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CYP2C19-Guided Voriconazole Therapy: A Precision Medicine Approach to Mitigate Adverse Effects in Japanese Patients

Yoshiki Katada^{1,2}  | Daiki Hira¹  | Keisuke Umemura¹  | Yurie Katsube¹  | Hiroki Ishimura¹ | Yusuke Kojima^{1,2} | Machiko Hirai^{1,2} | Moto Kajiwarai¹ | Mitsuhiro Sugimoto¹ | Hiroki Endo¹ | Junru Cao¹ | Saki Ohta¹ | Kinuka Kotani¹ | Sakiko Hatazoe¹ | Masahiro Tsuda^{1,3}  | Shunsaku Nakagawa¹  | Koh Shinohara^{2,4}  | Yasuhiro Tsuchido^{2,4}  | Miki Nagao^{2,4}  | Tomohiro Terada¹ 

¹Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan | ²Department of Infection Control and Prevention, Kyoto University Hospital, Kyoto, Japan | ³Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan | ⁴Department of Clinical Laboratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence: Yoshiki Katada (katada@kuhp.kyoto-u.ac.jp)

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ABSTRACT

Voriconazole (VRCZ) is a triazole antifungal agent with a broad antifungal spectrum. It is metabolized by hepatic cytochrome P450 (CYP) isozyme CYP2C19, whose genetic polymorphism causes significant variability in drug efficacy and safety. Poor metabolizer alleles of *CYP2C19* are more common in Asian populations, increasing the risk of supratherapeutic VRCZ levels. We have developed a novel nomogram based on *CYP2C19* genetic polymorphisms. This study aimed to evaluate whether *CYP2C19* genotype-guided VRCZ therapy reduces toxicity in Japanese patients. This retrospective study included 64 patients (genotype-guided group, $n=26$; comparison group, $n=38$). The primary outcome was defined as the composite incidence of adverse events commonly observed with VRCZ, represented by the combined occurrence of grade ≥ 2 hepatotoxicity and visual symptoms. Secondary outcomes included the proportion of patients maintaining VRCZ trough concentrations within the therapeutic range (1–4 $\mu\text{g/mL}$) and the treatment response at 28 days. The composite incidence of adverse events was significantly lower in the genotype-guided group than in the comparison group ($p=0.003$). VRCZ discontinuation due to adverse events occurred in nine patients (23.7%) in the comparison group and one (3.8%) in the genotype-guided group ($p=0.039$). More patients in the genotype-guided group were achieved through concentrations within the therapeutic range at the initial sampling point. However, treatment response rates did not differ significantly between the groups. VRCZ administration based on *CYP2C19* genotyping improved therapeutic trough levels management and reduced adverse effects while maintaining therapeutic efficacy. These findings highlight the importance of *CYP2C19* genotyping for VRCZ treatment in Japanese patients.

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Study Highlights

- What is the current knowledge on the topic?
 - Voriconazole exposure is highly variable due to *CYP2C19* polymorphisms and poor metabolizers, which are common in Asian populations, being prone to toxicity.
 - Although TDM is recommended, genotype-guided initial dosing is not routinely implemented in clinical practice in Japan.
- What question did this study address?
 - Does initial voriconazole dosing based on *CYP2C19* genotype reduce adverse effects and improve therapeutic drug exposure compared to conventional dosing in Japanese patients?
- What does this study add to our knowledge?
 - Genotype-guided dosing significantly reduced hepatotoxicity, visual disturbances, and drug discontinuation while improving early attainment of therapeutic trough levels, demonstrating the clinical utility of *CYP2C19*-guided therapy in populations with high poor metabolizer prevalence.
- How might this change clinical pharmacology or translational science?
 - This study supports integrating *CYP2C19* genotyping into antifungal stewardship to individualize voriconazole dosing, reduce early toxicity, and improve drug continuation in populations with high frequencies of loss-of-function alleles, advancing precision pharmacotherapy in infectious disease management.

1 | Introduction

Voriconazole (VRCZ) is a second-generation triazole antifungal agent widely used to treat fungal infections, including invasive aspergillosis and candidiasis [1, 2]. However, its clinical use is challenging because of its narrow therapeutic range, nonlinear pharmacokinetics, and significant individual variability. This variability is influenced by *CYP2C19* genetic polymorphisms and other factors, including drug interactions, altered intestinal absorption, inflammation, age, and body weight. To optimize VRCZ therapy, therapeutic drug monitoring (TDM) plays a crucial role in managing fungal infections effectively and improving patient outcomes [3].

Antifungal stewardship aims to improve patient outcomes, minimize toxicity, and reduce the emergence of antifungal resistance [4]. As part of this approach, VRCZ TDM is recommended to enhance treatment efficacy and mitigate adverse effects, including hepatotoxicity and neurotoxicity (e.g., confusion and visual hallucinations) [5]. Subtherapeutic levels may result in treatment failure, antifungal resistance, and the progression of invasive infections, whereas supratherapeutic levels increase the risk of severe adverse effects. A recent meta-analysis proposed a therapeutic trough concentration range of 1.0–6.0 µg/mL³, although optimal serum concentrations may vary among individual patients [6].

VRCZ is primarily metabolized by the hepatic cytochrome P450 (CYP) isozyme *CYP2C19*, and genetic polymorphisms contribute to significant inter-individual variations in its therapeutic efficacy and safety [7]. The wild-type allele, *CYP2C19*1*, has the full drug-metabolizing capacity, whereas the *CYP2C19*2* and *CYP2C19*3* alleles are associated with reduced enzyme activity and slower drug metabolism than the wild-type allele [8]. In contrast, the *CYP2C19*17* allele increases enzyme expression, enhancing metabolic capacity [8]. Patients with *CYP2C19*2* or *CYP2C19*3* alleles may have elevated VRCZ concentrations, increasing the risk of toxicity, while those with the *CYP2C19*17* allele may have reduced drug levels, leading to treatment failure. The *CYP2C19*2* and *CYP2C19*3* alleles are more prevalent in Asians than in individuals of European ancestry [9], making Asian patients more susceptible to supratherapeutic drug responses. In Japanese patients, maintaining a target trough concentration of 1–4 µg/mL is recommended to minimize the risk of concentration-dependent adverse effects [10]. Although the *CYP2C19* genotype-guided dosing approach may help achieve target VRCZ concentrations, pharmacogenetic (PGx) testing for *CYP2C19*, alongside conventional TDM, has not yet been implemented in Japan.

Hicks et al. reported that a prospective *CYP2C19* genotype-guided VRCZ therapy, particularly for rapid metabolizers, helped prevent subtherapeutic trough concentrations in patients with neutropenic acute myeloid leukemia [11]. Similarly, Patel et al. demonstrated that preemptive *CYP2C19* genotyping and VRCZ dose adjustments reduced the incidence of subtherapeutic concentrations in allogeneic hematopoietic cell transplant recipients [12]. However, these studies [11, 12] primarily involved European ancestry patients with a relatively low proportion of *CYP2C19* poor metabolizers [9]. As a result, the benefits of preemptive PGx testing for VRCZ initiation in Japanese patients remain uncertain.

Given the high prevalence of *CYP2C19* loss-of-function alleles in Japanese patients, standard VRCZ dosing may increase the risk of toxicity. While TDM helps mitigate this risk, early dose individualization based on the *CYP2C19* genotype may further optimize treatment. This retrospective observational study aimed to evaluate whether *CYP2C19* genotype-guided initial dosing, in combination with TDM, more effectively reduces adverse effects and improves target trough attainment compared with conventional label-based dosing.

2 | Methods

2.1 | Patients and Data Collection

We conducted a retrospective observational study from January 2021 to October 2024 involving 68 inpatients treated with VRCZ at Kyoto University Hospital. All inpatients who received VRCZ for therapeutic purposes during the study period were included in the analysis. Eligible participants were Japanese patients aged ≥ 18 years who had received intravenous or oral VRCZ. Patients who had taken contraindicated agents that induced CYP-mediated VRCZ metabolism (e.g., rifampicin, carbamazepine, or phenytoin) or increased VRCZ concentration (e.g., efavirenz or ritonavir) were excluded. Patients without an initial VRCZ

trough concentration measurement ($n=3$) and those requiring target concentrations of $>4\mu\text{g/mL}$ due to central nervous system infection ($n=1$) were excluded. Only inpatients were included to ensure accurate assessment of adverse effects and adherence, as outpatient monitoring is limited, and VRCZ measurement costs are not covered by Japanese medical insurance. The collected data included patient demographics, comorbidities, laboratory results, VRCZ dosage, duration, type of fungal infection, and *CYP2C19* genetic polymorphisms, all retrospectively retrieved from electronic medical records. The follow-up period lasted until VRCZ was discontinued during hospitalization or the patient was discharged while still receiving VRCZ.

VRCZ plasma trough concentration values were measured by the LSI Medience Corporation (Tokyo, Japan) using a liquid chromatography-tandem mass spectrometer (LCMS-8040; Shimadzu, Kyoto, Japan) equipped with a quadrupole mass analyzer. Concentrations below the assay detection limit were $<0.3\mu\text{g/mL}$ and treated as $<0.3\mu\text{g/mL}$ for analysis. TDM for VRCZ was conducted as part of routine clinical care. This study and its amendments were performed in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of Kyoto University Graduate School of Medicine and Kyoto University Hospital (Approval number: R4826).

2.2 | Antifungal Stewardship Using Therapeutic Drug Monitoring Based on *CYP2C19* Genotyping

Conventional VRCZ dosing followed the package insert recommendations and was applied to 38 patients in the comparison group, defined as those who received VRCZ treatment before the implementation of PGx testing in Kyoto University Hospital (i.e., prior to November 2022). After TDM, dose adjustments were determined by the physicians and pharmacists based on clinical responses and TDM results. PGx tests have been implemented at Kyoto University Hospital since November 2022, and 26 patients who received VRCZ therapy thereafter and provided consent for *CYP2C19* genotyping tests were included in the genotype-guided group. At our institution, *CYP2C19* genotyping is routinely performed as part of standard clinical practice, although it is not covered by insurance. For many patients in the genotype-guided group, testing was particularly conducted to guide VRCZ therapy. However, in some cases, *CYP2C19* genotyping had already

been performed prior to VRCZ initiation—most commonly for clopidogrel therapy—allowing genotype data to be available at the time of hospitalization. In this group, initial doses were determined by the antifungal stewardship team (Table 1), primarily following a modified strategy based on previous reports by other groups [13–15]. Although the clinical pharmacogenetic implementation consortium (CPIC) guidelines recommend considering alternative antifungal agents or dose reductions for *CYP2C19* poor metabolizers, they do not provide specific dosing instructions for VRCZ [16]. Therefore, in our genotype-guided group, initial dosing was individualized using a locally developed nomogram based on both published evidence and clinical experience. Subsequent dose adjustments were guided by clinical responses, TDM results, and genetic polymorphism data. For both groups, the first TDM was conducted 3–5 days after VRCZ initiation in accordance with Japanese guidelines [17]. The minimum increment for VRCZ dose adjustments was 25 mg.

2.3 | Assessment of *CYP2C19* Polymorphisms

Genomic DNA was extracted from peripheral blood samples using DNA Extract All Reagents (Applied Biosystems, Foster City, CA, USA). *CYP2C19* genetic polymorphisms were then analyzed using TaqMan polymerase chain reaction (PCR) on a StepOnePlus real-time PCR system (Applied Biosystems, Foster City, CA, USA). *CYP2C19* variants were classified as follows: *1 (wild-type), *2 (681G>A, rs4244285), *3 (636G>A, rs4986893), and *17 (–806C>T, rs12248560). The *2 and *3 alleles were considered loss-of-function, while the *17 allele was associated with higher enzymatic expression and activity than that of the wild-type *1 allele. Metabolizing phenotypes were categorized according to the standard nomenclature [18]: patients without *2, *3, or *17 alleles (i.e., *1/*1) were classified as normal metabolizers; those with one *2 or *3 allele (i.e., *1/*2, *1/*3, *2/*17, and *3/*17) as intermediate metabolizers; those with two *2 or *3 alleles (i.e., *2/*2, *2/*3, or *3/*3) as poor metabolizers; those of *17 allele heterozygotes (i.e., *1/*17) as rapid metabolizers; and those of *17 homozygotes (i.e., *17/*17) as ultrarapid metabolizers. Dosing recommendations for VRCZ treatment based on *CYP2C19* phenotype in Kyoto University Hospital are provided in Table 1. Two liver transplant patients were included in the genotype-guided group, and their VRCZ dosing was guided by the donors' *CYP2C19* genotypes.

TABLE 1 | Dosing recommendations for VRCZ treatment based on *CYP2C19* phenotype in Kyoto University Hospital.

<i>CYP2C19</i> phenotype (genotype)	Ultrarapid or rapid metabolizer (*1/*17, *17/*17)	Normal metabolizer (*1/*1)	Intermediate metabolizer (*1/*2, *1/*3, *2/*17, *3/*17)	Poor metabolizer (*2/*2, *2/*3, *3/*3)
Day 1 (loading dose)	6 mg/kg every 12h	6 mg/kg every 12h	5 mg/kg every 12h	4 mg/kg every 12h
Day 2~	4 mg/kg every 12h	3.5 mg/kg every 12h	3 mg/kg every 12h	2.5 mg/kg every 12h

Note: This is the recommended dose for adults. Dosage design should be based on a comprehensive evaluation of concentration, laboratory values, and patient condition. Do not exceed the dosage specified in the package insert.

Abbreviation: VRCZ: voriconazole.

2.4 | Outcome

The primary objective of this study was to evaluate whether genotype-guided VRCZ dosing reduces the incidence of adverse effects, including hepatotoxicity and visual disturbances. The primary outcome was defined as the composite incidence of adverse events commonly observed with VRCZ, represented by the combined occurrence of grade ≥ 2 hepatotoxicity and visual symptoms. Liver function was assessed by measuring aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels. Adverse events were graded according to the Common Terminology Criteria for Adverse Events v5.0. Grade 1 hepatotoxicity was defined as AST or ALT levels above the upper limit of normal (ULN) up to 3.0 times ULN or total bilirubin greater than ULN up to 1.5 times ULN. Grade 2 was defined as AST or ALT levels exceeding 3.0 to 5.0 times ULN or total bilirubin between 1.5 and 3.0 times ULN. Grade 3 hepatotoxicity involved AST or ALT elevations greater than 5.0 to 20.0 times ULN or total bilirubin between 3.0 and 10.0 times ULN. Grade 4 was defined as AST or ALT elevations exceeding 20 times ULN or total bilirubin above 10 times ULN, indicating life-threatening toxicity. Grade 5 corresponded to death related to hepatotoxicity. Visual disturbances were defined as any visual symptom suspected to be VRCZ-induced adverse effects, including changes in color perception, blurred vision, bright spots, wavy lines, hallucinations, or photophobia. These symptoms were assessed daily by nurses and systematically documented in the medical records. As part of the safety evaluation, we also assessed the patients for acute kidney injury and QTc interval prolongation. Acute kidney injury was defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or a 1.5-fold increase from baseline within 7 days. QTc prolongation was defined as an abnormal increase in the QTc interval of $\geq 25\%$ from baseline or an absolute QTc interval of ≥ 500 ms following VRCZ administration, based on 12-lead electrocardiogram measurements. If the discontinuation of VRCZ therapy was due to an adverse reaction, causality was assessed using the Naranjo scale [19]. Secondary outcomes included the proportion of patients whose VRCZ trough concentrations were within the therapeutic range and treatment response within 28 days of VRCZ initiation. In this study, the therapeutic range was defined as 1–4 $\mu\text{g/mL}$, considering population-specific data for Japanese patients [10]. Treatment response was assessed by infectious disease specialists from the antifungal stewardship team based on the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the Mycoses Study Group criteria. Responses were categorized as complete response, partial response, stable disease, disease progression, or death. Treatment success was defined as a complete or partial response, whereas treatment failure included stable disease, disease progression, or death [20].

2.5 | Statistical Analysis

Formal power calculations were not performed due to the retrospective observational design; therefore, all inpatients treated with VRCZ at our institution between January 2021 and October 2024 were included.

Continuous variables were analyzed using the Mann–Whitney *U* test, while categorical variables were compared using Fisher's exact test. Kaplan–Meier curves were evaluated using the Gehan–Breslow–Wilcoxon test. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using GraphPad PRISM 9.0 (GraphPad Software Inc., San Diego, CA, USA).

3 | Results

3.1 | Patient Clinical Characteristics

A total of 64 patients were included in the study, with a median age of 67 years (range: 19–93 years). The baseline characteristics of the patients are summarized in Table 2. In both groups, most patients received VRCZ for aspergillosis, accounting for 39.5% of the comparison group and 61.5% of the genotype-guided group. No significant differences were observed in the demographic or clinical characteristics between the two groups, except for sex and primary disease (solid organ transplantation). The distribution of *CYP2C19* genetic polymorphisms in the genotype-guided group was as follows: normal metabolizers, 34.6% (9/26); intermediate metabolizers, 42.3% (11/26); and poor metabolizers, 19.2% (5/26). No ultrarapid metabolizers were identified in the cohort. For the two liver transplant patients in the genotype-guided group, the donors and respective recipients shared the same genotype, which allowed us to use the donors' genotype results for dosing decisions.

3.2 | Safety of VRCZ Therapy

Table 3 provides the distribution of VRCZ-related toxicities in the comparison and genotype-guided groups. The composite incidence of adverse events was significantly higher in the comparison group than in the genotype-guided group (42.1% vs. 7.7%, $p = 0.003$). These adverse events typically emerged during the initial phase of VRCZ treatment, coinciding with elevated blood concentrations exceeding the optimal range (1–4 $\mu\text{g/mL}$). VRCZ treatment was discontinued because of adverse events in nine patients from the comparison group and one patient from the genotype-guided group (23.7% vs. 3.8%, $p = 0.039$). Figure 1A illustrates the percentage of patients who continued VRCZ therapy. Treatment discontinuation was more frequent shortly after VRCZ initiation in the comparison group than in the genotype-guided group. Hepatotoxicity was the primary cause of discontinuation. Patients who discontinued VRCZ due to treatment completion or were discharged while continuing therapy were considered censored. The median time to VRCZ discontinuation due to adverse events was 7 and 24 days in the comparison and genotype-guided groups, respectively. Figure 1B shows the time to onset of composite adverse events. Among the patients with adverse events, the median time to onset was 6 days in the comparison group and 13 days in the genotype-guided group.

Although VRCZ is associated with adverse effects such as acute kidney injury and QTc prolongation, none of the patients in this study experienced these events.

TABLE 2 | Patient demographic and clinical characteristics.

	Comparison group (<i>n</i> = 38)	Genotype-guided group (<i>n</i> = 26)	<i>p</i>
Age (year), median (range)	71 (19–93)	65 (21–89)	0.187
Body weight (kg), median (range)	50.9 (26.9–68.5)	53.2 (29.9–67.7)	0.543
Male, <i>n</i> (%)	28 (73.7)	11 (42.3)	0.018
Primary disease, <i>n</i> (%)			
Benign respiratory tract disease	14 (36.8)	5 (19.2)	0.168
Collagen disease	9 (23.7)	8 (30.8)	0.573
Solid organ transplantation	1 (2.6)	7 (26.9)	0.006
Lung transplantation	—	4 (15.4)	—
Liver transplantation	1 (2.6)	2 (7.7)	—
Kidney transplantation	—	1 (3.8)	—
Hematological malignancy	8 (21.1)	3 (11.5)	0.502
Solid organ malignancy	2 (5.3)	1 (3.8)	0.999
Other	4 (10.5)	2 (7.7)	0.999
CYP2C19 phenotype, <i>n</i> (%)			
Normal metabolizer (*1/*1)	—	9 (34.6)	—
Intermediate metabolizer (*1/*2, *1/*3, *2/*17, or *3/*17)	—	11 (42.3)	—
Poor metabolizer (*2/*2, *2/*3, or *3/*3)	—	5 (19.2)	—
Rapid metabolizer (*1/*17)	—	1 (3.8)	—
Ultrarapid metabolizer (*17/*17)	—	—	—
Diagnosis of the fungal disease, <i>n</i> (%)			
Invasive aspergillosis	15 (39.5)	16 (61.5)	0.126
Proven	2 (5.3)	2 (7.7)	—
Probable ^a	6 (15.8)	13 (50.0)	—
Possible	7 (18.4)	1 (3.8)	—
Candidiasis (candidemia)	2 (5.3)	1 (3.8)	0.999
Other invasive fungal disease ^a	4 (10.5)	1 (3.8)	0.641
Chronic pulmonary aspergillosis	11 (28.9)	2 (7.7)	0.057
Undiagnosed (empirical therapy)	6 (15.8)	7 (26.9)	0.348
Initial dose of VRCZ (mg/kg/day), median (range)	10.9 (6.1–15.8)	10.8 (5.4–13.5)	0.716
Normal metabolizer (*1/*1)	—	12.0 (10.0–13.6)	—
Intermediate metabolizer (*1/*2, *1/*3, *2/*17, or *3/*17)	—	10.8 (7.4–12.0)	—
Poor metabolizer (*2/*2, *2/*3, or *3/*3)	—	7.9 (7.8–8.6)	—
Rapid metabolizer (*1/*17)	—	12.3	—
Maintenance dose of VRCZ (mg/kg/day), median (range)	6.2 (2.9–9.2)	5.8 (3.2–11.0)	0.089
Normal metabolizer (*1/*1)	—	6.7 (4.5–11.0)	—

(Continues)

TABLE 2 | (Continued)

	Comparison group (<i>n</i> = 38)	Genotype-guided group (<i>n</i> = 26)	<i>p</i>
Intermediate metabolizer (*1/*2, *1/*3, *2/*17, or *3/*17)	—	5.7 (4.8–6.7)	—
Poor metabolizer (*2/*2, *2/*3, or *3/*3)	—	5.1 (3.2–6.1)	—
Rapid metabolizer (*1/*17)	—	7.6	—
Administration route of VRCZ, <i>n</i> (%)			
Intravenous only	3 (7.9)	2 (7.7)	0.999
Per oral only	29 (76.3)	16 (61.5)	0.267
Intravenous followed by per oral	6 (15.8)	8 (30.8)	0.219
Length of VRCZ administration during hospitalization (days), median (range)	21.5 (7–71)	25 (6–83)	0.643
Timing of the first measurement of VRCZ trough concentrations (days after initiation), median (range)	5 (3–5)	5 (3–5)	0.891
Number of VRCZ trough concentrations per patient, median (range)	3 (1–10)	3 (1–12)	0.178

Note: Data are expressed as the median (range) or *n* (%). Continuous variables were compared using the Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test. The alpha level of significance was set at *p* < 0.05.

Abbreviations: CYP, cytochrome P450; VRCZ, voriconazole.

^aThere was one case of combined probable invasive pulmonary aspergillosis and invasive lomentosporiosis in the genotype-guided group.

TABLE 3 | Voriconazole-related adverse events in the comparison and genotype-guided groups.

	Comparison group (<i>n</i> = 38)	Genotype-guided group (<i>n</i> = 26)	<i>p</i>
Composite incidence of hepatotoxicity (grade ≥ 2) and visual symptoms, <i>n</i> (%)	16 (42.1)	2 (7.7)	0.003
Hepatotoxicity (grade 1) only, <i>n</i> (%)	2 (5.3)	3 (11.5)	0.388
Hepatotoxicity (grade 2) only, <i>n</i> (%)	0 (0)	1 (3.8)	0.406
Visual disturbances only, <i>n</i> (%)	1 (2.6)	0 (0)	0.999
Drug discontinuation of VRCZ due to adverse events, <i>n</i> (%)	9 (23.7)	1 (3.8)	0.039
VRCZ trough concentrations at the onset of hepatotoxicity (grade ≥ 2) or visual disturbances (μg/mL), median (range)	5.4 (1.4–8.7)	4.3 (3.3–5.0)	0.351
Days from VRCZ initiation to discontinuation (days), median (range)	7 (4–12)	24	—

Note: Data are expressed as the median (range) or *n* (%). Continuous variables were compared using the Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test. The alpha level of significance was set at *p* < 0.05.

Abbreviation: VRCZ, voriconazole.

3.3 | Comparison of VRCZ Trough Concentrations Between the Comparison and Genotype-Guided Groups

Figure 2A,B illustrate the initial VRCZ trough concentrations and the average concentrations after the first TDM for each patient. The median initial VRCZ trough concentration was significantly higher in the comparison group than in the genotype-guided group (4.05 μg/mL vs. 2.69 μg/mL, *p* = 0.019). However, the average VRCZ trough concentration after the initial TDM did not differ significantly between the genotype-guided and comparison groups

(2.68 μg/mL vs. 2.23 μg/mL, *p* = 0.259). Figures 2C,D show the proportions of patients whose VRCZ trough concentrations were within the therapeutic range (1–4 μg/mL) at the initial TDM and thereafter. In the comparison group, 37% of the patients had VRCZ trough concentrations within the therapeutic range at the first TDM point. In contrast, 77% of patients in the genotype-guided group were within the therapeutic range at the first TDM point. While 58% of patients had average VRCZ trough concentrations within the therapeutic range, 91% of those in the genotype-guided group achieved this target. Table 4 represents the proportion of patients in the genotype-guided group who reached the target range

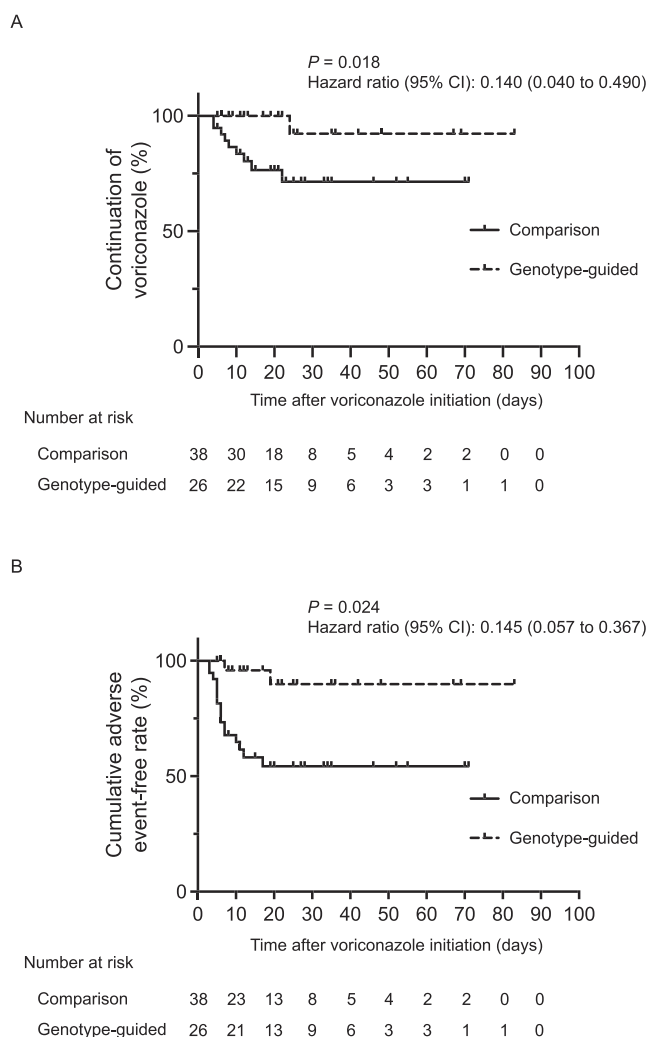


FIGURE 1 | (A) Percentage of patients in each group who continued VRCZ therapy. p -values, hazard ratios, and 95% confidence intervals (CIs) are displayed in the top-right corner of the graph. The number of patients at risk of fungal infections at 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90 days after VRCZ initiation is listed at the bottom of the graph. (B) Time to onset of composite adverse events for the comparison and genotype-guided groups. p -values, hazard ratios, and 95% confidence intervals (CIs) are displayed in the top-right corner of the graph. The number of patients at risk of fungal infections at 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90 days after VRCZ initiation is listed at the bottom of the graph.

at each nomogram dose. The percentage of patients achieving the VRCZ trough concentration on days 3–5 was 0% in rapid metabolizers, 88.9% in normal metabolizers, 81.8% in intermediate metabolizers, and 60% in poor metabolizers.

3.4 | Efficacy of VRCZ Therapy

The response to VRCZ treatment was evaluated in 38 patients from the comparison group and 26 from the genotype-guided group based on clinical, microbiological, and radiological outcomes. Table 5 provides details of the treatment responses. The rates of treatment failure were 21.1% in the comparison group and 11.5% in the genotype-guided group. Mortality within

28 days of treatment initiation did not differ significantly between the two groups ($p = 0.509$). The treatment success rates were 39.5% in the comparison group and 46.2% in the genotype-guided group. These findings suggest that no significant differences were observed in treatment efficacy (failure/success) between the two groups.

4 | Discussion

VRCZ dosage determination significantly influences patients' clinical outcomes. Standard dosing based on package inserts often results in subtherapeutic or supratherapeutic VRCZ trough concentrations [7, 21]. Recent studies suggest that PGx testing is useful for achieving safe and effective drug exposure [16]. Our findings indicate that genotype-guided VRCZ dosing reduces adverse events more effectively than package insert-based dosing. Implementing VRCZ therapy guided by *CYP2C19* genotyping is crucial for populations with a high prevalence of loss-of-function variants.

Previous studies have indicated that initially elevated VRCZ trough concentrations are associated with a higher incidence of adverse effects, complicating the continuation of VRCZ therapy. This can lead to unfavorable clinical outcomes, including increased mortality [22]. A previous study suggested that excessively high drug concentrations are often observed in *CYP2C19*-poor metabolizers [16]. Additionally, a recent study reported that even intermediate metabolizers can frequently experience supratherapeutic VRCZ levels [23]. In Asian populations, VRCZ trough concentrations exceeding 4 µg/mL strongly correlate with adverse events [10, 24]. In the comparison group, VRCZ-induced hepatotoxicity occurred in 47.3% (18/38) of patients, while visual disturbances were observed in 44.7% (17/38). These findings align with Japanese Phase III clinical trial data, which reported hepatotoxicity in 36% of patients and visual disturbances in 52% [25]. In our study, the incidence of hepatotoxicity and visual disturbances was notably lower in the genotype-guided group than in the comparison group. This outcome may be attributed to fewer patients in the genotype-guided group exhibiting supratherapeutic VRCZ trough concentrations. Additionally, the number of toxicity-related discontinuations was significantly higher in the comparison group than in the genotype-guided group, with most discontinuations occurring early in the treatment course. These findings suggest that adjusting the VRCZ dose based on *CYP2C19* polymorphisms reduces the risk of hepatotoxicity and visual disturbances. Furthermore, it may improve VRCZ continuation rates by reducing the incidence of VRCZ-related toxicity.

No significant differences in treatment efficacy were observed between the groups, as the study was not sufficiently powered to detect such differences. Although more patients in the comparison group discontinued VRCZ, treatment outcomes may have been maintained using alternative antifungal agents. Four patients changed to other antifungal agents after VRCZ discontinuation: one to liposomal amphotericin B, one to itraconazole, and two to micafungin. In addition, some patients were later found to have non-fungal infections, which may have influenced the observed outcomes.

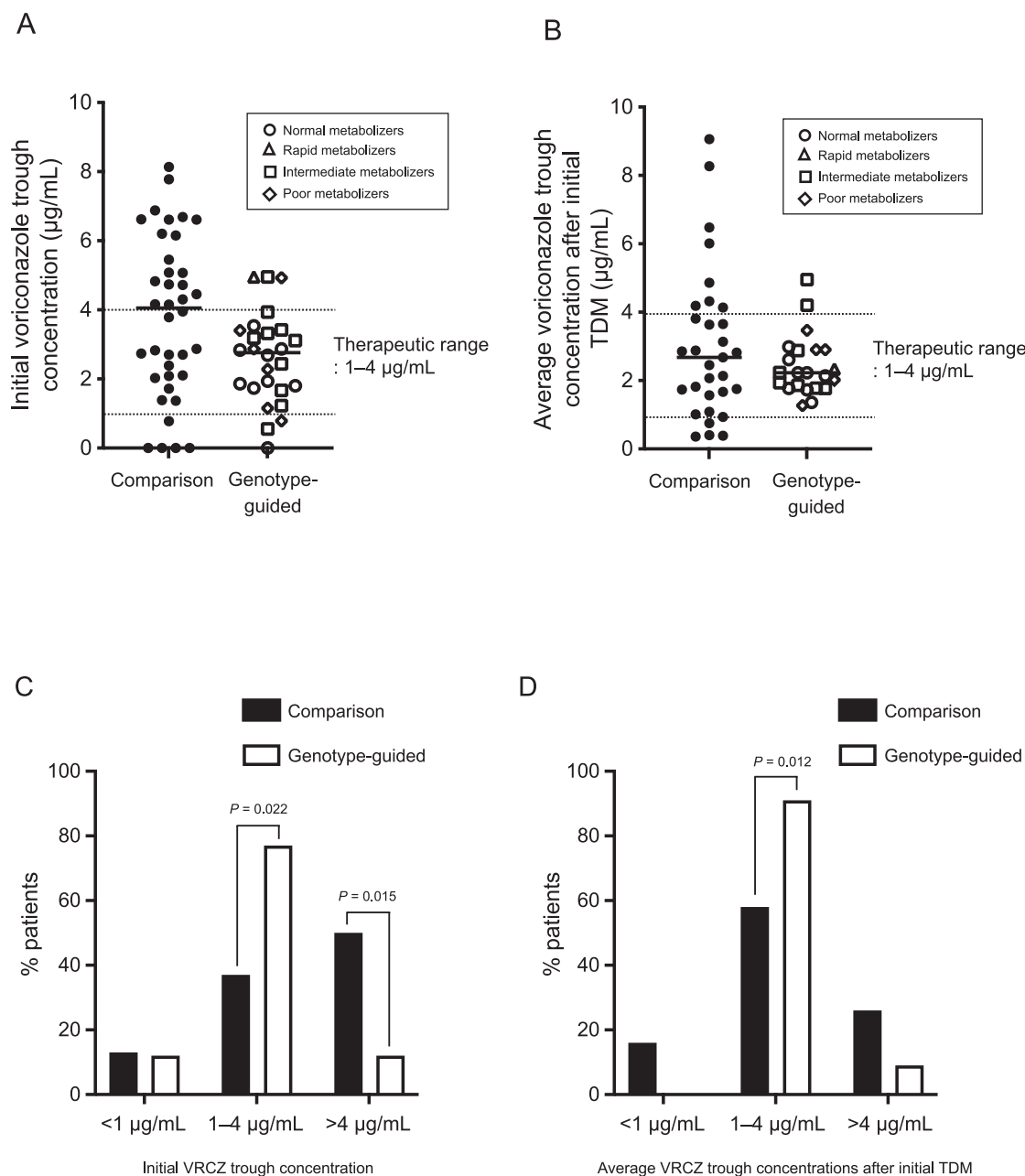


FIGURE 2 | (A, B) Comparison of voriconazole (VRCZ) trough concentrations after treatment initiation between the comparison and genotype-guided groups. (A) Initial VRCZ trough concentrations (3–5 days after initiation) in the comparison and genotype-guided groups. (B) Average VRCZ trough concentration after the initial therapeutic drug monitoring (TDM) in the comparison and genotype-guided groups. The solid lines in panels A and B indicate the median VRCZ trough concentration, while the dotted lines represent the therapeutic range for VRCZ. White circles represent normal metabolizers, white triangles represent rapid metabolizers, white squares represent intermediate metabolizers, and white diamonds represent poor metabolizers in the genotype-guided group. (C, D): Percentages of patients with VRCZ trough concentration < 1 µg/mL, 1–4 µg/mL, and > 4 µg/mL in the comparison and genotype-guided groups. (C) Percentages of patients with an initial VRCZ trough concentration of < 1 µg/mL, 1–4 µg/mL, and > 4 µg/mL in the comparison (black bar) and genotype-guided (white bar) groups. (D) Percentages of patients with average VRCZ trough concentrations after initial TDM < 1 µg/mL, 1–4 µg/mL, and > 4 µg/mL in the comparison (black bar) and genotype-guided (white bar) group.

In our study, 77% of genotype-guided patients achieved target VRCZ concentrations at the first TDM, and 91% reached target concentrations after the initial TDM. Among the genotype-guided groups, over 80% of patients in the normal and intermediate metabolizer groups and 60% in the poor metabolizer group achieved target concentrations at the initial TDM. Consequently, the constructed nomograms are valid for patients with these

genetic polymorphisms. Genotype-guided dosing optimized VRCZ trough concentrations at both treatment initiation and steady state. Similarly, a previous prospective study on PGx testing in VRCZ therapy reported a high rate of VRCZ concentration attainment at a steady state (71.8%) in adult allogeneic hematopoietic cell transplant recipients [12]. In that study, ultrarapid, rapid, and normal metabolizers were observed at higher

TABLE 4 | Proportion of patients in the genotype-guided group achieving the target range at each nomogram dose.

Initial VRCZ trough concentration on the 3–5 days ($\mu\text{g/mL}$)	Rapid metabolizer ($n=1$)	Normal metabolizer ($n=9$)	Intermediate metabolizer ($n=11$)	Poor metabolizer ($n=5$)
< 1 $\mu\text{g/mL}$, n (%)	0 (0%)	1 (11.1%)	1 (9.1%)	1 (20%)
1–4 $\mu\text{g/mL}$, n (%)	0 (0%)	8 (88.9%)	9 (81.8%)	3 (60%)
> 4 $\mu\text{g/mL}$, n (%)	1 (100%)	0 (0%)	1 (9.1%)	1 (20%)

Abbreviation: VRCZ, voriconazole.

TABLE 5 | Treatment response in the comparison and genotype-guided groups.

	Comparison group ($n=38$)	Genotype-guided group ($n=26$)	p
Response to treatment			
28 days, n (%)			
Success	15 (39.5)	12 (46.2)	0.616
Failure	8 (21.1)	3 (11.5)	0.502
Not determined	15 (39.5)	11 (42.3)	0.999
Survival analysis, n (%)			
Death within 28 days	7 (18.4)	3 (11.5)	0.509

Note: Data are expressed as n (%). Categorical variables were compared using Fisher's exact test. The alpha level of significance was set at $p < 0.05$.

proportions than those in our study. *CYP2C19* genotype-guided VRCZ dosing effectively reduced subtherapeutic concentrations and prevented invasive fungal infections [12]. Our study suggests that genotype-guided dosing can help reduce supratherapeutic VRCZ exposure. This advantage of PGx testing is particularly relevant for Japanese patients, who have a high prevalence of the *2 or *3 alleles. We did not consider PGx testing superior or inferior to TDM. Rather, PGx may be ideal for guiding initial dosing, while TDM is more suitable for dose adjustments. However, a few patients in the genotype-guided group still failed to achieve optimal VRCZ concentrations. In one rapid metabolizer, the initial VRCZ trough concentration remained outside the target range despite the application of the constructed nomogram. Therefore, further refinement—such as developing a population pharmacokinetic model—may be necessary to improve dosing precision.

The CPIC guidelines for VRCZ treatment recommend prescribing alternative antifungals, such as isavuconazole, liposomal amphotericin B, or posaconazole, for ultra-rapid (*17/*17) and poor metabolizers. A lower-than-standard dose of VRCZ should be administered with careful TDM [16]. In our study, no ultra-rapid metabolizers were identified, and the proportion of poor metabolizers was higher than that previously reported [11]. Our findings indicate that VRCZ therapy can be safely managed

even in poor metabolizers. However, in Japan, *CYP2C19* testing for VRCZ treatment is not covered by insurance, making cost a significant barrier to the clinical adoption of PGx testing. Patel et al. demonstrated that preemptive *CYP2C19* testing could save approximately \$4700 per patient [12]. We believe that clinical implementation of PGx testing is essential for optimizing VRCZ therapy.

In addition to genetic factors, several other variables can influence VRCZ concentration, including medication adherence, liver function, and drug–drug interactions [21, 26]. In this study, adherence was well managed, as it was directly monitored by the nursing staff. Liver dysfunction significantly reduces VRCZ clearance, with decreases of up to 47% in patients with grade ≥ 3 liver dysfunction [15]. The package insert recommends that patients with mild-to-moderate liver dysfunction (classified as Child-Pugh class A or B cirrhosis) receive the standard loading dose on the first day, followed by half of the usual maintenance dose from the second day. Since our study excluded patients with liver dysfunction, further research is required to determine the optimal VRCZ dose for this population. Additionally, none of the patients in our study received concomitant medications known to affect VRCZ concentration, as indicated in the package insert.

This study has certain limitations. First, it had a small convenience sample and employed a single-center design. Further research, including a multicenter study with a larger sample size, is required to confirm the robustness of our results. Second, in this retrospective observational study, the comparison group was not well matched to the genotype group in terms of demographic characteristics, which may have biased the results. Third, the comparison group consisted of patients whose *CYP2C19* polymorphisms were unknown. In the Japanese population, the reported frequencies of *CYP2C19* genotypes are 1.1% for rapid or ultra-rapid metabolizers (i.e., *17/*17 and *1/*17), 35.5% for normal metabolizers, 45.3% for intermediate metabolizers, and 18.8% for poor metabolizers [27]. Given the similar genotype distribution in the genotype-guided group, it is reasonable to assume a comparable pattern in the comparison group. Fourth, there were notable demographic differences between the two groups, particularly in terms of sex and organ transplantation status. Regarding the relationship between VRCZ concentration and sex differences, variations in fat distribution, plasma protein concentrations, and sex hormones have been reported, with males typically exhibiting higher VRCZ concentrations when given the same dose [28]. Furthermore, organ transplant patients often take multiple concomitant medications, including

tacrolimus, requiring careful consideration of potential drug interactions with VRCZ [29]. Two liver transplant recipients were included in this study, and their VRCZ dosing was guided by the donor genotype, which matched that of the recipient. However, in cases of donor–recipient genotype mismatch, it remains unclear which genotype should guide dosing, and further research is needed to clarify this issue. In addition, we observed differences in treatment indications, including the proportion of patients treated for chronic pulmonary aspergillosis. Patients with chronic pulmonary aspergillosis often have a stable chronic lung disease and typically require long-term VRCZ therapy. In this study, PGx testing appeared beneficial early after VRCZ initiation; therefore, differences in treatment indications, including chronic pulmonary aspergillosis, are unlikely to have had a major impact on the observed outcomes. Despite these limitations, our findings provide valuable insights into the benefits of *CYP2C19* genotype-guided VRCZ therapy. Further research involving a more homogeneous patient population must confirm and extend our results.

In conclusion, *CYP2C19* genotyping is a valuable tool for optimizing initial VRCZ dosing in Japanese patients. Genotype-guided dosing significantly reduced the incidence of adverse effects, including hepatotoxicity and visual symptoms. Furthermore, this approach improved the proportion of patients who achieved therapeutic VRCZ trough concentrations early during treatment while maintaining comparable treatment efficacy. These findings support the incorporation of *CYP2C19* genotyping into routine clinical practice to enhance the safety and precision of VRCZ therapy, particularly in populations with a high prevalence of poor metabolizer alleles.

Author Contributions

Y. Katada, D.H., and K.U. wrote the manuscript; Y. Katada, D.H., H.I., and T.T. designed the research; Y. Katada, H.I., Y. Kojima, M.H., M.K., H.E., J.C., S.O., K.K., S.H., M.T., S.N., K.S., Y.T., and M.N. performed the research; Y. Katada, D.H., K.U., and Y. Katsube analyzed the data; D.H., Y. Katsube, and M.S. contributed new reagents/analytical tools.

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Conflicts of Interest

The authors declare no conflicts of interest.

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