Pharmacogenetic Directed Dosing Leads to Optimized Voriconazole Levels in Pediatric Patients Receiving Hematopoietic Stem Cell Transplants

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Disclosures

- I have no conflicts of interest to disclose

Learning Objective

- Recognize the impact of pharmacogenetic directed dosing on the achievement of voriconazole levels

Voriconazole Mechanism of Action

- Voriconazole is an extended spectrum triazole antifungal agent
- Mechanism of action:
  - Inhibition of 14-α-sterol demethylase, thus impairing the synthesis of ergosterol for the cytoplasmic membrane

Voriconazole Spectrum of Activity

	Organism	5-FC	Fluc	Vori	Posa	Itra	AMB	ECH
Yeasts	C. albicans	+	+	+	+	+	+	+
	C. tropicalis	+	+	+	+	+	+	+
	C. parapsilosis	+	+	+	+	+	+	+/-
	C. lusitaniae	-	+	+	+	DD	-	+/-
	C. glabrata	+	DD	DD	DD	DD	+	+
	C. krusei	+/-	-	+	+	+/-	+	+
	Cryptococcus spp	+	+	+	+	+	+	-
Dimorphic fungi	Histoplasmosis	-	+	+	+	+	+	-
	Blastomycosis	-	+	+	+	+	+	-
	Aspergillosis	-	-	+	+	+	+	+
Molds	Zygomycetes	-	-	-	+	-	+	-
	Fusarium spp	-	-	+	+/-	-	+	-
	Scedosporium spp	-	-	+	-	-	+/-	-

5-Fc=flucytosine; Fluc=Fluconazole; Vori=Voriconazole; Posa=Posaconazole; Itra=Itraconazole; AMB=Amphotericin B; ECH= Echinocandins; DD= dose dependent

John Hopkins Antibiotic Guide Online
Biol Blood Marrow Transplant. 2004; 10:73-90

Voriconazole Pharmacokinetics

Pharmacokinetic parameter	Pediatrics	Adults
Bioavailability	45-80%	96%
Volume of Distribution	4.6 L/kg	1.1-1.2 L/kg
Metabolism	CYP2C19 CYP2C9 CYP3A4	CYP2C19 CYP2C9 CYP3A4
Clearance	1.1 - 24 mL/min/kg	166 – 216 mL/min
Elimination (T ½)	3.1-29.2 hours	6 hours

Clin Infect Dis. 2010; 50: 27-36
Antimicrob Agents Chemother. 2009:53: 935-44
Antimicrob Agents Chemother. 2010:54: 4116-4123
Antimicrobial Agents and Chemother; 56:3032-3042

Voriconazole Efficacy and Safety

- Associated with the AUC/MIC ratio
- Low voriconazole exposure and trough concentrations have been linked to therapeutic failure in both treatment and prophylactic setting
- High voriconazole plasma concentrations (**> 5.5 mg/L- 6 mg/L)** have been linked to various adverse effects

Clin Infect Dis 2002:563-571
Agents Chemother. 2012:56:3032-3042
Bone Marrow Transplantation:2007:451-56
Ther Drug Monit. 2012:77
Eur J clin Microbiol Infec Dis. 2011: 283-287

Our Pilot Study

- Patients for whom voriconazole was determined to be a suitable antifungal prophylaxis underwent testing for CYP2C19 genotype
- Voriconazole was started at 5 mg/kg/dose q12h
- Prior (0.5 to 1 hour) to the 9th dose a voriconazole serum concentration was drawn
  - Target trough: 1-5 mg/L
- Doses were adjusted per protocol until target range was achieved

Our Pilot Study

- Adjustments made to achieve target voriconazole levels:

Level < 1 mg/L
- Increase daily dose by 25% (level to be repeated prior to 9th new dose)

Levels ≥ 1 mg/L and ≤ 5 mg/L
- Make no changes to therapy (repeat level every week x 1 month, then every 2 weeks for months 2-3)

Levels > 5 mg/L
- Two doses held and then restarted at 50% of the previous dose (level to be repeated prior to 9th new dose)

Our Pilot study results

Results	Number (range or %)
Total number of patients	25
Median age in years	7 (0.8-23)
CYP2C19 genotyping	
Extensive metabolizers	17 (68%)
Intermediate Metabolizers	3 (12%)
Poor metabolizers	2 (8%)
Not tested	3 (12%)

Our Pilot study results

Results	Median (range)
Voriconazole serum concentrations	1.1 mg/L (<0.1-6.1)
Days to therapeutic level	
Overall	30 (3-65)
Extensive metabolizers	30 (5-65)
Intermediate metabolizers	51.5 (47-56)
Poor metabolizers	11 (11)

Our Pilot Study Results

Dose of voriconazole required to reach therapeutic level (mg/kg/ day)	
Overall	**12.5 (5.4-36.3)**
Extensive metabolizers	**13.3 (5.4-36.3)**
Intermediate metabolizers	**16.3 (11-18.9)**
Poor metabolizers	**10.6 (9.8-11.4)**

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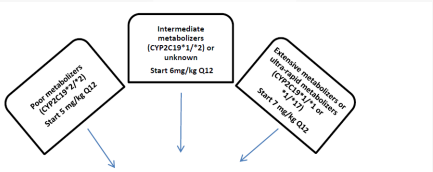
Background

- **Aims**
  - **Primary**: Determine if genotype directed initial voriconazole dosing would result in decreased time to reach desired target range
  - **Secondary**: Determine if the incidence of adverse effects increase as a result of higher initial dosing

Methods

- All patients receiving voriconazole prophylaxis at our institution between June 2013 and September 2013 were followed prospectively
- All patients were genotyped for CYP2C19 polymorphisms
- Initial voriconazole dose decided on based on patients genotype
- Dose changes made based on protocol

Methods



Voriconazole trough serum concentration	Adjustment to be made
Level < 0.1 mcg/mL	Increase dose by 50%; recheck level prior to 9th new dose
0.1 mcg/mL ≤ **Level** < 1 mcg/mL	Increase dose by 25%; recheck level prior to 9th new dose
1 mcg/mL < **Level** ≤ 5 mcg/mL	No changes to dose; recheck level in one week
Level > 5 mcg/mL	Hold 2 doses restart at lower dose (25-50% reduction)

ASBMT CIBMTR

Results

	Number (range or %)
Total number of patients	21
Median age in years	10.7 (0.8-26.4)
CYP2C19 genotyping	
Extensive metabolizers	11 (52.4%)
Intermediate Metabolizers	7 (33.3%)
Poor metabolizers	0 (0%)
Ultra-rapid metabolizers	2 (9.5%)
Unknown	1 (4.8%)

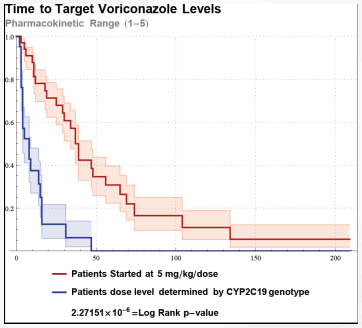
ASBMT CIBMTR

Results

	Median (range)
Voriconazole serum concentrations	1.3 mg/L (0.1-5.3)
Days to therapeutic level	
Overall	8 (2-47)
Extensive metabolizers	7 (3-47)
Intermediate metabolizers	6 (3-16)
Poor metabolizers	N/A
Ultra-rapid metabolizers	8.5 (8-9)

ASBMT CIBMTR

Results



Conclusions

- Our results show that CYP450-2C19 genotype directed initial dosing and subsequent dose adjustments per the algorithm can successfully achieve prophylactic voriconazole target levels in pediatric patients undergoing HSCT
- Strongly recommend genotype directed dosing in HSCT and establishment of center-specific protocol

Audience Response Question

RJ is a 5-year-old male being transplanted for hemophagocytic lymphohistiocytosis (HLH). His primary physician is writing his transplant preparative and supportive medication orders now. The physician calls you to determine what dose of voriconazole they should start for RJ's fungal prophylaxis. You look in his chart and discover RJ's CYP2C19 genotype is *2/*2. What do you recommend?

A. Start voriconazole 4 mg/kg/dose every 12 hours. Draw a voriconazole level prior to the 4th dose
B. Start voriconazole 5 mg/kg/day divided every 12 hours. Draw a voriconazole level prior to the 4th dose
C. Start voriconazole 5 mg/kg/dose every 12 hours. Draw a voriconazole level prior to the 9th dose
D. Start voriconazole 9 mg/kg/dose every 12 hours. Draw a voriconazole level prior to the 9th dose

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Questions?

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