a phase I clinical trial among healthy individuals, coadministration of letermovir reduced the area under

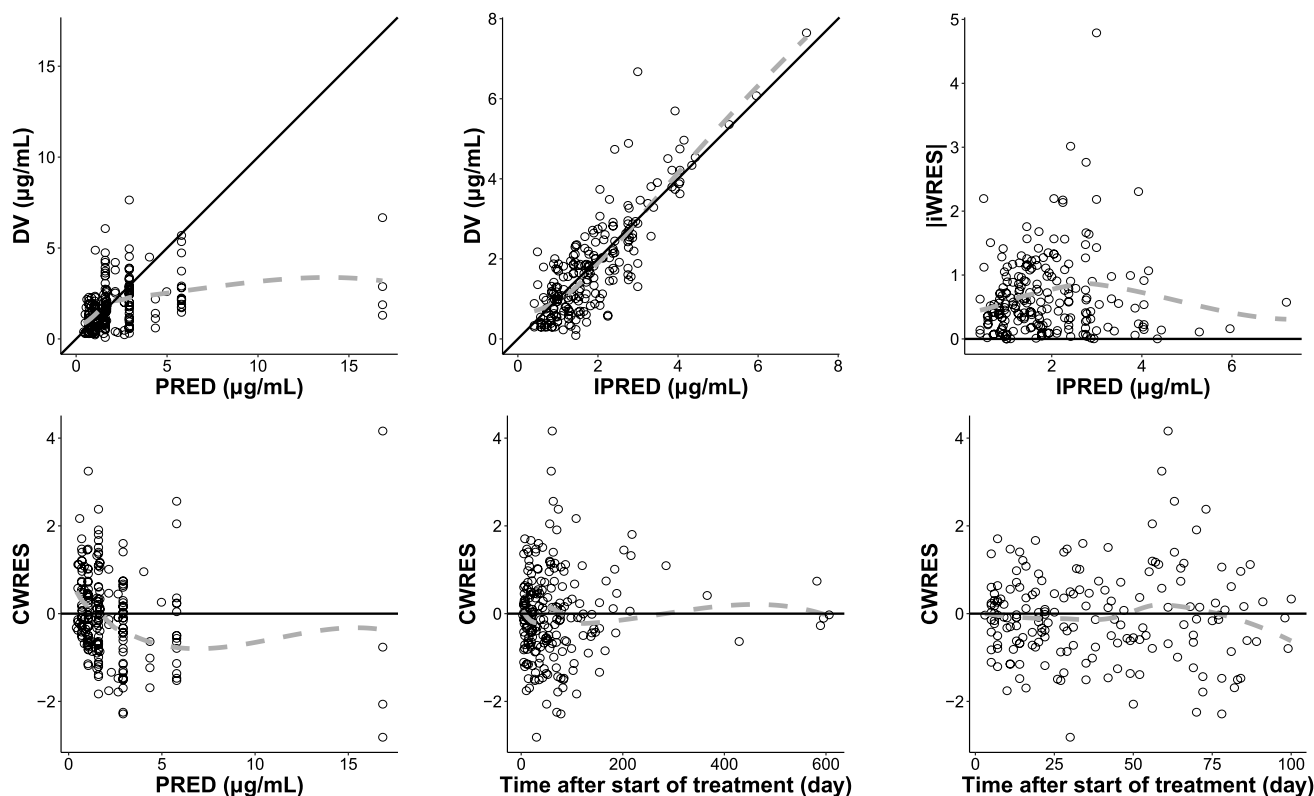


Fig. 2 Goodness-of-fit plots of the final model. The DV represents the observed steady-state trough concentration of voriconazole. PRED values were obtained using population parameters. IPRED values were obtained using individual empirical Bayesian estimated

parameters. *Straight solid lines* represent line of identity (a, b) and $y = 0$ (c–f). *CWRES* conditional weighted residuals, *DV* dependent variable, *IPRED* individual prediction, *I|WRES|* absolute individual weighted residuals, *PRED* population prediction

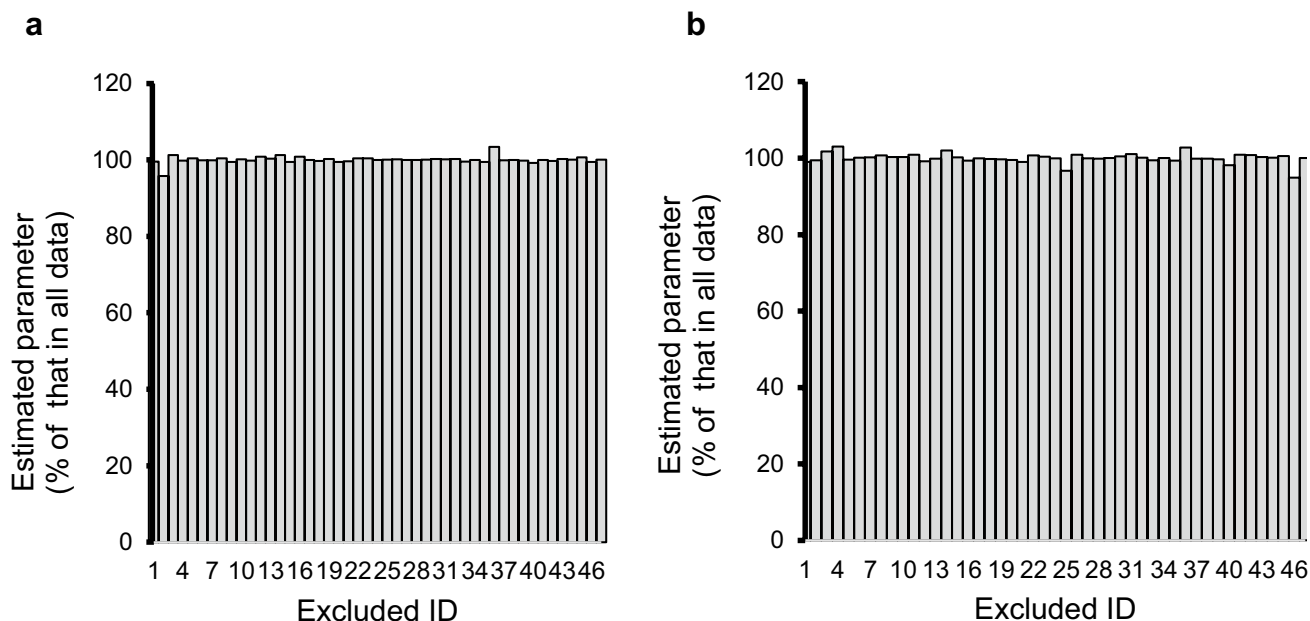
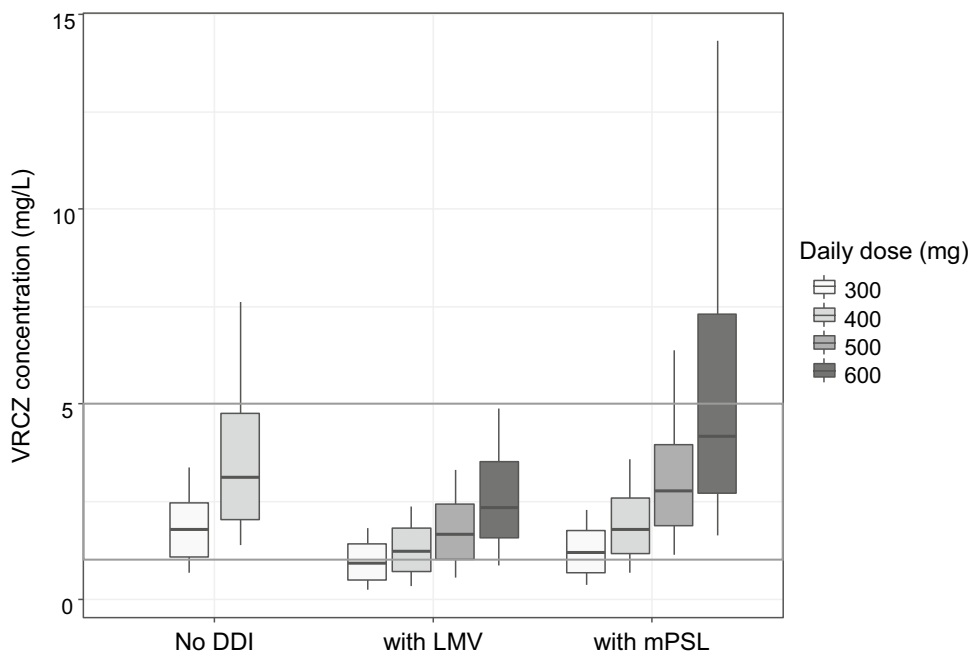


Fig. 3 Percentage changes in estimated parameters of covariate effect (cotreatment with (a) letermovir and (b) methylprednisolone) for maximum elimination rate in case deletion diagnostic analysis. Grey

shaded bars represent estimated parameter using all data and data with each ID excluded

Fig. 4 Simulated steady-state trough concentrations of VRCZ. Dosing schedules were set at 300, 400, 500, and 600 mg/day. Boxes indicate the 25th, 50th, and 75th percentiles; whiskers indicate the 10th–90th percentiles. The gray concentration range represents 1–5 mg/L, which is the target trough concentration range. *DDI* drug–drug interaction, *LMV* letermovir, *mPSL* methylprednisolone, *VRCZ* voriconazole



the curve and maximum plasma drug concentration of voriconazole by 44 and 39%, respectively [20]. Hikasa et al. [43] revealed that the voriconazole blood concentrations of allo-HSCT recipients treated with prophylactic letermovir were 33.2% lower than those not treated with letermovir. Nakashima et al. [44] previously reported that the median fold change of the voriconazole trough concentration during

letermovir administration was 0.40. Voriconazole is primarily metabolized by CYP2C9 and CYP2C19 [15–17]. Letermovir is assumed to increase the expression of CYP2C9/CYP2C19 by activating the pregnane X receptor, a transcriptional regulator involved in regulating the expression of drug-metabolizing enzymes [20, 45]. Further investigation of the letermovir-mediated induction of CYP2C9/CYP2C19

is warranted; however, letermovir-induced increases in the capacity of the metabolic enzymes of voriconazole play a critical role in the remarkable reduction of plasma voriconazole concentrations in allo-HSCT recipients. To the best of our knowledge, this is the first study to identify the effect of letermovir on voriconazole concentrations through a PPK analysis.

Of the three types of corticosteroids analyzed in this study, only methylprednisolone remained a significant influencing factor in the final model. Coadministration of methylprednisolone could increase the V_{\max} of voriconazole by 1.3-fold, leading to a requirement for a dosage of voriconazole 400 or 500 mg/day to achieve an appropriate voriconazole trough concentration among allo-HSCT recipients. Dolton et al. [34] reported that glucocorticoids significantly reduced voriconazole blood concentrations; among the glucocorticoids, methylprednisolone and dexamethasone exhibited stronger effects on voriconazole blood concentrations than prednisolone. In addition, under in vitro conditions, dexamethasone induced CYP2C19 through interaction of the glucocorticoid receptor with a glucocorticoid-responsive element in the promoter region of *CYP2C19* [46]. However, we could not confirm the effects of dexamethasone on voriconazole trough concentrations, presumably because of the very small number of patients treated with dexamethasone. In allo-HSCT settings, high-dose (1–2 mg/kg) methylprednisolone is usually initiated for the prophylaxis and/or treatment of acute graft-versus-host disease [47]. Czock et al. [48] reported that high doses of glucocorticoids induced CYP3A4, which was involved, albeit with a minor contribution, in voriconazole metabolism [49], suggesting that high-dose methylprednisolone may also reduce voriconazole trough concentrations by inducing CYP3A4. Imataki et al. [50] reported a reduction in voriconazole blood concentration in a steroid dose-dependent manner in patients with hematological malignancies. Based on these findings, the induction of both CYP2C19 and CYP3A4 by high-dose methylprednisolone may have contributed to the decreased voriconazole concentrations in the current study.

In the present PPK analysis, we used an equation expressing the relationship between steady-state trough concentration and daily dose. Because the voriconazole pharmacokinetics were characterized by nonlinear elimination, a nonlinear pharmacokinetic model with the Michaelis–Menten equation was selected as the base model. Previous PPK analyses often described voriconazole concentration profiles using one-compartment or two-compartment models [8, 51–54]. All 216 points obtained in this study were trough levels, without points in the absorption and distribution phases. These conditions contributed to the construction of a simplified equation model in this study.

4.1 Limitations

This study had several limitations. First, we did not estimate the absolute oral bioavailability of voriconazole. Although we assumed the bioavailability of voriconazole was 100%, several studies have reported a reduced bioavailability of voriconazole when used at low doses or in special populations such as transplant patients or extensive metabolizers [18, 55, 56]. Therefore, we conducted a sensitivity analysis assuming oral bioavailability of 45.9% [55]. Even in this case, letermovir and methylprednisolone were still identified as significant covariates. The simulation results for dose adjustment during oral administration were also similar to those assuming that the bioavailability was 100% (ESM-4). Therefore, we believe that this assumption did not result in a bias. However, since the dataset of this study included only 28 voriconazole concentrations during intravenous administration (about 13% of the total), it is difficult to recommend an optimal dose for intravenous administration of voriconazole based on the present analysis. Second, we did not evaluate the effects of genetic polymorphisms of drug-metabolizing enzymes, especially *CYP2C19* polymorphisms, on voriconazole concentrations in this PPK analysis. The CYP2C19 poor metabolizer phenotype is known to exist in approximately 20% of the Japanese population [57–59]. A previous PPK analysis indicated that this phenotype was associated with a remarkable reduction in voriconazole clearance [52]. Because the present study was retrospective, we could not conduct genotyping of *CYP2C19*. Therefore, a prospective study including information about *CYP2C19* polymorphisms and more patients is warranted to confirm our findings. Another limitation of this study was that we did not evaluate the absorption and distribution of voriconazole because we used only trough concentrations for this analysis. However, since the main purpose of this analysis was to evaluate concomitant medications that could change the elimination of voriconazole, we believe that the analysis with only the trough concentration was reasonable for this study.

5 Conclusion

The voriconazole trough concentration profiles were quantitatively described using the developed PPK model among allo-HSCT recipients. Coadministration of letermovir and/or methylprednisolone, frequently used during the posttransplant period, led to a remarkable decrease in voriconazole trough concentrations. Therefore, individualized dosage regimens of voriconazole are important to ensure its efficacy against IFI and to minimize the risk of adverse effects, especially in the setting of allo-HSCT.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40268-021-00365-0>.

Declarations

Funding This work was supported by JSPS KAKENHI Grant number JP20K16078.

Conflict of interest Kimitaka Suetsugu, Shota Muraki, Junshiro Fukumoto, Ryosuke Matsukane, Yasuo Mori, Takeshi Hirota, Toshihiro Miyamoto, Nobuaki Egashira, Koichi Akashi, and Ichiro Ieiri have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki and its amendments; the study was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval no. 652–03).

Consent to participate No informed consent from patients was required as this as a retrospective study.

Consent for publication All authors approved this manuscript for submission.

Availability of data and material The datasets generated and/or analyzed during the current study are not publicly available because of privacy issues but are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions KS, SM, and II contributed to the study design. Data collection and analysis was performed by KS, SMki, and JF. The first draft of the manuscript was written by KS, and the final version of the manuscript was approved by all authors.

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