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PHARMACOLOGY AND PHARMACODYNAMICS OF ANTIFUNGAL AGENTS (P GUBBINS, SECTION EDITOR)

Therapeutic Drug Monitoring and Genotypic Screening in the Clinical Use of Voriconazole

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Abstract Voriconazole is an antifungal triazole that is the first-line agent for treatment of invasive aspergillosis. It is metabolized by CYP2C19, CYP2C9, and CYP3A4 and demonstrates wide interpatient variability in serum concentrations. Polymorphisms in CYP2C19 contribute to variability in voriconazole pharmacokinetics. Here, evidence is examined for the use of voriconazole therapeutic drug monitoring (TDM) and the role of CYP2C19 genotyping in voriconazole dosing. The majority of studies exploring the impact of voriconazole TDM on efficacy and safety have found TDM to be beneficial. However, most of these studies are observational, with only one being a randomized controlled trial. High-volume multicenter randomized controlled trials of TDM are currently not available to support definitive guidelines. There is a significant relationship in healthy volunteers between CYP2C19 genotype and voriconazole pharmacokinetics, but this association is markedly less visible in actual patients. While CYP2C19 genotype data may explain variability of voriconazole serum levels, they alone are not sufficient to guide initial dosing. The timeliness of availability of CYP2C19 genotype data in treatment of individual patients also remains challenging. Additional studies are needed before implementation of CYP2C19 genotyping for voriconazole dosing into routine clinical care.

Keywords Voriconazole · CYP2C19 · Pharmacokinetics · Pharmacogenomics

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Introduction

Voriconazole is an antifungal triazole approved by the FDA for the treatment of invasive aspergillosis, esophageal candidiasis, candidemia in non-neutropenic patients, disseminated *Candida* infections, and infections caused by *Scedosporium apiospermum* and *Fusarium* spp. [1]. Infectious Diseases Society of America (IDSA) guidelines recommend voriconazole as a first-line agent for the treatment of invasive aspergillosis and as an alternative agent for the treatment of candidemia [2, 3].

Voriconazole is metabolized in the liver by CYP3A4, CYP2C9, and CYP2C19 and demonstrates wide interpatient variability in serum concentrations [4, 5]. Polymorphisms in CYP2C19, but not in CYP3A5 or CYP2C9, have been reported to affect its pharmacokinetics [6, 7, 8•]. Other factors including age, liver function, and concomitant medications contribute to variability in voriconazole concentrations [4, 5]. In addition, voriconazole demonstrates saturable, non-linear pharmacokinetics in adults [9].

The field of pharmacogenomics seeks to understand variations in the response to medications based on inherited and acquired genetic differences between patients [10, 11]. The

prospect of pharmacogenomics testing has been explored for a myriad of medications including CYP2C19 genotyping to aid voriconazole dosing [12•]. Guidelines from the Royal Dutch Pharmacists Association Pharmacogenetics Working Group recommend monitoring voriconazole serum concentrations in patients expressing the CYP2C19 poor metabolizer (PM) and CYP2C19 intermediate metabolizer phenotypes [13]. However, there is a paucity of guidelines for pharmacogenomic testing in patients treated with voriconazole. Common side effects of voriconazole include hepatotoxicity, neurotoxicity, blurry vision, skin rash, and hyperfluorosis [14]. Some of these adverse effects are more likely to occur at higher than necessary voriconazole serum/plasma concentrations, while low voriconazole levels may result in therapeutic failure [12•]. As such, voriconazole therapeutic drug monitoring (TDM) has become commonplace in the management of serious fungal infections. The objective of this review is to critically examine the evidence of the relationships among CYP2C19 genotype, voriconazole serum concentrations, and clinical outcomes.

CYP2C19 Polymorphisms

CYP2C19 catalyzes the metabolism of numerous commonly prescribed drugs including antidepressants, anticancer agents, clopidogrel, proton pump inhibitors, diazepam, and voriconazole [15–17]. The CYP2C19 gene exhibits significant ethnic differences in expression among the 34 identified alleles [18]. The fully functional allele (**1*) is associated with normal CYP2C19 activity; individuals' homozygous for this allele are considered extensive metabolizers (EM). Individuals who carry two null alleles are considered poor metabolizers (PMs). The two most common non-functional (null) alleles are *CYP2C19*2* and *CYP2C19*3*, which account for 95 % of individuals considered PMs [19]. Additional null alleles include *CYP2C19*4*, *CYP2C19*5*, *CYP2C19*6*, and *CYP2C19*8* [15, 20]. Approximately, 3–5 % of Caucasians, 12–23 % of Asians, 7 % of African Americans, and 0.9 % of Hispanics are CYP2C19 PMs, indicating that they encode non-functioning enzymes [21–24]. Conversely, intermediate metabolizers carry one null and one wild-type allele (i.e., *CYP2C19*1/*3*).

An allelic variant associated with increased CYP2C19 expression (*CYP2C19*17*) and catalytic activity has also been identified [25]. Individuals possessing this allelic variant are considered ultra-rapid metabolizers (URM) [17]. *CYP2C19*17* is a relatively common allele in Europeans and Africans (18–27 and 10–26 % frequencies, respectively), yet it occurs infrequently in Asians (0.15–0.44 % prevalence) [17].

Voriconazole Concentrations and Efficacy/Toxicity

Voriconazole exhibits a narrow therapeutic index, non-linear pharmacokinetics, marked genotypic variability in CYP2C19 metabolizer status, and a high propensity for drug-drug interactions [5, 26]. Consequently, a fixed dose of voriconazole yields a myriad of plasma concentrations [27–29], which do not necessarily predict future concentrations even in the same individual [30, 31]. Voriconazole is also commonly used for fungal infections such as invasive aspergillosis that are associated with significant mortality among susceptible hosts. These factors underscore the need for voriconazole TDM. Indeed, the majority of studies that explore the impact of voriconazole TDM on efficacy and safety have found it to be beneficial. However, most of these studies are observational, with only one being a randomized, assessor-blinded, controlled trial [32•]. Furthermore, voriconazole TDM studies exhibit marked heterogeneity in quality and design, including assay techniques, voriconazole sampling methodology [29, 32•, 33], and target concentration ranges, all of which pose difficulties when comparing results across studies. Nonetheless, the IDSA guidelines support the use of voriconazole TDM [3].

Studies examining the role of voriconazole TDM have used a variety of voriconazole-exposure metrics. Most of the early studies reported random blood sampling. Voriconazole efficacy has been shown to correlate well in vivo with the AUC/MIC [34, 35] or mean unbound voriconazole concentration/MIC ratio [36]. However, these measurements entail repeated sampling and are difficult to perform in the clinical setting. Assessment of the trough/MIC ratio is a less robust, but more clinically achievable approach, which was found to predict clinical response in a 5000-patient Monte Carlo simulation using data from multiple phase 2 and phase 3 clinical trials [36].

The optimal target concentration range for voriconazole is not clearly defined. The suggested lower end cut-off for efficacy has ranged widely between 0.25 mcg/mL [33] and 2.51 mcg/mL [37]. Most initial studies used a voriconazole concentration >1 mcg/mL as the lower cut-off on the basis of in vitro studies that reported voriconazole MICs between 0.5 and 1 mcg/mL for most *Aspergillus* spp. and *Candida* spp. [38, 39]. However, data now suggest a voriconazole concentration of 2 mcg/mL may be a more appropriate lower-end threshold concentration [40–42]. Because the unbound circulating fraction (40–50 %) of voriconazole is microbiologically active [29], such a recommendation seems pharmacologically plausible. Suggested upper-end threshold concentrations for voriconazole range from 4 to 7 mcg/mL and are based on concentrations above which toxicities were observed across studies. Studies reporting relationships among voriconazole concentrations and efficacy and toxicity are summarized in Table 1 and discussed in detail below [29, 31, 32•, 33, 36, 43, 44•, 45•, 46–50].

Table 1 Studies reporting the relationship between voriconazole concentrations and efficacy and/or toxicity

Study design	Sample size	Population	TDM efficacy relationship	TDM toxicity relationship	Suggested thresholds (mcg/mL)		Ref.
					Lower	Upper	
RCT (assessor blinded; single center)	110 (1:1 randomization)	Patients with IFIs receiving targeted or empiric therapy	Higher success in TDM group[a] (86 vs. 63 %; $p=0.04$)	No difference in AE incidence, but lesser drug discontinuations in the TDM group (4 vs. 17 %; $p=0.02$)	1	5.5	[32•]
Retrospective data analysis	825	Heterogeneous subjects from 9 published phase 2 and phase 3 trials	Nonlinear relationship ($p<0.003$)	None (analysis not reported)	2[b]	5[b]	[36]
Descriptive meta-analysis	509	Patients with deep mycosis from 12 reports	Seen using graded cut-offs (between 1 and 3 mcg/mL) only[c]	Seen with hepato- and neurotoxicity using graded cut-offs (between 3 and 6 mcg/mL) only[c]	1	4	[43]
Prospective cohort[d]	52	Patients with clinical indications for receiving voriconazole	Higher success at >1 mcg/mL (88 vs. 54 %; $p=0.02$)	Seen with encephalopathy >5.5 mcg/mL (31 vs. 0 %; $p=0.002$) but not with hepatotoxicity	1	5.5	[29]
Population PK analysis	55	Patients with clinical indications for receiving voriconazole	Seen with Log-transformed C_{max}, C_{min}, and $AUC_{0\text{-}12h}$ and efficacy using oral ($p<0.001$) but not IV therapy	Seen with C_{max}, C_{min}, and $AUC_{0\text{-}12h}$ and grade 3 neurotoxicity ($p<0.01$) but not hepatotoxicity	1.5	4.5	[44•]
Retrospective cohort (multicenter)	201[e]	Patients with clinical indications for receiving voriconazole[e]	Higher success at ≥1.7 mcg/mL (93 vs. 74 %; $p<0.01$)	Seen with neurotoxicity at >5 mcg/mL (32 vs. 1.2 %; $p<0.01$)	2	5	[45•]
Prospective non-comparative cohort (multicenter)	116[f]	Proven and probable cases of IA	Higher success at >0.25 mcg/mL	6/22 (27 %) of patients with plasma concentration >6 mcg/mL developed abnormal liver function or liver failure	0.25	6	[33]
Retrospective cohort	108[g]	Patients with clinical indications for receiving voriconazole	No relationship with clinical or radiological response 12 weeks	Levels >5.5 mcg/mL, not associated with higher rates of encephalopathy or hepatotoxicity	NR	NR	[46]
Retrospective cohort (multicenter)	264[h]	Patients with clinical indications for receiving voriconazole	No relationship (higher success when troughs were lower)	Very few samples >5 mcg/mL; incidence of AEs low; underpowered to show exposure-toxicity relationship	NR	NR	[31]
Retrospective data analysis	1053	Subjects from 10 phase 2 and 3 trials	Not assessed	Seen with visual AEs ($p=0.01$) and AST, ALP, and bilirubin ($p<0.001$) but not ALT ($p=0.17$)	NR	NR	[47]
Retrospective cohort	26	Patients with IA or invasive candidiasis	Not assessed	Neurotoxicity hazard ratio 2.27 per 0.1 mcg/mL increase ($p<0.001$)	NR	4	[48]
Retrospective cohort	39	Patients with clinical indications for receiving voriconazole	Not assessed	Hepatotoxicity seen with higher initial troughs and sustained levels >4 mcg/mL	NR	4	[49]
Prospective cohort	95	Patients with clinical indications for receiving voriconazole	Not assessed	Visual hallucinations associated with higher levels (4.5 vs. 2.5 mcg/mL; $p=0.004$); no relationship seen with hepatotoxicity	–	NR	[50]

These studies are limited to the use of voriconazole with therapeutic intent with a sample size of >50 for evaluation of efficacy and >25 when solely for evaluation of toxicity

TDM therapeutic drug monitoring, *RCT* randomized controlled trial, *IFI* invasive fungal infection, *AE* adverse event, *IA* invasive aspergillosis, *AST* aspartate transaminase, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *NR* not reported, C_{max} maximum observed concentration, C_{min} minimum observed concentration, $AUC_{0\text{-}12h}$ area under the concentration versus time curve over the course of a single dosing interval

[a] Subset of proven or probable IFI

[b] Trough/MIC ratio

[c] Relationship not seen when concentration was treated as a continuous variable

[d] Cases without TDM ($N=39$) were studied retrospectively

[e] Treatment $N=170$ and prophylaxis $N=31$

[f] 116 patients assessed for efficacy and 137 patients assessed for safety

[g] Efficacy only evaluated in those with proven or probable IFI ($N=46$)

[h] Efficacy only evaluated in those with proven or probable IA ($N=53$)

Voriconazole TDM and Efficacy

The only clinical trial investigating the impact of voriconazole TDM on the incidence of adverse drug events and treatment response was a 1:1 randomized, single-center study from South Korea. In this study, voriconazole dosage was adjusted using pre-specified algorithms based on trough voriconazole concentrations drawn on day 4 of therapy in the intervention group (55 of 110 patients) in which the targeted range was 1 to 5.5 mcg/mL [32•]. The control group received standard voriconazole dosing during the study. Although the incidence of adverse drug events did not differ significantly between groups (p=0.97), the likelihood of voriconazole discontinuation due to adverse effects was fourfold higher among controls compared to the intervention group (p=0.02). With the availability of voriconazole trough levels to guide dose adjustments, providers tended to continue voriconazole longer in the TDM arm despite the occurrence of a similar number of adverse events. Importantly, TDM was associated with a higher clinical response rate compared to no TDM (81 vs. 59 %, p=0.04).

Several observational studies have also evaluated the role of voriconazole TDM (Table 1); the largest of which involved a secondary analysis of 825 subjects with yeast or mold infections from nine phase 2 and phase 3 clinical trials. At a mean plasma concentration (C_{avg}) <0.5 mcg/mL, the voriconazole response rate was 57 % compared to 74 % when C_{avg} was between 0.5 and 5 mcg/mL. Moreover, a non-linear relationship between C_{avg} and clinical response was determined by logistic regression (p<0.003) [36]. Higher responses were seen with primary rather than salvage therapy, and with yeast rather than mold infections, and specifically within these groups with *Candida* spp. rather than *Aspergillus* spp. Although informative, this study combined patients and pathogens with widely different exposure-response relationships, making it difficult to extrapolate these results to other patient populations.

In a study of voriconazole TDM during 2388 treatment days in 52 patients at a single center, investigators found that trough concentrations >1 mcg/mL yielded a higher response rate (88 %) compared to troughs ≤1 mcg/mL (54 %; p=0.02) [29]. The authors did not find a relationship between voriconazole dose and trough concentration, but did observe that trough concentrations were a significant predictor of clinical response (probability 0.7 at a trough of 1 mcg/mL). In a population pharmacokinetic analysis from 505 plasma concentration values from another 55 patients, the same authors reproduced this concentration-response relationship [44•]. In this study, plasma concentrations ranging from 1.5 to 4.5 mcg/mL were associated with a probability of response greater than 85 %. The relationship was statistically significant only when voriconazole was administered orally (p<0.001), supporting variability in oral bioavailability as a major determinant of subtherapeutic voriconazole levels.

Similar findings have been observed in several multicenter studies. In an open-label study involving 201 adult patients, voriconazole trough concentrations were significantly lower (median 0.9 mcg/mL) in patients who failed treatment compared to those who responded (median 2.1 mcg/mL; p<0.05) [45•]. Among those patients with proven or probable invasive fungal infections and voriconazole trough concentrations <1.7 mcg/mL, the treatment failure rate was 35 %, compared to a 6 % failure rate in patients with voriconazole concentrations ≥1.7 mcg/mL. In another multicenter study of 116 assessable patients with invasive aspergillosis, 3 out of 5 patients with voriconazole trough concentrations <0.25 mcg/mL failed to demonstrate any sustained meaningful treatment response, which underscores the importance of knowing when trough voriconazole concentrations are exceedingly low (<0.25 mcg/mL) [33]. Several others have found voriconazole TDM to beneficially influence treatment efficacy in studies involving relatively few patients (N<50) [40, 51, 52].

In children 2 to 11 years old administered standard adult dosages (3 to 4 mg/kg every 12 h), voriconazole demonstrates linear pharmacokinetics, which has been attributed to higher first-pass metabolism and systemic metabolic rates in the pediatric population [53–55]. However, at the recommended dosage for ages 2 to 12 (7 to 8 mg/kg every 12 h), nonlinear pharmacokinetics, as seen in adults, are observed [55, 56]. The inability to reach adequate levels at standard adult doses (especially in critically ill children [57]) and the variability in trough concentrations at recommended doses, suggests voriconazole TDM may also be helpful in children. Three pediatric studies using voriconazole target trough concentrations ≥1 mcg/mL demonstrated a relationship between voriconazole concentrations and efficacy [58–60].

Fewer studies have explored the usefulness of voriconazole TDM in the prophylactic setting (i.e., to reduce breakthrough fungal infections) [61–64]. Among 93 lung-transplant recipients receiving prophylactic voriconazole, absence of any trough values >1.5 mcg/mL was associated with a significantly greater number of respiratory cultures growing fungal species (p=0.01) [61]. Notably, some of the positive cultures represented colonization, and the value of preventing fungal colonization remains unclear. A similar study in allogeneic hematopoietic stem cell transplant recipients with hematologic malignancies reported six cases of breakthrough candidiasis among 43 patients with voriconazole trough concentrations ≤2 mcg/mL and no cases among the 24 patients with concentrations >2 mcg/mL (p=0.061) [62]. Both of these studies saw four breakthrough infections each with molds [61, 62]. Another study in immunocompromised patients failed to show any relationship between TDM of prophylactic voriconazole and efficacy, but involved cases with both prophylactic and therapeutic indications for voriconazole [63]. Current

evidence is insufficient to recommend voriconazole target concentrations to ensure adequate prophylaxis.

Some studies failed to demonstrate a relationship between voriconazole monitoring and efficacy [31, 41, 46, 65]. In these studies, the number of cases included in the efficacy analysis was low (maximum 53 cases). In one of the studies [41], the trough-efficacy correlation became statistically significant after excluding patients with refractory hematological conditions from the analysis. Another study [46] found a relationship between trough concentrations and efficacy 6 but not 12 weeks after commencing therapy. A meta-analysis of 12 studies was performed to investigate the optimal blood concentration range of voriconazole [43]. Analysis of the extracted data on voriconazole concentrations as a continuous variable from 3 of the 12 studies [41, 66, 67], and its relationship with efficacy, suggested that the distribution of voriconazole plasma concentrations did not differ significantly between treatment success and failure [weighted mean difference 1.95 (−2.18 to 1.84); $p=0.35$]. The addition of one study [29] and dichotomous treatment of extracted data using graded cut-off values between 1 and 3 mcg/mL, demonstrated that a trough of 1 mcg/mL (including a subset analysis limited to cases of invasive aspergillosis), discriminated between treatment success and failure [OR 7.23 (2.84 to 18.37); $p<0.0001$]. However, the limited number of studies actually analyzed as well as small sample sizes and observational nature, preclude strong conclusions about the drug concentration-efficacy relationship. Notwithstanding these underpowered studies, the majority of studies show a positive benefit of voriconazole TDM on efficacy.

Voriconazole TDM and Safety

Voriconazole can produce a variety of adverse effects that vary in severity. Hepatotoxicity, visual disturbances, visual hallucinations, and other neurologic disorders have been directly correlated with plasma concentrations of voriconazole (Table 1). A pooled PK/PD analysis of ten phase 2 and phase 3 clinical studies suggested a relationship between voriconazole concentrations and visual disturbances, which occurred in 16 % of patients when plasma voriconazole concentrations were <1 mcg/mL, and rose to 28 % at >9 mcg/mL [47]. Despite this relationship, the usefulness of TDM for this application is limited because voriconazole-associated visual disturbances are typically mild, reversible, and generally do not result in discontinuation of therapy [68]. Other neurological adverse effects including visual hallucinations and less commonly encephalopathy may be more debilitating. Their relationship to voriconazole concentrations has been studied as well, with almost all of these studies reporting a statistically significant positive correlation [29, 43, 44•, 45•, 48, 50, 69].

The association between plasma voriconazole concentrations and hepatotoxicity has been extensively investigated [29, 33, 41, 43, 44•, 45•, 46, 47, 49, 50, 70, 71]. Investigators reported that 6 of 22 patients with voriconazole concentrations >6 mcg/mL developed liver function test abnormalities, resulting in 1 death [33]. Based on these and other data, TDM was suggested to avoid voriconazole hepatotoxicity [71, 72], but this has not been unanimously accepted [73]. In the largest PK/PD analysis of voriconazole hepatotoxicity, investigators [47] reported a statistically significant relationship between voriconazole concentrations and risk of aspartate transaminase, alkaline phosphatase, and bilirubin elevation ($p<0.001$), but this relationship was not observed for alanine transaminase ($p=0.17$). More importantly, receiver-operator characteristic curves denoted poor prediction of any liver function tests abnormalities across a range of voriconazole concentrations [47]. One study has suggested that sustained elevated voriconazole concentrations might be associated with an increased risk of hepatotoxicity [49]. Nonetheless, the absolute incidence of hepatotoxicity with voriconazole use remains low and is comparable to that of other antifungal agents [74]. Thus, there is no universally acceptable concentration threshold, above which voriconazole-related hepatotoxicity is known to occur.

When used in the prophylactic setting, voriconazole toxicity must be weighed against its ability to reduce breakthrough invasive fungal infections. A study evaluating the role of voriconazole in preventing invasive fungal infections among lung transplant recipients demonstrated that toxicities were significant enough to warrant drug discontinuation in 27 % (25/93) of cases [61]. The usefulness of voriconazole TDM in the prophylactic setting requires further study.

Voriconazole Pharmacokinetics and CYP2C19 Polymorphisms

Studies in Healthy Volunteers

A study in healthy volunteers receiving voriconazole 200 or 300 mg po BID×10 days found that voriconazole C_{max} and AUC were increased in CYP2C19 PMs compared to EMs [75]. The impact of CYP2C19 genetic variants on voriconazole pharmacokinetics has been confirmed and characterized in a number studies in adult healthy volunteers (Table 2) [7, 8•, 76–80]. Pharmacokinetic parameters including half-life ($t_{1/2}$) and AUC are significantly increased in CYP2C19 PM compared to CYP2C19 EM receiving oral voriconazole. In single-dose studies, the voriconazole $t_{1/2}$ has ranged from 8.7 to 15.2 h in PM and 3.3 to 8.1 h in EM [7, 76, 77, 79, 80]. In a multiple-dose study, the voriconazole $AUC_{0\text{-}T}$ geometric mean ratio of PM to EM was 3.3 [8•]. This increase is consistent with the results of several single-dose

Table 2 Pharmacokinetics of voriconazole in healthy volunteers with CYP2C19 polymorphisms

Study design	Age, race	Total *N*	Voriconazole dosage regimen	CYP2C19 Genotype (*N*)	Pharmacokinetic parameters				Ref.
					$AUC_{0-\infty}$ (h×mcg/mL)	AUC_{0-T} (h×mcg/mL)	Cl (mL/min)	$t_{1/2}$ (h)	
RCT, double blinded, placebo-controlled, two-way crossover study (ritonavir /voriconazole DI study)	Adults White	20	Voriconazole 400 mg po×1	*CYP2C19*1/** (*N*=8)	16.52±7.21		463±168	8.11±1.35	[76]
				*CYP2C19*1/** (*N*=8)	22.65±10.88		343±127	8.07±2.22	
				*CYP2C19*2/** (*N*=4)	47.96 +/− 23.33[a]		158±54[a]	15.21±3.06[a]	
Open label	21±2 years old	20	Voriconazole 200 mg po×1	*CYP2C19*1/*17* (*N*=4)	3.63±0.52[b]		932.02±120.99[b]	7.19±3.27	[77]
	Chinese			*CYP2C19*1/*1* (*N*=8)	6.92±2.11		521.53±154.51	8.28±2.02	
				*CYP2C19*2/*2* (*N*=8)	23.9±5.94[c]		146.7±33.88[c]	13.98±3.92[c]	
RCT, open label, two-way crossover study	Adult	20	Voriconazole 400 mg po×1 or voriconazole 400 mg IV×1	*CYP2C19*1/*1*[d] (*N*=8)					[78]
				PO	38.8±12.8[e]		572±352	7.5±1.2	
				IV	53.7±22.5[e]		420±221	7.8 +/− 1.4	
	White		After 14 day washout, voriconazole administered by other route.	*CYP2C19*1/*2*, **1/*3*[d] (*N*=8)					
				PO	88.6±40.5[e]		241±82.1	9.5±5	
				IV	107±46.7[e]		194±56	9±4	
				*CYP2C19*2/*2*, **2/*3*, **3/*3* (*N*=4)					
				PO	119±13.8[c,e]		157±18.8[c]	9.6±2.3	
				IV	127±21.7[c,e]		149±28.3[c]	9.4±1.6	
RCT, open, crossover study (erythromycin/ voriconazole DI study)	Mean age 19 to 23 years old Chinese	18	Voriconazole 200 mg po × 1	*CYP2C19*1/*1* (*N*=6)	7.7±2.99		499±228	3.72±2.12	[79]
				*CYP2C19*1/*2* (*N*=4)	10.75±9.42		452±233	4.09±2.84	
				*CYP2C19*1/*3* (*N*=2)					
				*CYP2C19*2/*2* (*N*=5)	30.95±19.2[f]		153±110[g]	8.69±5.17[g]	
				*CYP2C19*2/*3* (*N*=1)					
Analyzed placebo groups of two studies (voriconazole and ritonavir or St. John's Wort)	Adults	35	Voriconazole 400 mg po × 1	*CYP2C19*1/*17* (*N*=8), **2/*17* (*N*=2)	13.27±3.17		526.9±118	6.96±1.71	[7]
	Caucasian (*N*=32)			*CYP2C19*1/*1* (*N*=9)	16.44±6.93		465.5±175.7	7.23±2.11	
	Asian (*N*=2)			*CYP2C19*1/*2* (*N*=11)	25.66±12.82		319.2±152.2	8.25±3	
	American (*N*=1)			*CYP2C19*2/*2* (*N*=4)	45.73±20.81[a]		162.9±47.6[a]	14.28±3.36[a]	
				*CYP2C19*2/*2*17*(*N*=1)					
RCT, two-phase crossover study (ginkgo biloba/ voriconazole DI study)	Adults	14	Voriconazole 200 mg po × 1	*CYP2C19*1/*1* (*N*=7)	5.17(3.73 to 6.88)[h]		644.85 (484.39 to 894.44)[h]	3.27 (2.56 to 3.99)[h]	[80]
	Chinese			*CYP2C19*2/*2* (*N*=7)	20.96 (18.81 to 28.45)[c,h]		159.01 (117.18 to 117.25)[c,h]	11.26 (10.21 to 16.17)[h]	
Open-label parallel group study	Adults	18	Voriconazole 200 mg IV × 1.	*CYP2C19*1/*1* (*N*=6)					
	Korean		1 week wash out. Voriconazole 200 mg po × 1. Next day voriconazole 200 mg po	IV	6.513±2.573		563.3±161.7	3.2±2.5	[8•]
				PO (single dose)	5.055±1.771		715±198.3	2.7±1.7	
				PO (multiple dose)		19.305±9.594	210±108.3	9.6±5.1	

Table 2 (continued)

Study design	Age, race	Total *N*	Voriconazole dosage regimen	CYP2C19 Genotype (*N*)	Pharmacokinetic parameters				Ref.
					$AUC_{0-\infty}$ (h×mcg/mL)	AUC_{0-T} (h×mcg/mL)	Cl (mL/min)	$t_{1/2}$ (h)	
			BID for 5 days, then once on last day	*CYP2C19*1/*2,*1/*3* (*N*=6)					
				IV	10.098±4.151		383.3±160	5.5±3.3	
				PO (single dose)	8.868±3.644		448.3±221.7	5.8±3.1	
				PO (multiple dose)		42.369±19.090	98.3±58.3	16.9±7.2	
				*CYP2C19*2/*2*, **2/*3* (*N*=6)					
				IV	20.479± 5.077[i]		171.7±40	13.3±6.1	
				PO (single dose)	16.582±3.893[j]		208.3±40	12±3.1	
				PO (multiple dose)		58.697±11.113[k]	58.3±15	32.3±9.4	

Statistics from studies only included in table for EM versus PM and EM versus URM

RCT randomized controlled trial, *DI* drug interaction, *N* number of patients, $AUC_{0-\infty}$ area under the concentration versus time curve extrapolated to infinity, AUC_{0-T} area under the concentration versus time curve from dosing to the time point of the next dose, *Cl* clearance, $t_{1/2}$ half-life

[a] $P<0.01$ for *1/*1 versus *2/*2

[b] $P<0.05$ for *1/*1 versus *1/*17

[c] $P<0.05$ for *1/*1 versus *2/*2

[d] Six out of eight EM group were *CYPC19*1/*17* and 2 of heterozygous EM group were *CYPC19*2/*17* when reanalyzed

[e] AUC is $AUC_{0\text{-last}}$ in h × nmol/mL

[f] $P<0.01$ for *1/*1 versus *2/*2,*2/*3

[g] $P<0.05$ for *1/*1 versus *2/*2,*2/*3

[h] Values are median and interquartile range

[i] Geometric mean ratio PM/EM 3.23 (90 % CI 2.38 to 4.4)

[j] Geometric mean ratio PM/EM 3.36 (90 % CI 2.54 to 4.44)

[k] Geometric mean ratio PM/EM 3.29 (90 % CI 2.22 to 4.9)

studies, which determined that the voriconazole $AUC_{0-\infty}$ was 2.8 to 4.1 times higher in PM compared to EM [7, 8•, 76–80]. In single oral dose studies, significant reductions in voriconazole clearance have been observed in PM versus EM [7, 76–80]. A multiple-dose study reported that the voriconazole apparent oral clearance (Cl/F) decreased from 210 to 58.3 mL/min in EM compared to PM [8•]. However, changes in clearance in this trial were not subjected to statistical evaluation.

Alternations in voriconazole pharmacokinetics in CYP2C19 genetic variants has also been observed with intravenous voriconazole [8•, 78]. After a single dose (voriconazole 200 mg i.v.), the $AUC_{0-\infty}$ geometric mean ratio of PM to EM was 3.23 in healthy volunteers [8•]. In another single-dose study (voriconazole 400 mg i.v.), the $AUC_{0-\infty}$ was significantly increased and clearance significantly decreased in PM compared to EM [78]. However, in this study 6 out of 8 patients initially categorized as EM were later found to possess the *CYP2C19*1/*17* genotype.

Two studies have produced conflicting data on the effect of the *CYP2C19*17* allele on voriconazole pharmacokinetics [7, 77]. Unfortunately, only volunteers who were heterozygous for the *CYP2C19*17* allele (*CYP2C19*1/*17*) and not homozygous (*CYP2C19*17/*17*) were enrolled in these trials. One study of healthy volunteers receiving a single oral voriconazole dose (200 mg) demonstrated a significant increase in apparent Cl/F and a decrease in $AUC_{0-\infty}$ in EM (*CYPC19*1/*1*) compared to URM (*CYP2C19*1/*17*) [77]. In contrast, an analysis of the placebo groups from two drug interaction studies reported no statistical differences for $AUC_{0-\infty}$, apparent Cl/F, or $t_{1/2}$ when comparing EM (*CYPC19*1/*1*) to URM (*CYP2C19*1/*17*, *CYP2C19*2/*17*) [7]. Based on the results of these trials, it was proposed that the *CYP2C19*17* allele may possibly lead to subtherapeutic voriconazole concentrations [81].

Studies in Patients

In contrast to the mostly positive results reported in healthy volunteers, studies on the impact of CYP2C19 genetic variants on voriconazole concentrations in patients have demonstrated conflicting results (Table 3). While retrospective studies have indicated an association between CYP2C19 genotype and voriconazole concentrations [83, 85, 87, 88], several prospective studies have reported no association [50, 84]. For example, a retrospective study in adults reported a minimum observed concentration (C_{min}) of 3.67 mg/L and 1.98 mg/L in PM and EM, respectively ($p<0.05$) [87]. However, in a prospective observational trial in adult Korean patients, median trough concentrations were not significantly different in EM and PM (2.12 and 2.75 mg/L, respectively, $p=0.859$) [84].

The different results in patients compared to healthy volunteers may be due to confounding factors present in patients such as drug interactions, comorbidities, and organ dysfunction [89]. Additionally, the CYP2C19 genotype does not appear to account for all of the intrinsic variability in voriconazole pharmacokinetics between individuals. An analysis of placebo groups from two healthy volunteer studies revealed that the CYP2C19 genotype explained 49 and 39 % of variability in voriconazole apparent Cl/F and $AUC_{0-\infty}$, respectively [7]. Similarly, in a retrospective review of cystic fibrosis lung transplant recipients, the CYP2C19 genotype only explained 38 % of variability in voriconazole maintenance dose [83].

Several studies indicate that the *CYP2C19*17* allele may lead to subtherapeutic voriconazole concentrations [82, 83, 85]. In cystic fibrosis lung transplant recipients, the proportion of below range concentrations was 37.9 and 15.6 % in *CYP2C19*17* and *CYP2C19*1* groups, respectively ($p<0.01$) [83]. In a retrospective study, immunocompromised patients with cancer possessing the *CYP2C19*17/*17* genotype had lower median dose-normalized trough concentrations than those with the *CYP2C19*1/*1* genotype [88]. In that study, all of the patients with the *CYP2C19*17/*17* genotype ($N=4$) failed to achieve therapeutic voriconazole concentrations. Furthermore, in a retrospective study of patients with voriconazole levels ≤0.2 mcg/mL and excluding those receiving enzyme inducers, allogeneic stem cell transplant or liver transplant patients, inadequate dosing, or timing of levels, the *CYP2C19*1/*17* or *CYPC219*17/*17* genotypes were found in 8 out of 10 patients (80 %) [90]. In complicated dosing settings such as obesity genetic screening may also be informative and clinically helpful. For example, sustained elevations in voriconazole serum concentrations in an obese patient despite appropriate adjusted weight-based dosing were attributed to a CYP2C19 homozygous PM genotype (*CYP2C19*2/*2*) [91].

Several studies have described voriconazole pharmacokinetics in immunocompromised pediatric patients with CYP2C19 polymorphisms [89, 92]. When comparing pediatric PMs to EMs, the increase in voriconazole AUC was consistent with the results observed in adults [89, 92]. However, the genotypic variability observed in these patients precluded statistical analysis.

Other important issues related to the CYP2C19 genotype include the association between genotype and efficacy or toxicity and CYP2C19 genotype-guided dosing of voriconazole. Clinical studies have reported that the CYP2C19 genotype is not associated with the efficacy or toxicity of voriconazole (Table 3). Investigators found no significant difference among CYP2C19 genotypes in treatment response, all-cause, and invasive aspergillus mortality [86•]. The authors concluded that with therapeutic drug monitoring, an association was not observed between CYP2C19 genotype and voriconazole efficacy. Multiple studies have failed to find an association between CYP2C19 genotype and adverse effects [70, 82–84, 86•]

Table 3 Published studies on the relationship of CYP2C19 polymorphisms on voriconazole concentrations and efficacy and/or toxicity in patients

Study design	Age race	Total *N*	Population	Voriconazole dosage regimen	CYP2C19 genotype (*N*)	CYP2C19 genotype associated with voriconazole:			Ref.
						Concentrations	Efficacy	Adverse effects	
Retrospective study	17 to 84 years old; race not reported	86	Hematological malignancy	Voriconazole 6 mg/kg po BID for the 1st 24 h, 4 mg/kg po BID days 2 to 7, then 200 mg po BID 12 patients received IV voriconazole for the 1st 7 days	CYP2C19 wild type[a] (*N*=63) CYP2C19 non-wild type[a] (*N*=23)			No significant relationship between CYP2C19 genotype and serum liver enzymes levels	[82]
Retrospective review	15 to 40 years old Caucasian	24	Cystic fibrosis lung transplant recipients	Voriconazole 6 mg/kg BID, then MD	*CYP2C19*1/*17* (*N*=6) *CYP2C19*17/*17* (*N*=1) *CYP2C19*1/*1*(*N*=7) *CYP2C19*1/*2* (*N*=10)	Voriconazole exposure influenced by CYP2C19 genotype Proportion of below range concentrations were 37.9, 15.6, and 13 % in CYP2C19*17, CYP2C19*1, and CYP2C19*2 groups, respectively ($p<0.01$)		No significant relationship between CYP2C19 genotype and adverse drug reactions ($p=0.4$)	[83]
Prospective study	57.3±19.3 years old Japanese	29	Fungal infections[b]	Voriconazole 6 mg/kg BID for 1 day, then 3.6±0.8 mg/kg BID Wild-type MD 7.8±1.9 mg/kg/day and non-wild-type MD 6.7±1.2 mg/kg/day	CYP2C19 wild type[a] (*N*=10) CYP2C19 non-wild type[a] (*N*=19)			No significant relationship between CYP2C19 genotype and hepatotoxicity	[70]
Prospective observational trial	Adult Korean	25	Hematological malignancies, probable or proven IA	Voriconazole 6 mg/kg IV BID day 1, then 4 mg/kg IV BID Median MD 7.7 mg/kg/day; (interquartile range 7.1 to 8.3)	*CYP2C19*1/*1* (*N*=6) *CYP2C19*1/*2* (*N*=9) *CYP2C19*1/*3* (*N*=8) *CYP2C19*2/*2* (*N*=1) *CYP2C19*3/*3* (*N*=1)	Trough concentrations did not depend on CYP2C19 genotype Median trough concentrations in EM, HEM, and PM were 2.12, 3.76, and 2.75 mg/L, respectively ($p=0.859$)		No difference in severe adverse event frequencies between CYP2C19 genotypes	[84]
Retrospective study	1 to 15 years old Japanese	37	Received IV voriconazole and had levels measured	Voriconazole median dose 7.7 mg/kg/day (range 3.5 to 18.8 mg/kg/day)	*CYP2C19*1/*17*, *17/*17* (*N*=2) *CYP2C19*1/*1* (*N*=12) *CYP2C19*1/*2*,**1/*3* (*N*=16) *CYP2C19*2/*2*, **2/*3*, **3/*3* (*N*=7)	Voriconazole concentrations associated with CYP2C19 phenotype. Trough levels higher in PM/HEM group than EM/URM group, median 0.54 mg/dL, and 0.06 mg/dL, respectively, ($p=0.004$) CYP2C19 phenotype not independently associated with high concentrations by multivariate logistic regression analysis			[85]
Prospective observational study	53±13 years old Korean	104	Hematologic diseases, probable or proven IA	Voriconazole 6 mg/kg IV BID day 1, then 4 mg/kg BID or 200 mg po BID	*CYP2C19*1/*1* (*N*=37) *CYP2C19*1/*17*[c] (*N*=2) *CYP2C19*1/*2* (*N*=32) *CYP2C19*1/*3* (*N*=18) *CYP2C19*2/*2* (*N*=6)	The initial voriconazole trough concentrations 1.8, 2.7, and 3.2 mg/L in EM, HEM, and PM, respectively ($p=0.068$)	No significant difference in treatment response, all cause, and IA mortality between CYP2C19 genotypes	No significant difference in voriconazole-related adverse events between CYP2C19 genotypes	[86•]

Table 3 (continued)

Study design	Age race	Total *N*	Population	Voriconazole dosage regimen	CYP2C19 genotype (*N*)	CYP2C19 genotype associated with voriconazole:			Ref.
						Concentrations	Efficacy	Adverse effects	
					*CYP2C19*3/*3* (*N*=9)				
Prospective study	13 to 76 years old White, non-Latino (*N*=59); White, Latino (*N*=22); African American (*N*=16); Asian (*N*=3)	95			*CYP2C19*1/*1* (*N*=63) *CYP2C19*1/*2*; (*N*=18) *CYP2C19*1/*3* (*N*=1) *CYP2C19*2/*2* (*N*=4) *CYP2C19*1/*9* (*N*=1) *CYP2C19*1/*11* (*N*=1) *CYP2C19*1/*15* (*N*=1) Other (*N*=3)	CYP2C19 genotype minor influence over levels. Voriconazole concentration 4.33 and 2.468 mcg/mL in PM and EM, respectively			[50]
Retrospective study	18 to 99 years old Race not reported	144	Proven or probable invasive fungal infection	Dose based on the voriconazole package insert	*CYP2C19*1/*17* (*N*=3) *CYP2C19*1/*1* (*N*=62) *CYP2C19*1/*2,*1/*3* (*N*=62) *CYP2C19*2/*2,*2/*3* (*N*=17)	Voriconazole C_{min} influenced by CYP2C19 genotype. C_{min} higher in PM than EM and HEM (3.67, 1.98, and 2.36 mg/L, respectively) $p<0.05$ for EM versus PM			[87]
Retrospective review	1 to 19 years old; African (*N*=6); European (*N*=23); Hispanic (*N*=2); Multiple race; (*N*=2)	33	Immunocompromised patients with cancer	Initial MD 200 mg BID (≥12 years old), and 7 mg/kg BID (<12 years old); <12 years old: dose administered 2.6 to 41.2 mg/kg/day ≥12 years old: dose administered 3.6 to 16.1 mg/kg/day	<12 years old *CYP2C19*17/*17* (*N*=2) *CYP2C19*1/*17* (*N*=6) *CYP2C19*1/*1* (*N*=8) *CYP2C19*1/*2A, *1/*2B* (*N*=3) ≥12 years old *CYP2C19*17/*17* (*N*=2) *CYP2C19*1/*17* (*N*=2) *CYP2C19*1/*1*; (*N*=3) *CYP2C19*1/*2A, *1/*2B* (*N*=6) *CYP2C19*2A/*2A* (*N*=1)	CYP2C19 diplotype associated with voriconazole concentrations (p=0.002) Median dose normalized trough concentrations (mcg/mL/mg/kg) 0.01, 0.14, 0.62, 0.07 in *CYP2C19*17/*17*, *CYP2C19*1/*2A*, **1/*2B*, *CYP2C19*2A/*2A*, *CYP2C19*1/*1* genotype, respectively			[88]

MD maintenance dose, *IA* invasive aspergillosis, C_{min} minimum observed concentration

[a] Specific genotype not reported in the study

[b] Pulmonary aspergillosis, sinus aspergillosis, pulmonary cryptococcosis, cryptococcal meningitis

[c] *CYP2C19*1/*17* categorized as EM in this study

including hepatotoxicity [70, 82]. Nonetheless, several investigators have proposed voriconazole dosing based on CYP2C19 genotype. Matsumoto et al. recommended an initial voriconazole dose of 7.2 to 8.9 mg/kg/day and 4.4 to 6.5 mg/kg/day in CYP2C19 wild type and CYP2C19 non-wild type, respectively, in Japanese patients [70]. Wang et al. suggested a voriconazole dose of 200 mg orally or intravenously twice daily in PM and voriconazole 300 mg orally twice daily or 200 mg intravenously twice daily in non-PM [87]. However, to our knowledge, a strategy of prospective CYP2C19 genotyping to select an initial voriconazole dose has not been validated prospectively.

Discussion/Conclusion

In this review, we describe the evidence supporting the use of voriconazole TDM and the role of CYP2C19 genotyping for voriconazole dosing. The impact of voriconazole TDM on safety and efficacy is still not entirely clear. Most evidence to date was acquired retrospectively in the absence of a non-TDM comparison group and with discretionary post-concentration dosage adjustments. The cost associated with voriconazole TDM is the only identifiable barrier to its routine use. The only randomized controlled trial that assessed the role of voriconazole TDM was from a single center and underpowered to detect differences in their primary outcome of adverse events [32•]. High-volume multicenter randomized controlled trials in this area are currently not available to support definitive guidelines. Until then, we support routine voriconazole TDM given substantial retrospective and prospective observational data supporting its benefit in regards to efficacy, avoidance of neurotoxicity, and minimizing discontinuation of therapy.

While a significant relationship exists in healthy volunteers between CYP2C19 genotype and voriconazole pharmacokinetics, including AUC, Cl/F, and $t_{1/2}$, this association is markedly less apparent in actual patients. Studies also indicate that CYP2C19 genotype is not related to the efficacy or toxicity of voriconazole. Additional studies are needed before routine CYP2C19 genotyping is performed to facilitate initial dose selection of voriconazole. Finally, there is no validated model that allows for an accurate initial dosage of voriconazole based upon CYP2C19 allelic profile. While CYP2C19 genotype data may explain variability of voriconazole serum levels, they alone are not sufficient to guide initial dosing. This is in agreement with several reviews that state further research is needed before the widespread implementation of clinical voriconazole pharmacogenomics [12•, 14, 93, 94].

The logistics of timeliness of data from TDM and genotyping remain a continued challenge to patient care. While the "turn around" time for TDM data has improved in both reference laboratories and in hospital laboratories, availability of genotyping data remains difficult. Genotyping data are typically not available for patients as a guide to initial dosing in patients receiving voriconazole therapy.

If the current data are insufficient to recommend CYP2C19 genotyping for all patients, when should it be performed? We feel that institutional resources should first be used to implement voriconazole TDM with a reasonable turnaround time. Once voriconazole TDM is implemented, CYP2C19 genotyping, if available, may be a useful adjunct to assist in characterizing the voriconazole disposition of select patients with particularly unpredictable concentrations and a clinical need for aggressive treatment. As a reminder, alternative specimens than blood are needed for CYP2C19 genotyping in allogeneic stem cell or liver transplantation patients and those who have recently received heterologous blood transfusions [95]. We also note that genotyping may be useful in specific clinical situations such as dosing of voriconazole in critically ill patients (especially for patients from ethnicities associated with high rates of PM status such as Asians), in patients on multiple interacting medications, in obese patients receiving intravenous voriconazole, and in selected pediatric patients in whom therapeutic levels are difficult to obtain. In patients receiving initial doses of voriconazole above manufacturer recommendations, CYP2C19 genotyping may be helpful to identify PMs and thereby prevent excessive levels and toxicity. Furthermore, the presence of the CYP2C19*17 allele in critically ill patients may lead to the decision to administer combination antifungal therapy until therapeutic levels of voriconazole are achieved. Knowledge of the CYP2C19 genotype may also aid in the management of voriconazole vincristine drug interactions. In PMs, the half-life of voriconazole may be prolonged, requiring the drug to be held longer than 24 to 48 h before starting vincristine to avoid this serious drug interaction [96, 97]. Similar recommendations were recently made by others assessing of the role of pharmacogenomic screening of patients with hematological malignancies [14].

In conclusion, CYP2C19 genotyping to aid voriconazole dosing is an appealing concept, but further studies are needed before this practice is widely implemented into routine clinical care.

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Compliance With Ethics Guidelines

Conflict of Interest Sameer Kadri, Stacey A. Henning, Robert L. Danner, and Scott R. Penzak declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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