Original Article

Therapeutic drug monitoring and *CYP2C19* genotyping guide the application of voriconazole in children

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Background: This study used therapeutic drug monitoring (TDM) and *CYP2C19* gene polymorphism analysis to explore the efficacy and safety of different doses of voriconazole (VCZ) for the clinical treatment of pediatric patients, with the aim of providing guidelines for individualized antifungal therapy in children.

Methods: Our study enrolled 94 children with 253 VCZ concentrations. The genotyping of *CYP2C19* was performed by polymerase chain reaction (PCR)-pyrosequencing. VCZ trough concentration (C_{trough}) was detected by high-performance liquid chromatography-tandem mass spectrometry. SPSS 23.0 was used to analyze the correlations between VCZ concentration, *CYP2C19* phenotype, adverse effects (AEs), and drug-drug interactions.

Results: A total of 94 children aged between 1 and 18 years (median age 6 years) were enrolled in the study. In total, 42.6% of patients reached the therapeutic range at initial dosing, while the remaining patients reached the therapeutic range after the adjustment of the dose or dosing interval. *CYP2C19* gene polymorphism was performed in 59 patients. Among these patients, 24 (40.7%) had the normal metabolizer (NM) phenotype, 26 (44.1%) had the intermediate metabolizer (IM) phenotype, and 9 (15.3%) had the poor metabolizer (PM) phenotype. No cases of the rapid metabolizer (RM) or ultrarapid metabolizer (UM) phenotypes were found. The initial VCZ C_{trough} was significantly higher in patients with the PM and IM phenotypes than in those with the NM phenotype. The combination of immunosuppressive drugs (ISDs) did not affect VCZ C_{trough}. The incidence of AEs was 25.5%, and liver function damage (46.2%) and gastrointestinal reactions (19.2%) were the most common.

Conclusions: Our study showed significant individual differences of VCZ metabolism in children. Combining TDM with *CYP2C19* gene polymorphism has important guiding significance for individualized antifungal therapy in pediatric patients.

Keywords: Voriconazole (VCZ); therapeutic drug monitoring (TDM); *CYP2C19*; therapy

Submitted Mar 07, 2022. Accepted for publication Jul 19, 2022.

doi: 10.21037/tp-22-156

View this article at: https://dx.doi.org/10.21037/tp-22-156

Introduction

Invasive fungal infections (IFIs) have increased incidence and are associated with morbidity and mortality in immunocompromised children (1). Voriconazole (VCZ) is a second-generation synthetic triazole antifungal agent with broad-spectrum antifungal activity, which is recommended as a primary therapy for IFI (2) and used as prophylaxis in immunosuppressed patients (3,4). The efficacy of VCZ treatment differs in adults and children. Therefore, studies investigating the efficacy and safety of VCZ in children are needed.

Optimizing the dose strategy of VCZ remains a challenge due to significant interpatient variability in exposure. VCZ serum concentrations are highly variable due to nonlinear pharmacokinetics, and they are further influenced by factors such as drug interaction, altered intestinal absorption, genetic polymorphism, inflammation, and individual age and weight. To account for this variability, VCZ therapeutic drug monitoring (TDM) has been used as a tool to guide therapy (5). It is supposed in *in vitro* susceptibility testing that VCZ trough values generally should be maintained above 0.50 μg/mL for prophylaxis and at 1.00 μg/mL or higher for treatment (6). However, the toxic and side effects are significantly increased when the concentration is greater than 6.00 μg/mL (7). And we suggest VCZ above 1.00 μg/mL for prophylaxis and at 2.00 to 5.00 μg/mL for treatment.

VCZ is primarily metabolized by the hepatic cytochrome P450 (CYP) isozyme *CYP2C19*, with contributions from *CYP2C9* and *CYP3A4* (8,9). Meanwhile, the drug metabolism of VCZ has the characteristics of non-linear metabolism, and even at the same dose, huge differences in pharmacokinetics between patients can be found by TDM, which is most likely caused by *CYP2C19* gene polymorphism. *CYP2C19* polymorphisms are associated with large interindividual variations in therapeutic efficacy and safety in patients treated with VCZ (10). Wild-type *CYP2C19*1* has full drug-metabolizing capacity, while *CYP2C19*2* and *CYP2C19*3* are the most common alleles associated with decreased enzyme activity and slow drug metabolism (11). By contrast, *CYP2C19*17* shows increased protein transcription and thus increased metabolic capacity (11). Individuals can be classified into the following phenotypes depending on genotype and enzyme activity: ultrarapid metabolizer (UM; *CYP2C19*17/*17*), rapid metabolizer (RM; *CYP2C19*1/*17*), normal metabolizer (NM; *CYP2C19*1/*1*), intermediate metabolizer (IM; *CYP2C19*1/*2*, *CYP2C19*1/*3*, and *CYP2C19*2/*17*), and poor metabolizer (PM; *CYP2C19*2/*2*, *CYP2C19*2/*3*, and *CYP2C19*3/*3*) (12). *CYP2C19*2* and *CYP2C19*3* are more common in Asians than in Caucasians (13). Thus, due to the combined effects of *CYP2C19*2* and **3* variants, Asian patients are at a particularly higher risk of supratherapeutic drug responses. However, studies of VCZ TDM in Asian children are limited.

In this study, clinical data were collected from children who were subjected to detected the VCZ trough concentration (C_{trough}) at a tertiary pediatric center, with doses adjusted accordingly. This paper mainly wants to reflect the influence of *CYP2C19* gene polymorphism on the blood concentration of VCZ through a retrospective analysis of TDM, and to reflect how physicians feedback and adjust the drug dose in clinical work to achieve clinical effectiveness.The aim of this research was to study dose adjustments of VCZ and the factors influencing VCZ C_{trough} in Asian children as a reference for pediatricians seeking to optimize daily VCZ administration. We present the following article in accordance with the MDAR reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-156/rc).

Methods

Patients and data collection

This was a retrospective cohort study of 94 children aged between 1 and 18 years who were treated for a probable or definite IFI as pediatric inpatients between June 1st, 2015 and April 30th, 2020 at Nanfang Hospital of Southern Medical University. The exclusion criteria were as follows: (I) patients aged <1 year or >18 years; (II) patients with abnormal liver and kidney function results; and (III) patients who received VCZ for less than 3 days. We browsed patients' medical history singly using standardized data collection form. Since the first VCZ treatment, researchers tracked and accurately recorded the dosing information (symptom for therapy, dosage and administration routes, administration time, and sampling time) and drugs token together with VCZ [proton pump inhibitors (PPIs), including omeprazole, esomeprazole, pantoprazole, lansoprazole, ilaprazole, and glucocorticoid]. In addition, numerical data (age, gender, and weight), results of laboratory test (blood, liver, and kidney function index), and the time at which transplantation was completed were collected, and blood samples were obtained to analyze

for *CYP2C19* alleles (*CYP2C19*1*, *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17*). The 94 pediatric patients were analyzed and then grouped by age, dosage forms, dose, and dosing interval. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Nanfang Hospital of Southern Medical University (No. NFEC-2022-259). Due to the retrospective nature of this study, an exemption from informed patient consent was granted by the ethics committee of Nanfang Hospital of Southern Medical University.

Blood sampling and measurement of VCZ plasma levels

Blood samples were taken at 72 hours (every patient had at least 3 samplings) after receiving the first intravenous or oral VCZ dose (every patient received VCZ at least 5 times). Plasma concentrations were collected 30 minutes before the next dose was administered and were considered to be at a steady state on day 5 (or later) of treatment without loading doses. Most of the children in the cases were diagnosed with malignant diseases, had a history of repeated hospitalizations, and required the use of VCZ in each hospitalization, so each patient could have one or more TDM data, but the TDM data collected by each patient No more than 3 times.

VCZ plasma concentrations were measured by a two-dimensional high-performance liquid chromatography-tandem mass spectrometer (2D HPLC-MS/MS; Demeter Instrument Co., Ltd., Hunan, China) as described in a previous study (14).

DNA purification and CYP2C19 genotyping

Genomic DNA from whole blood was isolated using a E.Z.N.A.® SQ II Blood DNA Kit (Omega Bio-Tek, Inc., Norcross, GA, USA). *CYP2C19* genotyping for *CYP2C19*2* (rs4244285, c.681G>A), *CYP2C19*3* (rs4986893, c.636G>A), and *CYP2C19*17* (rs12248560, c.-806C>T) was carried out by using the Sanger dideoxy DNA sequencing method with an ABI 3730XL DNA Analyzer (ABICo., BioSune Biotechnology Co., Ltd., Shanghai, China).

Statistical analysis

SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used to analyze the characteristics affecting VCZ C_{trough} in children, the correlations between *CYP2C19* gene polymorphism and VCZ C_{trough}, and the clinical efficacy and safety of TDM guidance. Patient characteristics are reported as frequencies and percentages for categorical variables based on the number of patients with no missing data for each variable. Means, standard deviations (SDs), medians, and ranges are reported for continuous variables. Univariate analysis was performed using the analysis of variance (ANOVA) test. Enumeration data analysis was performed using a chi-squared test. Multiple linear regression was used to analyze the linear relationship between the initial VCZ C_{trough} and these factors. A P value of <0.05 was considered statistically significant.

Results

Clinical characteristics of patients

A total of 94 pediatric patients were enrolled in the study, including 57 boys (60.7%) and 37 girls (39.4%), with a median age of 6 (range, 1–15) years. The baseline characteristics of these patients are summarized in *Table 1*. Polymerase chain reaction (PCR)-pyrosequencing was used to detect *CYP2C19* gene polymorphism in 59 patients with IFIs. We observed 3 different *CYP2C19* phenotypes in these patients. As indicated in *Table 1*, 24 patients (40.7%) had the NM phenotype, 26 patients (44.1%) had the IM phenotype, and 9 patients (15.3%) had the PM phenotype. No cases of the RM and UM phenotypes were found. Early diagnosis of IFI in routine clinical practice is challenging. In 5 patients with proven IFI, 2 patients had infections caused by *Aspergillus*, 1 patient had an infection caused by *Candida glabrata*, 1 patient had an infection caused by *Candida albicans*, and 1 patient had an infection caused by *Pneumocystis jirovecii*. A total of 35 patients received VCZ in combination with an immunosuppressant in the initial treatment.

Association between initial VCZ C_{trough} and dosage forms

Among the 253 levels from the 94 patients, the median VCZ C_{trough} was 2.12 (range, 0.16–15.37) mg/L. Based on the C_{trough} measurements, 40 patients (42.6%) achieved the therapeutic range (2–6 mg/kg). Of the 54 patients who did not achieve the therapeutic range, 31 (32.9%) were subtherapeutic and 23 (24.5%) were supratherapeutic.

In the 89 patients (94.7%) who received VCZ via intravenous administration, the median initial VCZ C_{trough} was 2.11 (range, 0.16–15.37) mg/L. In the 5 patients (5.3%)

Table 1 Characteristics of the study subjects (n=94)

Characteristics	Total	<3 years old (n=26)	3–6 years old (n=14)	>6 years old (n=54)
All patients, median [range]				
Age (years)	6 [1–15]			
Weight (kg)	19.8 [8.2–59.1]	10.0 [8.2–15.5]	15.3 [13.0–23.0]	24.5 [13.5–59.1]
CYP2C19 phenotypes (n=59), %				
NM	24 (40.7)	8 (33.3)	3 (12.5)	13 (54.2)
IM	26 (44.1)	5 (19.2)	5 (19.2)	16 (61.6)
PM	9 (15.3)	0	3 (33.3)	6 (66.7)
Clinical diagnosis				
AML	60	23	4	33
TM	26	0	10	16
ALL	3	1	0	2
AML-M3	2	2	0	0
AA	2	0	0	2
Neuroblastoma	1	0	0	1
Diagnosis of IFIs				
Probable IFIs	56	13	12	31
Clinical diagnosis	33	11	2	20
Proven IFIs	5	2	0	3
VCZ dosages forms				
Intravenous VCZ (50 mg)	49	23	10	16
Intravenous VCZ (200 mg)	40	2	4	34
Oral VCZ (50 mg)	5	1	0	4
Treatment options for IFIs				
Preventive treatment	30	9	5	16
Therapeutic treatment	64	17	9	38
Combination immunosuppressant therapy				
Cyclosporine	19	3	6	10
Sirolimus	4	3	0	1
Tacrolimus	12	2	3	7

NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; AML, acute myelocytic leukemia; TM, thalassemia; ALL, acute lymphoblastic leukemia; AML-M3, acute promyelocytic leukemia; AA, aplastic anemia; IFI, invasive fungal infection; VCZ, voriconazole.

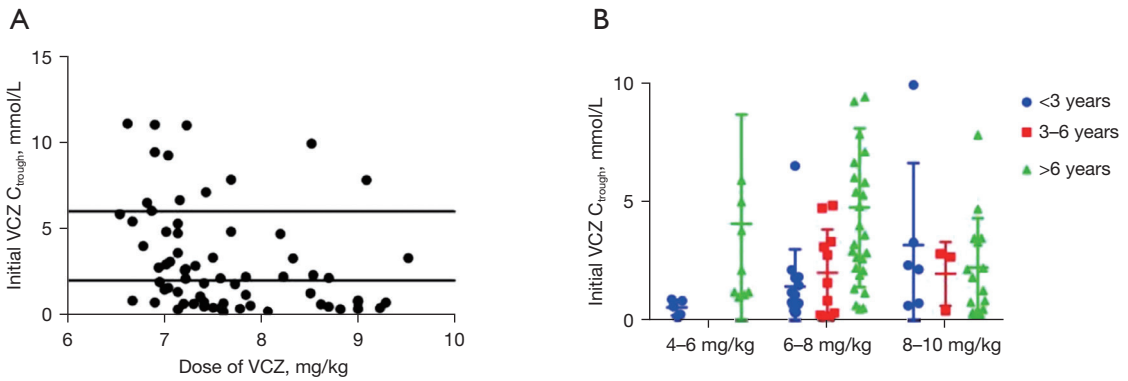

Figure 1 Association between initial VCZ dose and initial VCZ C_{trough}. (A) VCZ C_{trough}. (B) Patients were divided into three different age groups, and the initial VCZ C_{trough} in different doses is shown. VCZ, voriconazole; C_{trough}, trough concentration.

who received oral VCZ, the median initial VCZ C_{trough} was 2.13 (range, 0.54–6.04) mg/L. There was no significant difference (P=0.968) in the median initial VCZ C_{trough} between the 2 dosage forms.

Association between initial VCZ Ctrough and VCZ dose

Among the 94 patients, 68 received an initial VCZ dose of 7–9 mg/kg. The mean VCZ dose was 7.65±0.78 mg/kg, and the mean initial VCZ C_{trough} was 3.13±3.05 (range, 0.17–11.11) mg/L. There were 26 patients whose VCZ C_{trough} achieved the target range (2–6 mg/L). *Figure 1A* shows the large interindividual variation in VCZ C_{trough}. *Figure 1B* shows the initial VCZ C_{trough} in different age groups. There was no correlation between the initial VCZ C_{trough} and VCZ dose.

Optimizing the dose strategy based on TDM results

The initial VCZ C_{trough} was within the sub- or supratherapeutic range in most patients. Initial dosing and administration of VCZ were determined according to the summary of product characteristics (SmPC) of VCZ (15) and enhanced or decreased based on clinical indications and TDM results. If the initial VCZ C_{trough} was still out of the target range after dosing adjustment, the 12-hour dosing interval was shortened to 8 hours.

In the 31 patients who underwent dose adaptations, 14 dose increases and 17 dose decreases were made. The mean initial VCZ dose was 7.43±1.37 (range, 4.05–10.81) mg/kg, and the mean initial VCZ C_{trough} was 3.96±4.09 (range, 0.18–15.37) mg/L. After adapting the VCZ dose, the mean VCZ dose was 7.70±3.18 (range 2.30–14.71) mg/kg, and the mean initial VCZ C_{trough} was 2.07±1.04 (range, 0.18–15.37) mg/L. The initial VCZ C_{trough} was significantly reduced (P=0.015) following dose adaption. In the dose decrease group, the initial VCZ C_{trough} in 32.3% of patients (n=10) achieved the therapeutic range after dosing was decreased by 1/10–1/4, and the initial VCZ C_{trough} in 22.6% of patients (n=7) achieved the therapeutic range after dosing was increased by 1/3–2/3 (*Figure 2A*). In the dose increase group, the initial VCZ C_{trough} in 19.4% of patients (n=6) achieved the therapeutic range after dosing was increased by 1/3–2/3, and the initial VCZ C_{trough} in 25.8% of patients (n=8) achieved the therapeutic range after dosing was increased by 1/10–1/4.

However, in 17 patients, the initial VCZ C_{trough} did not reach the therapeutic range after increased VCZ dose. Therefore, shortened dose intervals were considered for these patients. In the 12-hour dosing interval group, the mean VCZ dose was 8.28±1.49 (range, 5.81–12) mg/kg, and the mean initial VCZ C_{trough} was 0.96±0.88 (range, 0.22–2.67) mg/L. After shortening the dosing interval to 8 hours, the mean VCZ dose was 7.42±1.96 (range, 5.56–13.33) mg/kg, and the mean initial VCZ C_{trough} was 2.18±1.37 (range, 0.22–2.67) mg/L, which achieved target concentration. There was no difference (P=0.156) in the VCZ dose before and after the adjustment of the dosing interval. However, the initial VCZ C_{trough} was significantly increased (P=0.004) after shortening the dosing interval (*Figure 2B*). In summary, a lower dose was used to achieve the target range in patients with high VCZ C_{trough}, and those patients with a subtherapeutic range could reach the target range with higher doses and/or shorter dosing intervals

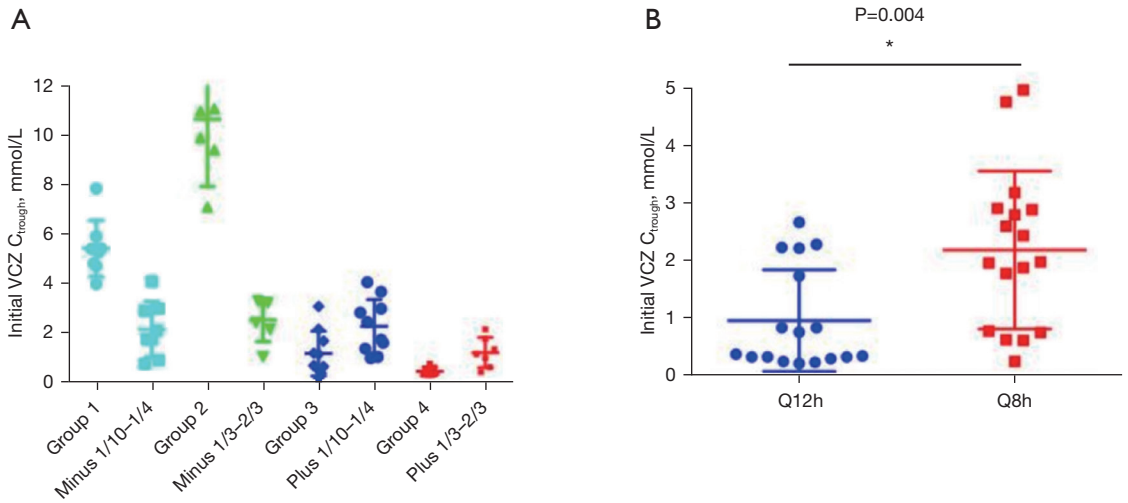

Figure 2 Initial VCZ C_{trough} after adjustment of dose and dosing interval. (A) The VCZ C_{trough} achieved the target range after adjustment of the dose. (B) After shortening the dosing interval (from 12 to 8 hours), the VCZ C_{trough} was increased and achieved the target range. *, P<0.05. VCZ, voriconazole; C_{trough}, trough concentration.

Table 2 Initial VCZ C_{trough} in different *CYP2C19* phenotypes

CYP2C19 phenotypes	No. of patients (n=59)	Initial C_{trough} of VCZ (mg/L)	Comparison	P value
NM	24	1.12±0.92	NM *vs.* PM	0.009
IM	26	3.41±3.27	IM *vs.* NM	0.000
PM	9	6.30±4.18	PM *vs.* IM	0.005

VCZ, voriconazole; C_{trough}, trough concentration; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

based on TDM results.

Association between CYP2C19 genotype and initial VCZ C_{trough}

PCR-pyrosequencing was used to detect *CYP2C19* gene polymorphism in 59 patients. The numbers and frequencies of variant alleles of *CYP2C19* are displayed in *Table 2*. Based on the *CYP2C19* genotype, 24 patients (40.7%) were determined to have the NM phenotype, 26 patients (44.1%) were determined to have the IM phenotype, and 9 patients were determined to have the PM phenotype. In patients with the PM phenotype, the mean initial VCZ C_{trough} was 6.30±4.18 mg/L, which was significantly higher than that of patients with the NM phenotype (1.12±0.92 mg/L, P=0.009) and the IM phenotype (3.41±3.27 mg/L, P=0.005). In comparison, the initial VCZ C_{trough} in patients with the IM phenotype was significantly higher (P=0.000) than that in patients with the NM phenotype. This suggested that VCZ C_{trough} was significantly associated with *CYP2C19* phenotype. We next compared the initial VCZ C_{trough} measurements of the different phenotypes to examine the association between *CYP2C19* phenotype and VCZ dose. The initial VCZ C_{trough} did not show significant differences between phenotypes in the <7 mg/kg (P=0.374) and >9 mg/kg doses (P=0.128), but it did show significant differences in the 7–9 mg/kg dose (*Figure 3*). The initial VCZ C_{trough} of each phenotype was significantly different (P=0.021, P=0.033, P=0.000). These results suggested that a significant association exists between initial VCZ C_{trough} and *CYP2C19* phenotype in children.

Impacts of immunosuppressants on initial VCZ C_{trough}

Immunosuppressive drugs (ISDs) are used for prophylaxis of graft versus host disease (GvHD), which is a condition that might occur after a hematopoietic stem cell transplant (HSCT). A total of 14 patients received VCZ as an

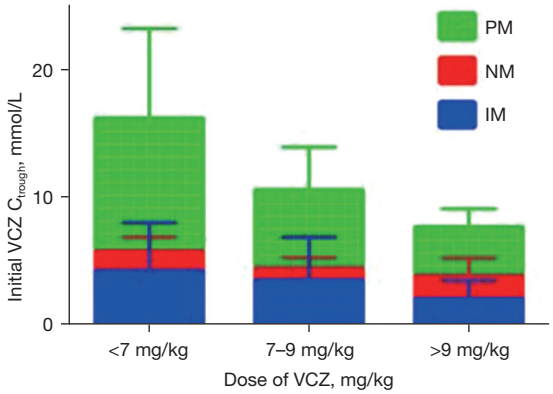

Figure 3 Association between *CYP2C19* phenotypes and initial VCZ C_{trough} in different dose groups. VCZ, voriconazole; C_{trough}, trough concentration; PM, poor metabolizer; NM, normal metabolizer; IM, intermediate metabolizer.

antifungal treatment before allogeneic HSCT. Then ISDs, including cyclosporine, sirolimus, and tacrolimus, were used in conjunction with VCZ in these patients. The initial cyclosporine (oral route) dose was 2–3 mg/kg/d. The dose was decreased by 50% when it was coadministrated with VCZ (16), and the C_{trough} was monitored. The initial dose of sirolimus was 1 mg/m^2, and the loading dose was 3 mg/m^2. VCZ is contraindicated when used concomitantly with sirolimus, although coadministration of sirolimus with VCZ may be safe if there is an empiric initial 90% sirolimus dose reduction combined with systematic monitoring of trough levels (17). The initial dose of tacrolimus was 0.3 mg/kg. When it was used in combination with VCZ, the dose was decreased by 2/3. Close monitoring of the blood concentration is warranted in transplant recipients treated with VCZ (18).

In patients who only received VCZ, the mean VCZ dose was 7.61±1.42 mg/kg, and the mean initial VCZ C_{trough} was 2.98±3.19 mg/L (*Figure 4A*). After allogeneic HSCT, patients received VCZ in combination with an ISD. The mean VCZ dose was 8.38±2.55 mg/kg, and the mean initial VCZ C_{trough} was 1.88±1.31 mg/L. There was no significant difference in VCZ dose (F=0.959, P=0.336) or initial VCZ C_{trough} (F=1.281, P=0.252) before and after ISD combination therapy (*Figure 4A*).

VCZ C_{trough} after HSCT

Five patients who received VCZ treatment before and after HSCT were analyzed. Before transplantation, the mean VCZ dose was 8.20±1.42 mg/kg, and the mean initial VCZ C_{trough} was 3.28±2.84 mg/L (*Figure 4B*). After transplantation, the mean VCZ dose was 9.03±2.59 mg/kg, and the mean initial VCZ C_{trough} was 1.73±1.08 mg/L. The VCZ C_{trough} was slightly decreased after transplantation but not significantly decreased (P=0.286).

Multiple linear regression analysis

The initial VCZ C_{trough} might be affected by multiple factors, such as gender, age, weight, *CYP2C19* gene polymorphism, route of drug administration, and liver function. We used multiple linear regression to analyze the linear relationship between the initial VCZ C_{trough} and these factors. The multiple linear regression analysis data showed that initial VCZ C_{trough} was related to age (P=0.007) and *CYP2C19* gene polymorphism (P=0.014; *Table 3*). The mean VCZ C_{trough} (6.30 mg/L) of patients with the PM phenotype was significantly higher than that of patients with the IM phenotype (3.41 mg/L) and the NM phenotype (1.12 mg/L).

The efficacy and safety of VCZ therapy

VCZ was given as the primary therapy. The median antifebrile time was 3 (range, 1–31) days. In 64 patients with fever, only 5 patients (8.6%) demonstrated positive results in microbiological tests. There was 1 death, and *Candida albicans* and *Stenotrophomonas maltophilia* were detected in this case. According to the lung CT scans of 38 patients, good responses were observed in 26 patients (26/38, 68.4%).

A total of 24 patients (24/94, 25.5%) developed VCZ-related adverse effects (AEs). These AEs were retinal hemorrhage (n=3, 11.5%), xanthopsia or chloropsia (n=2, 7.7%), arrhythmia (n=1, 3.8%), rash (n=3, 11.5%), gastrointestinal reaction (n=5, 19.2%), and high alanine transaminase (ALT) levels (n=12, 46.2%; *Table 4*). Liver function damage (46.2%) and gastrointestinal reactions (19.2%) were the most common side effects. One patient developed these toxicities (retinal hemorrhage, xanthopsia or chloropsia, and gastrointestinal reaction) concurrently, and his *CYP2C19* phenotype was PM.

Discussion

Differing dose recommendations in pediatric and adult patients may be due to age-related differences in VCZ

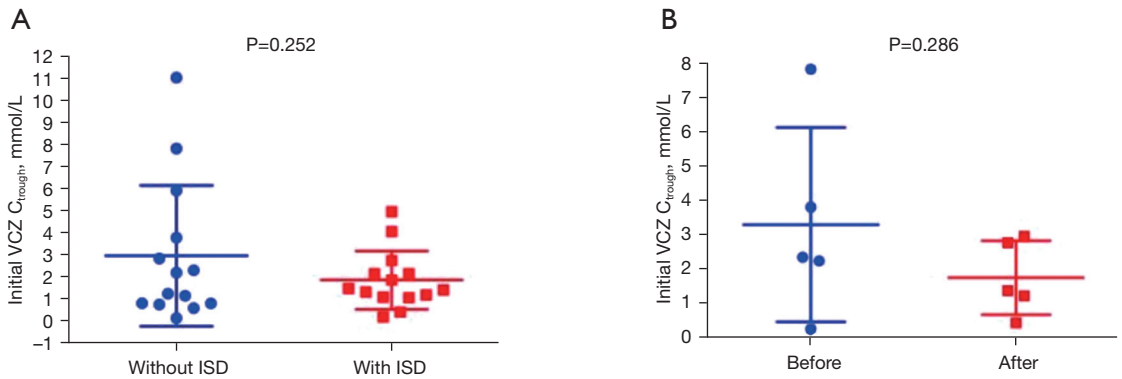

Figure 4 Initial VCZ C_{trough} in HSCT patients. (A) Initial VCZ C_{trough} in patients with and without ISD and VCZ. (B) Initial VCZ C_{trough} in patients before and after allograft. VCZ, voriconazole; C_{trough}, trough concentration; ISD, immunosuppressive drug; HSCT, hematopoietic stem cell transplant.

Table 3 Multiple linear regression analysis

Variables	Unstandardized coefficients		Standardized coefficients	T value	P value
	β	S	β		
Age	0.275	0.099	0.288	2.784	0.007
Gender	–0.201	0.213	–0.495	–0.944	0.352
Weight	0.057	0.066	0.327	0.866	0.352
CYP2C19 gene polymorphism	2.474	0.975	0.277	2.538	0.014
Drug administration	0.455	0.799	0.151	0.569	0.573
ALT	0.003	0.011	0.035	0.223	0.825

ALT, alanine transaminase.

Table 4 AEs of VCZ treatment

AE	No. of patients	%
Retinal hemorrhage	3	11.5
Xanthopsia or chloropsia	2	7.7
Arrhythmia	1	3.8
Rash	3	11.5
Gastrointestinal reaction	5	19.2
ALT >80 U/L	12	46.2

AE, adverse effect; VCZ, voriconazole; ALT, alanine transaminase.

pharmacokinetics (19). Specifically, VCZ displays linear pharmacokinetics in children but nonlinear pharmacokinetics in adults; therefore, pediatric patients have a higher capacity for elimination of VCZ (19). However, little is known about the efficacy and safety of VCZ and the relationship between initial VCZ and *CYP2C19* polymorphism in children. This study used TDM results and *CYP2C19* polymorphism to examine the impact of factors affecting initial VCZ C_{trough} in pediatric patients, with the aim of improving individualized antifungal therapy and patient care for children.

Previous research has reported that over half of pediatric patients in China could not reach the VCZ therapeutic target at initial dosing (20). This study also showed a low rate of target range achievement. Only 42.6% of the pediatric patients in the study achieved the therapeutic VCZ C_{trough}, while 32.9% of C_{trough} values were subtherapeutic and 24.5% were supratherapeutic. VCZ C_{trough} values showed inter- and intraindividual variability, and there were no predictable relationships between initial dose and C_{trough}. Thus, continuous TDM is necessary for individualizing

dosing adaptations and managing supra- or subtherapeutic VCZ exposure. The recommended dose should be increased, especially in the youngest age group. In the future, specific rules regulating dose adjustments need to be verified by a large prospective study with children from different ethnic groups.

A VCZ dose of 7 mg/kg twice a day i.v. or 200 mg twice a day p.o. in pediatric patients of 2 to <12 years of age is recommended for the treatment of serious fungal infections (21). Given the unpredictability of VCZ pharmacokinetics in pediatric patients, achieving target concentration is challenging; however, there are no guidelines for dose adjustment of VCZ in children based on TDM results. Therefore, the present research evaluating dose adjustment has great clinical value. According to the TDM-informed dose adjustment results, the patients who were in the subtherapeutic range reached the target range after the VCZ dose was increased by 1/10–1/4 in 58.8% of patients and 1/3–2/3 in 41.1% of patients, and these patients showed clinical improvement at the end of therapy. For those patients within the supratherapeutic range, the target range was achieved after the dose was decreased by 1/10–1/4 in 57.1% of patients and 1/3–2/3 in 42.9% of patients. Our TDM-informed dose adjustment generally worked well, which was consistent with previous studies (19,22). Multiple dose escalations and a more frequent dosing interval were required to reach a VCZ therapeutic C_{trough} for patients younger than 2 years old with subtherapeutic VCZ concentrations (23). According to the research results, it is more recommended to adjust the dose of VCZ according to the CYP2C19 gene polymorphism. At the same time, according to the measured TDM data, a single increase of 10–25% or a decrease of 1/3 to 2/3 may be better to reach the desired concentration. If C_{trough} was still below the target range after increased doses, shortened dosing intervals were considered. These results suggest that in pediatric patients, the VCZ dose strategy can be individualized based on TDM results.

VCZ is a substrate for CYP enzymes. *CYP2C19* is the primary enzyme that contributes to the main circulating metabolite of VCZ (24). The inter- and intraindividual variability of VCZ C_{trough} is correlated with the genetic polymorphisms of *CYP2C19* in children (25-27). It has been believed that *CYP2C19* polymorphisms are a predictor of VCZ concentrations and metabolism, but clinical implications are not established (28). A high prevalence of the *CYP2C19*17* allele exists among the Caucasian population, resulting in a large proportion of patients with subtherapeutic VCZ concentrations (29-31). No patients were carriers of this allele in our study. *CYP2C19* loss-of-function polymorphic alleles (**2* and **3*) have been shown to impair metabolic activity, and they represent a risk factor for major AEs in the follow-up of patients receiving VCZ. Our analysis of the association between the *CYP2C19* genotype and initial VCZ C_{trough} showed that initial VCZ C_{trough} was significantly higher in children with the IM and PM phenotypes than in children with the *NM* phenotype, which indicated that initial VCZ C_{trough} values were correlated with *CYP2C19* genotype. For those patients with the *CYP2C19*2* or **3* allele, the recommended dose decreased. This polymorphism could positively affect individual treatment. Therefore, analysis of the *CYP2C19* genotype may assist in clinical practice and improve patient outcomes. And it says the similar as García-García proved in 2021 (32).

In addition to *CYP2C19* polymorphisms, VCZ concentrations may be influenced by drug-drug interactions. IFIs are a major cause of morbidity and mortality in immunocompromised individuals, such as recipients of solid organ transplant (SOT) or HSCT (1,33,34). Following SOT or HSCT, patients are treated with ISDs. A previous study has indicated that the combined use of VCZ and ISDs modestly or markedly increases the exposure of the ISDs (35). However, little is known about the impacts of ISDs on initial VCZ C_{trough}. In this study, concurrent administration of ISDs slightly decreased the initial VCZ C_{trough} in HSCT patients but appeared to have no significant effect on initial VCZ C_{trough}. However, due to the high interindividual variability in VCZ exposure, monitoring VCZ C_{trough} and adjusting the dose of VCZ during coadministration of VCZ and ISDs is essential to reduce the risks of AEs or ineffective treatment. We recommend that all hospitals with conditions and capabilities allow to improve the *CYP2C19* gene polymorphism test before VCZ treatment to prospectively increase or reduce the initial dose of VCZ in children to improve the success rate of reaching the expected concentration and reduce side effects.

VCZ is well tolerated in pediatric patients, with an AE rate of 22.5–27.1% (36-38). In this study, the AE rate was 25.5%, and the most common AEs were liver function damage (46.2%) and gastrointestinal reactions (19.2%). The incidence of adverse reactions was high in children with slow metabolism phenotypes (IM or PM). Only 1 patient, who had the PM phenotype, experienced retinal hemorrhage, xanthopsia or chloropsia, and gastrointestinal reaction concurrently. In patients with the IM or PM

phenotypes, lowering the dose of VCZ reduced the likelihood of AEs. Therefore, *CYP2C19* genotype-guided VCZ dosing could be used clinically to reduce the risk of adverse drug effects in patients with the IM or PM phenotypes.

In conclusion, this study demonstrated the utility of VCZ TDM among children to ensure that the target range is achieved and the risks of side effects are minimized. Due to the high interindividual variability in VCZ exposure and the unpredictability of VCZ pharmacokinetics in pediatric patients, TDM should be conducted to ensure treatment efficacy and reduce the risks of AEs. When coupled with TDM, *CYP2C19* genotyping appears to be useful to guide initial VCZ dosing. Therefore, a combination of *CYP2C19* genotyping and TDM could help to advance individualized treatment in pediatric patients with IFIs and improve treatment response.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-156/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-156/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-156/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Nanfang Hospital of Southern Medical University (No. NFEC-2022-259). Due to the retrospective nature of this study, an exemption from informed patient consent was granted by the ethics committee of Nanfang Hospital of Southern Medical University.

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(English Language Editor: C. Gourlay)

Cite this article as: Chen X, Xiao Y, Li H, Huang Z, Gao J, Zhang X, Li Y, Van Timothee BM, Feng X. Therapeutic drug monitoring and *CYP2C19* genotyping guide the application of voriconazole in children. Transl Pediatr 2022;11(8):1311-1322. doi: 10.21037/tp-22-156