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CYP2C19 Polymorphisms and Therapeutic Drug Monitoring of Voriconazole: Are We Ready for Clinical Implementation of Pharmacogenomics?

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Abstract

Since its approval by the United States Food and Drug Administration in 2002, voriconazole has become a key component in the successful treatment of many invasive fungal infections, including the most common, aspergillosis and candidiasis. Despite voriconazole's widespread use, optimizing its treatment in an individual can be challenging due to significant interpatient variability in plasma concentrations of the drug. Variability is due to nonlinear pharmacokinetics and the influence of patient characteristics such as age, sex, weight, liver disease, and genetic polymorphisms in the cytochrome P450 2C19 gene (*CYP2C19*) encoding for the CYP2C19 enzyme, the primary enzyme responsible for metabolism of voriconazole. *CYP2C19* polymorphisms account for the largest portion of variability in voriconazole exposure, posing significant difficulty to clinicians in targeting therapeutic concentrations. In this review, we discuss the role of *CYP2C19* polymorphisms and their influence on voriconazole's pharmacokinetics, adverse effects, and clinical efficacy. Given the association between *CYP2C19* genotype and voriconazole concentrations, as well as the association between voriconazole concentrations and clinical outcomes, particularly efficacy, it seems reasonable to suggest a potential role for *CYP2C19* genotype to guide initial voriconazole dose selection followed by therapeutic drug monitoring to increase the probability of achieving efficacy while avoiding toxicity.

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Numerous factors influence how a patient responds to a particular therapy, including age, weight, comorbidities, polypharmacy, dietary factors, and liver and renal function. An individual's genetic makeup contains the fundamental blueprint for uniqueness. Personalized medicine, or individualized medicine, is a model of medical practice whereby the influence of genetics is taken into consideration in the therapeutic decision-making process for the prevention, diagnosis, and treatment of disease. Pharmacogenetics, a subset of personalized medicine, is simply the influence of genetics on an individual's response to medications.(1) This discipline can potentially guide healthcare providers to stratify which patient groups will potentially benefit from a therapy with minimal to no risk of adverse events or to guide drug dosing. Tremendous benefits may be derived from use of pharmacogenetics data for medications with high interpersonal variability, a narrow therapeutic index, and nonlinear pharmacokinetics, as observed with voriconazole.(1)

Voriconazole

Voriconazole is a triazole antifungal agent that truncates the biosynthesis of ergosterol from lanosterol by inhibiting the fungal cytochrome P450 (CYP)-dependent 14 α -sterol demethylase.(2)A derivative of fluconazole, voriconazole has an extended spectrum of activity compared to its predecessor.(3)Coverage includes, but is not limited to, *Aspergillus*, *Candida*, *Fusarium*, and *Scedosporium* species of fungi. Invasive fungal infections caused by these species are associated with increased morbidity and mortality, particularly in immunocompromised patients. The mortality rates associated with these conditions have been reported as 50 – 90%.(4, 5)Voriconazole is currently recommended as first-line therapy for acute invasive aspergillosis and as salvage therapy for infections caused by *Fusarium* and *Scedosporium*. Use may be limited by potentially serious adverse events such as hepatotoxicity and central nervous system effects. Visual disturbances are common, especially at higher concentrations, and should be closely monitored.

Voriconazole Pharmacokinetics

Voriconazole is commercially available as both oral and intravenous formulations. The high bioavailability (90%)(6)associated with the oral dosage forms makes it possible to convert between the oral and intravenous formulations. When converting from the intravenous formulation, a 300-mg oral dose is similar in exposure to 4 mg/kg intravenously, whereas a 200-mg oral dose is similar to 3 mg/kg intravenously.(3)

Two loading doses of voriconazole 6 mg/kg given 12 hours apart, followed by 4 mg/kg every 12 hours, is the recommended dosage.(3)??Dosage adjustments are recommended with the intravenous voriconazole formulation inpatients with hepatic or renal impairment.

Many patient factors affect voriconazole plasma concentrations, which leads to significant inter-and inpatient variability. Genetic polymorphisms in the *CYP2C19* gene encoding for

the CYP2C19 enzyme, the primary enzyme responsible for metabolism of voriconazole, are believed to explain approximately 30 – 50% of this variability, as reported in a study conducted in healthy individuals.(7, 8)Additional sources of variability include age, sex, drug interactions, and hepatic disease state.(3, 8–13)The administration of food with the oral voriconazole formulation reduces the peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) by 34% and 24% respectively, although alterations in pH have no effect. (3)Additionally, voriconazole displays nonlinear pharmacokinetics, believed to be due to saturable metabolism.(14)In a study by Trifilio and colleagues (15), a 50% dose increase produced disproportionate and inconsistent elevations in trough concentration (0.4 – 7.7 fold increases). Thus, a dose increase may result in nonlinear increases in concentrations, adding to the difficulty of maintaining concentrations within a therapeutic range. The lower doses (3–4 mg/kg every 12 hours) used in pediatric patients generally do not show this nonlinear increase(16); however, Michael et al. reported nonlinearity in pediatric patients administered 5–7 mg/kg intravenously.(17)

Therapeutic Drug Monitoring

Due to voriconazole's wide inter- and inpatient variability, the United States Food and Drug Administration and the Infectious Diseases Society of America recommend the use of therapeutic drug monitoring (TDM). Several observational studies demonstrate the clinical utility of TDM for voriconazole.(18–20) At the time of this writing, only one randomized controlled trial using a control group has been conducted.(21) Park et al. randomized 110 adult patients who received voriconazole for invasive fungal infections into two groups: those who received TDM versus those not receiving TDM. Patients in the TDM group underwent dosage adjustment, targeting a trough range of 1 to 5.5 µg/mL. The TDM group experienced fewer discontinuations due to adverse events as well as a greater number of complete or partial responses to treatment (81% vs. 57%). As demonstrated in this study, use of TDM identifies patients who may be at risk of therapeutic failure or adverse events, providing the clinician a chance to adjust treatment.

An important challenge to the optimal use of TDM is the selection of an appropriate therapeutic range. Early studies indicated that voriconazole trough values generally should be maintained above 0.50 µg/mL for prophylaxis and at 1.00 µg/mL or higher for treatment of more resistant pathogens, such as invasive molds (e.g., *Aspergillus*). (22) These cutoffs were based on in vitro data, which showed that voriconazole's minimum inhibitory concentration (MIC) ranged from 0.5 to 1 µg/mL for most pathogenic fungi.(22) More recent data suggest that higher concentrations may be required for more resistant pathogens. Two retrospective studies reported increased efficacy in patients with voriconazole concentrations above 2.0 µg/mL.(23, 24)Voriconazole has a narrow therapeutic index, and trough values greater than 6.0 µg/mL have been associated with increased liver enzyme levels. (20, 25) Other reported adverse effects associated with higher concentrations include visual disturbances (blurred vision, photophobia), hypoglycemia, electrolyte disturbances, and neurological effects (e.g., hallucinations, insomnia, and agitation).(26)

Another challenge with TDM is the identification of the appropriate pharmacokinetic parameter to monitor. The AUC:MIC ratio best correlates with voriconazole's effect; for

practical purposes, however, additional blood sampling is often not an option, and the trough concentration is routinely used as a surrogate for AUC to monitor voriconazole therapy. (27) Typically, trough concentrations are measured after five to six half-lives (steady state); however, voriconazole's half-life is dose dependent, making it difficult to identify when steady state occurs. At many institutions, trough concentrations are measured after 5 to 7 days; however, in certain circumstances, such as critically ill patients, one might consider obtaining trough concentrations earlier in treatment. Likewise, dosage adjustment varies among clinicians. At our institution, a dose increase of 1 mg/kg every 12 hours is made if the trough concentration is less than 1 µg/mL, and a dose decrease of 1 mg/kg every 12 hours if it is above 5 µg/mL. Others increase the dose by 50% if the trough concentration is less than 1 µg/mL and decrease the dose by 50% if it is greater than 5.5 µg/mL (19)

Voriconazole TDM and Efficacy

A medication with a narrow therapeutic index and nonlinear pharmacokinetics, such as voriconazole, coupled with a polymorphic drug-metabolizing enzyme such as CYP2C19 is a perfect recipe for yielding high interpersonal variability in clinical response. Table 1 summarizes the literature on how pharmacokinetic concentrations of voriconazole, especially trough concentrations, affect clinical response in different patient cohorts. Troke and colleagues conducted an observational analysis of nine phase II and phase III clinical studies completed before 2000 that included 825 patients. (28) They examined the relationship between mean voriconazole plasma concentration and clinical response. In their logistic regression analysis, they reported a nonlinear relationship between mean voriconazole plasma concentration and clinical response ($p < 0.003$), with the best response observed between 0.5 and less than 5.0 µg/mL and worse outcomes at the extremes (< 0.5 and > 5.0 µg/mL). Significantly better response was also observed in patients with candidiasis versus aspergillosis, when voriconazole was primary therapy versus salvage therapy and in patients with lower baseline bilirubin and alkaline phosphatase levels. These data suggest a strong relationship between drug concentration, particularly trough concentration, and therapeutic efficacy. However, limitations such as the study design and the combination of different patient types with a variety of predisposing conditions reduce the confidence that can be placed on the data.

In another prospective observational study, 52 adult patients treated with TDM-guided therapy were followed to assess the utility of voriconazole TDM. (19) The investigators found no correlation between voriconazole dose and trough concentrations ($r^2 = 0.07$), highlighting the large interpatient variability in voriconazole pharmacokinetics. Lack of response was greater in patients with trough concentrations < 1 µg/mL versus patients with trough concentrations > 1 µg/mL (46% vs. 12%, $p=0.02$). Lack of response in this study was defined by the authors as a persistent infection after two weeks of therapy or progressive infection after one week of therapy. To confirm these findings, a logistic regression model revealed that voriconazole trough concentration is a significant predictor of response to therapy, with a 70% probability of response at trough concentration of 1 µg/mL.

Similar findings were reported by Japanese investigators who conducted a prospective clinical study in 29 adult patients loaded with voriconazole 6mg/kg twice daily for one day,

then continued with a mean $\pm$ SD dose of 3.6 ± 0.8 mg/kg twice daily.(29) In this study, clinical response was achieved in 21 of the 29 patients (72%) who had trough concentrations ≥ 1.2 μ g/mL. Trough concentrations less than 1.2 μ g/mL were associated with treatment failure. In a retrospective study of 46 pediatric patients, Neely et al. showed a significant association between trough concentrations <1 μ g/mL and mortality.(30)

Additional small studies are also summarized in Table 2. The majority of the studies outlined in Table 1 lack ideal clinical study characteristics (e.g., prospective, randomized, multicenter, or well-powered trials); however, the consensus from these studies reflects a significant influence of trough concentration (as a surrogate for exposure) on the efficacy of voriconazole.

Voriconazole TDM and Adverse Events

In addition to efficacy, researchers have investigated the influence of voriconazole trough concentrations on adverse events. Tan et al. retrospectively analyzed safety and pharmacokinetic data from ten phase II and phase III voriconazole trials.(26) Analysis of 2925 weekly plasma voriconazole concentrations from 1053 patients revealed a relationship between voriconazole plasma concentration and visual adverse events ($p = 0.011$). Longitudinal logistic regression analysis also demonstrated a weak but statistically significant relationship between plasma voriconazole concentrations and abnormalities seen in aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin levels, but not alanine aminotransferase (ALT) level ($p = 0.171$). Receiver operating characteristic curve findings led the investigators to postulate that individual plasma voriconazole concentrations are not good predictors of liver function test (LFT) abnormalities. Comparable findings were published from a single-center observational study involving 96 adults of whom 52 were managed by TDM.(19) This study demonstrated an association between voriconazole trough concentrations > 5.5 μ g/mL and neurological adverse events ($p = 0.002$), with no significant relationship noted between voriconazole concentration and hepatotoxicity. Only one of the studies outlined in Table 2 found trough concentration to be a predictor of hepatotoxicity. (29) In summary, the limited available literature suggests that voriconazole trough concentrations may influence a patient's risk of developing neurological toxicities, but there is less evidence for the relationship between voriconazole concentration and hepatotoxicity. More studies are needed to fully appreciate whether clinically important links exist between adverse events and voriconazole trough concentration. Overall, TDM has proven beneficial in many retrospective and prospective observational studies and one randomized trial. Although it has been reported that trough concentrations greater than 1.5 μ g/mL(28) and less than 4.5 μ g/mL(31) favored clinical efficacy and reduced the risk of adverse events respectively, a target range of 1–6 or 2–6 μ g/mL appears to be the most promising to support efficacy and minimize adverse events for a majority of patients.

Voriconazole and CYP2C19

Hepatic CYP enzymes CYP2C19, CYP2C9, and CYP3A4 are responsible for the metabolism of voriconazole. The polymorphic enzyme, CYP2C19, is chiefly responsible for the conversion of voriconazole into its major inactive metabolite, voriconazole-*N*-oxide,

which accounts for about 72% of plasma metabolites.(6, 32) Furthermore, other inactive metabolites, hydroxyvoriconazole and dihydroxyvoriconazole, produced by the predominant hydroxylation pathway also seem to be under CYP2C19 influence. (6)In vitro studies indicate that the *N*-oxide metabolite might inhibit the activity of both CYP2C9 and CYP3A4.(3)The impact this may have on voriconazole concentrations cannot be predicted.

Cytochrome P450 genes encode most of the clinically relevant drug-metabolizing enzymes. CYP2C19 family 2, subfamily C, polypeptide 19 is one of the least expressed hepatic CYP2C isozymes.(33) Although it only accounts for approximately 5% of drug metabolism, (34) CYP2C19 is involved in the metabolism of agents in diverse therapeutic classes such as proton pump inhibitors, antiepileptic agents, antiplatelet agents, and antidepressants. The importance of the therapeutic agents that are under the influence of this enzyme, most notably clopidogrel, has heightened the awareness of *CYP2C19* and its genetic polymorphisms, especially the *2 allele of *CYP2C19*.(35)The genotypic inheritance of this gene varies from person to person, consequently resulting in variable CYP2C19 enzyme activity. With the exception of the normal function allele *1, most other alleles described in the literature are loss-of-function or null alleles (*2, *3, *4, *5, *6, *8) and, more recently, an increased or gain-of-function allele (*17). (36)The most common loss-of-function allele is *2 (rs4244285), a splice site mutation that leads to a premature stop codon. The *17 allele (rs12248560) is a promoter region polymorphism that is present in approximately 20%, 20%, and 5% of Caucasians, African populations, and Asians respectively.(37) As outlined in Table 3, carriers of two null alleles produce a poor metabolizer phenotype whereas carriers of one null allele and the wild-type allele, for example *1/*2, have been termed intermediate metabolizers. Subjects with two copies of the normal function allele are extensive metabolizers. There is debate in the literature about whether individuals possessing two copies of *17 or one wild-type allele and a *17 (i.e., *1/*17)should be considered ultrarapid metabolizers(35, 38, 39)or extensive metabolizers.(37)

As summarized in Table 3, depending on the racial-ethnic composition of any given population, the frequency of CYP2C19 ultrarapid metabolizers can range from approximately 1 – 33.3%, 35 – 58% for extensive metabolizers, 15 – 46% for intermediate metabolizers, and 0.87 – 19% for poor metabolizers.(35, 40)

As noted, it is the inactivation and elimination of voriconazole that is under the influence of CYP2C19. Hence, it can be inferred that poor metabolizers increase the chance of overshooting their targeted trough ranges, resulting in a higher risk of concentration-related adverse events. In contrast, ultrarapid metabolizers are at an increased risk of achieving lower than desired troughs, potentially leading to therapeutic failure and clinical deterioration.

The greatest benefit of identifying poor metabolizers may be in limiting drug interactions. In CYP2C19 poor metabolizers, voriconazole metabolism shifts to other CYP enzymes, namely CYP3A4 and CYP2C9. CYP3A4 appears to play a larger role than CYP2C9. (41–43)Therefore, both inhibitors and inducers of CYP3A4 will affect voriconazole concentrations. Shi et al. reported how erythromycin, a CYP3A4 inhibitor, increases exposure and C_{max} in a genotype-dependent manner, with the AUC and C_{max} of poor

metabolizers greater than 4 times those of extensive metabolizers. (9) Similarly, ritonavir increased voriconazole concentrations in both extensive and poor metabolizers, but to a much larger extent in poor metabolizers. (42)

CYP2C19 Polymorphisms and Voriconazole Pharmacokinetics

Several studies have evaluated the effect of *CYP2C19* genotype on the pharmacokinetics of voriconazole (Table 4). Wang et al. (44) conducted a clinical trial to assess the effect of *CYP2C19* polymorphisms on voriconazole in healthy volunteers. The study included 20 male subjects, including four ultrarapid metabolizers (**1/*17*), eight extensive metabolizers (**1/*1*), and eight poor metabolizers (**2/*2*). The pharmacokinetics of voriconazole differed across all three groups. Total body clearance was six times lower in the poor metabolizers compared with the ultrarapid metabolizers, whereas total body clearance in extensive metabolizers was approximately two times lower than that in ultrarapid metabolizers. AUC differed by the same magnitude as total body clearance across the three groups.

Weiss et al. conducted a pharmacokinetic study in 35 healthy individuals enrolled based on *CYP2C19* genotype to assess the effect of *CYP2C19* genotype on voriconazole. (7) Individuals received a single oral dose of voriconazole 400 mg. The study included 10 ultrarapid metabolizers, 9 extensive metabolizers, 11 intermediate metabolizers (**1/*2*), and 5 poor metabolizers (**2/*2*). AUC was 13.27, 16.44, 25.66, and 45.73 $\mu\text{g}\cdot\text{hr}/\text{ml}$ in ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers, respectively. Poor metabolizers demonstrated approximately 3.5 times higher AUC values compared to the ultrarapid metabolizers.

In a single-center, open-label, two-period crossover study, Scholz and colleagues enrolled 20 healthy Caucasian subjects to receive a single 400 mg dose of oral and intravenous voriconazole, assigned in a randomized fashion. (6) Patients were stratified into three groups by genotype: extensive, intermediate, and poor metabolizers. Consistent with the study by Weiss, et al, (7) this study showed that poor metabolizers demonstrated a higher AUC, approximately three times higher than that in extensive metabolizers and twice as high as that in intermediate metabolizers, irrespective of the route of administration. These differences did not attain statistical significance, although the magnitudes of differences were large. This likely represents a type 2 error (false negative) due to the small sample size and the study being underpowered to detect a difference.

Hassan and colleagues also performed a retrospective study that compared 335 patients with 747 plasma or blood samples collected during routine TDM with 51 healthy, nonsmoking subjects in hopes of developing a method to distinguish between rapid metabolism and nonadherence to voriconazole. The group of patients with observed VCZ concentrations of 0.2 $\mu\text{g}/\text{mL}$ or lower during routine TDM was reported to have a significantly higher frequency of ultrarapid metabolizers compared to the control group ($p=0.01$). (39).

In another retrospective analysis, 37 Japanese children were genotyped for *CYP2C19* **2*, **3*, and **17* and subsequently analyzed with previously measured voriconazole plasma concentrations. (38) The authors reported that all patients with trough concentrations greater than 5 $\mu\text{g}/\text{mL}$ (units corrected) were either poor or intermediate metabolizers. Significantly

higher troughs were observed in the poor and intermediate metabolizers compared with the extensive and ultrarapid metabolizers ($p = 0.004$). This report echoes the findings in the other studies discussed above in a younger patient population.

Pharmacokinetic end points rather than clinical end points were measured in these studies, making it difficult to measure the impact that a specific *CYP2C19* genotype may have on patient outcomes. Overall, *CYP2C19* genotype explains part of the interindividual variability related to voriconazole concentrations. Poor metabolizers might be at higher risk of adverse events because of higher trough concentrations, whereas ultrarapid metabolizers might have subtherapeutic trough concentrations.

***CYP2C19* Polymorphisms and Voriconazole Clinical Outcomes**

The impact of *CYP2C19* genotype on voriconazole pharmacokinetics has been demonstrated and replicated in numerous studies. (7, 9, 10, 39, 44, 45) The question remains whether this pharmacokinetic effect translates to clinical outcomes. Malingre and associates reported an incident regarding a 62-year-old Caucasian female with acute myeloid leukemia who underwent voriconazole treatment for suspected disseminated fungal infection.(46)A loading dose of oral voriconazole 400 mg twice daily was administered for one day then continued at 200mg twice daily. Her trough concentration after five days was $< 0.3 \mu\text{g/ml}$, prompting an immediate switch to intravenous dosing. A loading dose of 6 mg/kg was initiated, and the patient was maintained on 5mg/kg twice daily. After four days of intravenous therapy, the trough was determined to be $0.5 \mu\text{g/mL}$. This stimulated an inquiry into other modulators of low voriconazole concentrations, beginning with *CYP2C19* genotyping. The patient was found to have a *CYP2C19**17/*17 genotype, indicating an ultrarapid metabolizer. The patient was also comedicated with carbamazepine, a strong inducer of CYP3A4 and to a lesser extent *CYP2C19*. The patient's genotype, coupled with the presence of carbamazepine, was ruled to be the source of her low voriconazole concentrations. The patient's antifungal therapy was changed to intravenous caspofungin and later to oral posaconazole on discharge.

In Matsumoto and colleagues' prospective clinical study, the extent of the impact of *CYP2C19* polymorphisms on voriconazole adverse events, particularly liver abnormalities, was also assessed in 29 Japanese patients.(29) The authors did not find a significant association between *CYP2C19* and hepatotoxicity, although it can be argued that the genotype-guided dosing (higher doses in extensive metabolizers) might have undermined the *CYP2C19* genetic influence on the adverse events. Their finding, however, is in agreement with a retrospective study by Levin et al. conducted in 86 immunocompromised patients with liver abnormalities.(47)Although plasma concentrations were not reported in that study, the researchers concluded that *CYP2C19* did not predict voriconazole-induced hepatotoxicity.(48)Other retrospective studies evaluating both children and adult patients(10, 38, 48) also published conclusions that are in agreement with the aforementioned studies.

In all, *CYP2C19* genotype has been demonstrated to be a predictor of voriconazole pharmacokinetic interpatient variability, but there are essentially no data on the genotype-clinical outcomes relationship.

Genotype and TDM-guided Dosing of Voriconazole: Are We There Yet?

The role TDM plays in voriconazole therapy is yet to be firmly established. Although the aforementioned target range for voriconazole trough concentrations (1–6 or 2–6 µg/ml) is reasonable, no consensus guidelines in the United States or Europe exist to direct voriconazole dosing, nor has a therapeutic range been defined.(49, 50)

Voriconazole is indicated in very serious fungal infections such as invasive aspergillosis, fluconazole-resistant invasive candidiasis, candidemia in non-neutropenic patients, and other serious infections caused by *Scedosporium* and *Fusarium*.(51) In many of the patient populations in whom voriconazole is prescribed, use of this drug can be anticipated, so genotyping in advance is a possibility to aid in the initial dose selection. Given that the greatest risk of voriconazole is therapeutic failure due to inadequate concentrations, *CYP2C19* genotyping has the greatest potential benefit in ultrarapid metabolizers (carriers of *CYP2C19*17* allele). Hassan et al. observed low trough concentrations in ultrarapid metabolizers in their study and concluded that the *CYP2C19*17* polymorphism is a major player in determining the outcome of voriconazole therapy. (39) Subtherapeutic trough concentrations have been historically associated with voriconazole therapeutic failure, which, in immunocompromised and/or severely ill populations, can lead to extension of hospital stay, escalation of therapy, and potentially fatal complications. Apart from ultrarapid metabolizers, patients presenting with probable or proven invasive aspergillosis and other serious fungal infections will potentially benefit from preemptive *CYP2C19* genotyping for voriconazole therapy. Furthermore, TDM will theoretically be advantageous in patients receiving treatment doses of voriconazole and those receiving concomitant CYP3A4, 2C9, or 2C19 enzyme inducers such as carbamazepine (46), rifabutin, and glucocorticoids.

The detection of at-risk patients prior to administration of the voriconazole loading dose would allow the clinician to escalate the dose and monitor patients closely for any signs of therapeutic failure, such as deterioration of clinical signs and symptoms, and worsening of infection. This is especially critical since studies have shown that early administration of the optimal therapy at accurate doses for invasive infections decreases mortality.(52–54) Given the reversible nature of adverse events due to voriconazole, (19, 25) as opposed to the detrimental effects of treatment failure, dose escalation in *CYP2C19* ultrarapid metabolizers may provide more benefits than harm in the long run. Studies testing this hypothesis are needed. In this scenario, it is not genotype “versus” TDM, but how to use genotype “and” TDM in a complementary fashion to ensure optimal therapy—with genotype being used to guide initial dose selection and TDM used to refine the dosing. Additionally, the Royal Dutch Association for the Advancement of Pharmacy’s Pharmacogenetics Working Group has developed genome-informed therapy guidelines for numerous medications including voriconazole.(55) In their 2011 update, the Pharmacogenetics Working Group made no

recommendations for ultrarapid metabolizers; however, the group recommended serum concentration monitoring or TDM for poor and intermediate metabolizers.(56)

CYP2C19 genotyping kits are commercially available for use. The AmpliChip CYP450 Test (Roche Molecular Systems Inc., Pleasanton, CA) was approved in 2005, and the DMET Plus Panel (Affymetrix, Inc., Santa Clara, CA) can both test for *CYP2C19* polymorphisms. (57) At our institution, *CYP2C19* testing is currently being carried out on a customized pharmacogenomics genotyping array(58) for patients undergoing percutaneous coronary intervention or left heart catheterization. The results from the *CYP2C19* testing, which is reported in the patient's electronic medical record, provides guidance to the University of Florida Health interventional cardiologists to choose the best-suited antiplatelet agent for their patients. This practice can be witnessed at other institutions across the country for clopidogrel and other pharmacogenetically influenced therapies such as warfarin, thiopurine, codeine, and simvastatin.(59–62) The cost associated with gene sequencing and genotyping has been declining over the years.(63)A cost-effectiveness study reported an average fee of \$310 for *CYP2C19* genotyping. (64)Moreover, the September 2013 update of the Centers for Medicare and Medicaid Services Clinical Laboratory Fee Schedules provides a state-specific price ranging from \$183.68 to \$305. (<http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Gapfill-Pricing-Inquiries.html>).Aside from the potential costs of genotyping, which might prove challenging to certain institutions, lack of dosing recommendations for *CYP2C19*-guided voriconazole therapy is also a pressing concern. Matsumoto conducted a pharmacokinetic analysis on voriconazole plasma concentrations collected from 29 Japanese patients and concluded that extensive metabolizers of *CYP2C19* (*1/*1) should be initiated on approximately 4mg/kg/dose every 12 hours, whereas non-wildtypes should be dosed at roughly 3mg/kg/dose every 12 hours. (65) This is the only study attempting to devise a dosage recommendation for voriconazole based on *CYP2C19*polymorphisms. To the best of our knowledge, there are no pending studies focusing specifically on *CYP2C19*-guided voriconazole dosing. Further research is warranted to derive dosing recommendations according to genotype before proceeding to use in the clinical setting.

Although there are essentially no data on the relationship between *CYP2C19* genotype and clinical outcomes, there is enough evidence to support the relationship between *CYP2C19*genotype and voriconazole pharmacokinetics. All the studies to date suggest differences in voriconazole pharmacokinetics, although a few failed to achieve statistical significance for certain comparisons, likely due to the very small sample sizes of those studies. Given the association between *CYP2C19* genotype and voriconazole concentrations, and also between voriconazole concentrations and clinical outcomes, particularly efficacy, it seems reasonable to suggest a potential role for *CYP2C19* genotype to guide initial voriconazole dosing, followed by TDM to increase the probability of achieving efficacy while avoiding toxicity.

Conclusion

Presently, TDM represents an important clinical tool for individualizing therapy to achieve optimal patient outcomes with voriconazole. Trough concentrations are known to play a key

role in efficacy and likely the adverse events of voriconazole, and *CYP2C19* genotype has been proven to influence trough concentrations. Although additional data are needed, it appears that there is great potential for initial voriconazole dose selection to be guided by *CYP2C19* genotype. This potentially can reduce the chance for subtherapeutic voriconazole concentrations, reducing the risk for therapeutic failure and thus further optimizing therapy. As additional data accrue regarding voriconazole dosing for specific *CYP2C19* genotypes and as clinical pharmacogenetic testing becomes widely available, *CYP2C19* genotype-guided voriconazole dosing likely will become more common. Additionally, voriconazole TDM will continue to provide patient-specific dosing recommendations, leading to more effective antifungal regimens.

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Table 1
Summary of Studies Evaluating the Relationship Between Voriconazole Trough Concentration and Clinical Efficacy

Authors	Study Design	Patient Population	Intervention	Demonstrated Voriconazole Concentration-Response Relationship	Conclusions
Pascual et al 2008(19)	Single-center, observational study (patients receiving TDM were evaluated prospectively; patients not receiving TDM were evaluated retrospectively)	52 adults (of 96 study patients) had VCZ dosages adjusted with TDM (all were Caucasian)	Various VCZ doses for treatment of various fungal infections	Yes	No correlation found between VCZ dose and trough concentration ($r^2 = 0.07$); lack of response in patients with VCZ trough $1\mu\text{g/mL}$ vs. $> 1\mu\text{g/mL}$: 46% vs. 12% ($p = 0.02$); logistic regression showed that VCZ trough concentration is a significant predictor of response to therapy: 70% probability of response at trough of $1\mu\text{g/mL}$
Denning et al 2002(25)	Open-label, noncomparative, multicenter study	137 patients aged 14yrs with invasive aspergillosis	Two loading doses of VCZ 6mg/kg i.v., then 3mg/kg i.v. q12h, then 200mg p.o. twice/day for 4 – 24 weeks	Yes	60% of patients with VCZ troughs $< 0.25\mu\text{g/mL}$ failed therapy; 40% had either stable response or deteriorated then improved after dose escalation
Dolton et al 2012(13)	Multicenter, retrospective study	201 adults with at least one administered VCZ dose and one VCZ concentration	85% received treatment doses vs. 15% prophylactic doses; 97 patients received p.o. VCZ, 76 received i.v. and p.o. VCZ, and 28 received i.v.. VCZ	Yes	Median VCZ concentration was significantly lower in patients who failed therapy ($0.9\mu\text{g/mL}$) vs. patients who had treatment success ($2.1\mu\text{g/mL}$, $p < 0.05$); VCZ concentration was a significant predictor of treatment success; VCZ concentration $1.7\mu\text{g/mL}$ minimized the incidence of treatment failure ($p < 0.05$)
Smith, J et al. 2006(23)	Retrospective study	28 patients who received VCZ and were monitored for therapeutic concentrations due to disease progression or adverse events	All patients received a VCZ loading dose and 200mg p.o. twice/day for at least 2 weeks	Yes	100% of patients who had treatment failures ($n=17$) had VCZ concentrations $< 2\mu\text{g/mL}$; VCZ concentration $< 2\mu\text{g/mL}$ prompted dose increases in 11 patients, and 8 of the 11 patients survived; disease progression was significantly associated with VCZ concentration ($p < 0.025$); 100% (10/10) of patients with random concentrations $> 2.05\mu\text{g/mL}$ had positive clinical responses; 8/18 patients died who had random concentrations $< 2.05\mu\text{g/mL}$
Matsumoto et al 2009(29)	Prospective clinical study	29 Japanese patients	6mg/kg twice/day for 1 day, then $3.6 \pm 0.8\text{mg/kg}$ twice/day	Yes	VCZ response was observed in 21/29 patients (72%) who had troughs $1.2\mu\text{g/mL}$; troughs $< 1.2\mu\text{g/mL}$ were associated with treatment failure
Ueda et al 2009(66)	Prospective clinical study	34 adult Japanese patients with hematological disorders	Investigators conducted TDM and analyzed VCZ plasma concentration s; p.o. VCZ was initially used according to the manufacturer 's recommendation; if p.o. was not tolerated,	Inconclusive findings	100% of patients who had troughs $> 2\mu\text{g/mL}$ responded vs. 33.3% of patients with troughs $< 2\mu\text{g/mL}$ failed therapy; recommended trough range: 2–6 $\mu\text{g/mL}$

Authors	Study Design	Patient Population	Intervention	Demonstrated Voriconazole Concentration-Response Relationship	Conclusions
patients were switched to i.v. VCZ patients were switched to i.v. VCZ					
Troke et al 2011(28)	Observational analysis of data from 9 phase II and phase III clinical trials completed before 2000	825 patients receiving VCZ for primary or salvage therapy	Various VCZ doses; patients had recorded clinical responses and VCZ plasma concentrations from a total of 3052 plasma samples	Yes	Logistic modeling revealed a significant nonlinear relationship between mean VCZ plasma concentration and clinical response (p<0.003); probability of maximum clinical response was best with trough:MIC ratio of 2–5; better efficacy observed with primary therapy, yeast infections, candidiasis, and lower baseline bilirubin and alkaline phosphatase levels
Neely et al 2010(30)	Retrospective Study	46 pediatric patients from a pediatric referral hospital	Various VCZ doses; patients had recorded clinical responses and VCZ plasma concentrations from a total of 227 concentrations	Yes	Each VCZ trough concentration <1 µg/mL was associated with a 2.6-fold increase in the odds of death

TDM=therapeutic drug monitoring, VCZ=voriconazole

Table 2
Summary of Studies Evaluating the Relationship Between Voriconazole Concentration and Adverse Events

Authors	Study Design	Patient Population	Intervention	Demonstrated Voriconazole Concentration – Response Relationship	Conclusions
Matsumoto et al 2009 (29)	Prospective clinical study	29 Japanese patients	6mg/kg twice/day for 1 day, then 3.6 ± 0.8mg/kg twice/day	Yes	Hepatotoxicity (CTCAE v.3) ** associated with troughs > 4 µg/mL in 9 of 12 patients (p < 0.01); trough was a predictor of hepatotoxicity
Narita et al 2013(38)	Retrospective analysis	37 Japanese children	Patients received i.v. VCZ at a median dose of 7.7mg/kg/day (range 3.5 – 18.8 mg/kg/day); patients were genotyped for <i>CYP2C19</i> *2, *3 and *17 alleles	No	Severe hepatotoxicity was not associated with high voriconazole exposure
Pascual et al 2008(19)	Single-center, observational study (patients receiving TDM were evaluated prospectively; patients not receiving TDM were evaluated retrospectively)	52 adults (of 96 study patients) had VCZ dosages adjusted with TDM (all were Caucasian)	Various VCZ doses for treatment of various fungal infections	Yes	Neurologic AEs occurred more frequently in patients with troughs > 5.5µg/mL vs patients with troughs 5.5µg/mL (p=0.002) after 1 week of therapy; logistic regression confirmed significant association between VCZ trough concentration and neurotoxicity: odds ratio after a 2-fold increase of VCZ concentration = 284 (95% confidence interval 0.96– 84,407, p=0.05); 15% probability of neurotoxicity at trough of 5.5µg/mL vs. 90% at 8µg/mL; trend showed increased hepatotoxicity in patients with troughs > 5.5µg/mL vs patients with troughs 5.5µg/mL: 19% vs 8% (p=NS)
Denning et al 2002 (25)	Open-label, noncomparative, multicenter study	137 patients aged 14yrs with invasive aspergillosis	Two loading doses of VCZ 6mg/kg i.v., then 3mg/kg i.v. q12h, then 200mg p.o twice/day for 4 – 24 weeks	Inconclusive findings	6 of 22 patients (27.3%) with VCZ troughs > 6µg/mL developed abnormal liver function (>3 or 5 times the upper limit of normal) or liver failure (not defined in this study)
Dolton et al 2012 (13)	Multicenter, retrospective study	201 adults with at least one administered VCZ dose and one VCZ concentration	85% received treatment doses vs. 15% prophylactic doses; 97 patients (48%) received p.o. VCZ, 76 received i.v. and p.o. VCZ, and 28 received i.v. VCZ	Yes	21 patients (10.5%) had neurotoxic AEs (visual or auditory hallucinations); median trough was higher in patients with AEs vs those without AEs: 6.5 vs. 1.6 µg/mL (p < 0.01); trough concentration < 5µg/mL was found to minimize neurological AEs (p < 0.001); all AEs resolved after VCZ discontinuation or dosage reduction
Tan et al 2006(26)	Retrospective clinical study; analysis of safety and pharmacokinetic data	1053 patients (81.8% Caucasian, 9.8% African-American, 8.5% Asian)	VCZ empiric and treatment doses; 1053 patients had a	Yes	Relationship between plasma VCZ concentration and visual AEs (p = 0.011); weaker but statistically significant association with VCZ plasma

Authors	Study Design	Patient Population	Intervention	Demonstrated Voriconazole Concentration – Response Relationship	Conclusions
	from 10 phase II and phase III therapeutic trials from 10 phase II and phase III therapeutic trials		total of 2925 plasma voriconazole concentrations		concentration and AST, ALP, or bilirubin level, but not ALT level, abnormalities; 1-µg/mL elevation of VCZ concentration increased odds of LFT abnormalities from 1.07 to 1.17; individual VCZ plasma concentration cannot predict subsequent LFT abnormalities according to receiver operating characteristic curve analysis

VCZ=voriconazole, TDM=therapeutic drug monitoring, AE=adverse event, NS=not significant, AST=aspartate aminotransferase, ALP=alkaline phosphatase, ALT=alanine aminotransferase, LFT=liver function test

** National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Table 3
CYP2C19 Genotypes with Corresponding Phenotypes for Various Racial-Ethnic Groups (35, 40, 67, 68)

<i>CYP2C19</i> Genotype	Phenotype	Population Frequencies				
		Caucasian	African-American	Hispanic	Ashkenazi Jewish	Asian
*1/*17, *17/*17	Ultrarapid metabolizers	31.2%	33.3%	18.3%	24.6%	~ 1%
*1/*1	Extensive metabolizers	42%	39%	58%	46%	35 – 43%
*1/*2, *1/*3, *2/*17, *3/*17	Intermediate metabolizers	19%	15%	20%	22%	43 – 46%
*2/*2, *2/*3, *3/*3	Poor metabolizers	2.8%	6.7%	0.87%	1.8%	14 – 19%

Table 4
Summary of Studies Evaluating the Association Between *CYP2C19* Polymorphisms and Voriconazole Concentration

Authors	Study Design	Patient Population	Intervention	Demonstrated <i>CYP2C19</i> Voriconazole Concentration Relationship	Conclusions
Weiss et al 2009(7)		35 healthy, drug-free individuals	Single VCZ400-mg dose; genotyped for <i>CYP2C19</i> *2, *3 and *17	Yes	AUC differed significantly between <i>CYP2C19</i> phenotype groups: 3 times greater in PMs vs. EMs ($p < 0.01$); <i>CYP2C19</i> genotype accounts for 49% of VCZ's AUC variability after multiple regression analysis ($p < 0.0001$).
Shi et al. 2010 (9)	Single-center, randomized, crossover trial	18 Chinese male volunteers	Crossover between placebo and erythromycin 500mg t.i.d. for 4 days + VCZ 200mg given 30 min after 10th erythromycin dose	Yes	Significant differences in $t_{1/2}$ AUC ₀₋₂₄ , and AUC _{0-infinity} between PMs, IMs, and EMs ($p < 0.05$), with PMs having the highest concentrations and longest half-life; authors recommended dosage reduction in PMs and IMs for VCZ monotherapy
Lee et al 2011(69)	Open-label, single- and multiple-dose, parallel-group study	18 healthy Korean male volunteers	VCZ 200mg i.v. x 1 dose, then a 1-wk washout followed by a VCZ 200-mg p.o. single dose, then 200 mg b.i.d. for 5 days	Yes	Mean AUC _{inf} of IMs and PMs after i.v. dose was 1.5 and 3.4 times higher than EMs respectively ($p = 0.002$); these findings exhibited similar differences after p.o. administration ($p = 0.002$); mean troughs were 2.8 times higher in IMs than in EMs ($p = 0.005$) and 5.1 times higher in PMs than in EMs ($p = 0.008$)
Narita A et al 2013(38)	Retrospective analysis	37 Japanese pediatric patients	Patients received i.v. VCZ; genotyped for <i>CYP2C19</i> *2 *3, and *17	Yes	All patients with troughs $> 5 \mu\text{g/mL}$ (units corrected) were PMs or IMs; troughs were also higher in PMs and IMs compared with EMs and UMs ($p = 0.004$); two UMs had very low concentrations (0.09 and 0.12 $\mu\text{g/mL}$ (units corrected); VCZ plasma concentration in children is significantly correlated with <i>CYP2C19</i> phenotype.
Wang et al 2009(44)	Controlled, open-label	20 unrelated, healthy Han Chinese male volunteers	Single 200- mg p.o. dose of VCZ after being smoking, coffee, alcohol, and medication free for 1 week	Yes	C_{max} in UMs was higher than in EMs ($p = 0.036$) and PMs ($p = 0.035$); $t_{1/2}$ of UMs was 51% of $t_{1/2}$ of PMs ($p = 0.002$); UMs AUC _{0-infinity} was 48% and 85% lower than that of EMs ($p = 0.001$) and PMs ($p < 0.001$), respectively; significant differences in $t_{1/2}$, AUC, CL/F values were noted among all three groups (EMs, PMs, and UMs)
Ikedo et al 2004(45)	Observational study	12 healthy Japanese subjects	VCZ 200mg or 300mg p.o. b.i.d. for 10 days	Yes	VCZ plasma concentration was 3 times higher in PMs than in EMs
Lei et al 2009(70)	Randomized, 2-phase, crossover study	14 healthy Chinese males: 7Ms and 7 PMs	VCZ 200-mg single dose in control group; treatment group had ginkgo biloba 120mg b.i.d. for 12 days	Yes	PMs had 4 times higher AUC and 4 times lower CL/F than EMs ($p < 0.05$ for both); <i>CYP2C19</i> determines pharmacokinetics of VCZ; ginkgo biloba (inhibitor of <i>CYP2C19</i> and <i>CYP3A4</i>) did not significantly affect the pharmacokinetics of single- dose VCZ

Authors	Study Design	Patient Population	Intervention	Demonstrated CYP 2C19 Voriconazole Concentration Relationship	Conclusions
Hassan et al 2011(39)	Retrospective analysis	335 patients with 747 plasma or blood samples collected during routine TDM vs. control group of 51 healthy, nonsmoking subjects	Single dose of VCZ 400mg i.v. or p.o. was administered to controls; plasma samples were analyzed from patients who received i.v. VCZ and had observed VCZ concentrations of 0.2 µg/mL during routine TDM; genotyped for CYP2C19*2, *3, and *17	Yes	TDM group with low VCZ concentrations had significantly higher frequency of UMs compared with the control group (p=0.01)
Scholz et al 2009(6)	Single-center, open-label, two-period crossover study	20 healthy Caucasians	Single doses of VCZ 400mg p.o. and i.v. assigned in a randomized order; genotyped for CYP2C19*2 and *3	Yes	AUC in PMs was 3 times higher than in EMs and 2 times higher than in IMs regardless of route of administration; PMs had bioavailability of 94.4% vs. 75.2% in EMs (p=NS); PMs had 3–4 times slower CL/F than EMs (p < 0.05)
Berge et al 2011(40)	Retrospective exploratory study	24 Caucasian lung transplant recipients with cystic fibrosis who received VCZ therapy	Treatment and prophylactic doses of VCZ	Yes	Daily doses were significantly higher in *17 carriers (35% more; 14.1 ± 3.9 mg/kg) and EMs (29.6% more; 13.6 ± 3.2 mg/kg) vs. IMs (9.5 ± 1.7 mg/kg) (p < 0.05); multivariate analysis revealed that CYP2C19 accounted for 38% of maintenance (steady state) dose variability; time to achieve therapeutic range was significantly longer in carriers of *2 and *17 compared with EMs (p=0.012); mean time to therapeutic range 7 ± 5 days (range 2–0 days); CYP2C19 polymorphisms accounted for 38% of maintenance dose variability according to multivariate analysis; authors recommended CYP2C19 genotyping prior to VCZ therapy initiation to help determine initial dose to promptly achieve therapeutic plasma concentrations without out-of-range troughs

AUC=area under the concentration time curve; PM=poor metabolizer; EM=extensive metabolizer, VCZ=voriconazole, IM=intermediate metabolizer, UM=ultrarapid metabolizer, t_{1/2}=half-life, CL/F=clearance, TDM=therapeutic drug monitoring, NS=not significant