Investigational Agent VT-1161 Has a Low *In Vitro* Potential for the Emergence of Stable Resistance in *Candida* spp.

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Intro and Objectives

Increases in drug resistance have been reported for many antifungal agents. VT-1161, a novel CYP51 inhibitor in clinical development, has shown a promising cross-resistance profile. In an initial *in vitro* passage study, *C. albicans* (CA) 36082 was less prone to acquiring resistance to VT-1161 than to fluconazole (FLU). Passage studies were expanded to include 3 additional CA strains, and 1 strain each of *C. glabrata* (CG) and *C. tropicalis* (CT). We present the summary for all strains tested, with specific data shown for CA 24433 as an example.

Materials & Methods

The published *in vitro* CA passage system (Calvet et al., 1997) was modified by growing CA 90028, MYA2876, and 24433, and CT 750 in 8X and 32X MIC concentrations (and CG 2001 in 4X MIC concentration) of VT-1161 or FLU for 45 days in culture (containing YNB medium). When cultures reached ~10^8 organisms/ml, separate aliquots were collected for MIC testing and to pass into fresh medium containing the same concentration of drug. MICs were determined at 50% inhibition of growth relative to no-drug control in YNB medium (Calvet et al., 1997) or in RPMI medium (CLSI M27-A3) Isolates with higher MICs were tested for cross-resistance against different classes of antifungal agents, and also for stability of the elevated MICs by culturing in drug-free YNB medium.

Results

Table 1. Outcomes of *Candida* spp. *In Vitro* Passage Studies with VT-1161 and FLU

Species Isolate	VT-1161				Fluconazole			
	Wild-type MIC* (μg/ml)	Resistance Emergence	Resistance Stability	Cross-Resistance	Wild-type MIC* (μg/ml)	Resistance Emergence	Resistance Stability	Cross-Resistance
CA 90028	0.03	No	-	-	1	No	-	-
CA MYA2876	0.015	No	-	-	0.5	No	-	-
CA 24433**	0.03	133-fold ⇑	2-4-fold ⇑	No	2	64-fold ⇑	64-fold ⇑	Yes
CT 750	0.25	8-fold ⇑	No	No	4	64-fold ⇑	8-fold ⇑	Yes
CG 2001	4	≥4-fold ⇑	≥4-fold ⇑	Yes	64	≥16-fold ⇑	≥16-fold ⇑	Yes

*Resistance and stability passage and MIC measurements used YNB medium (Calvet et al., 1997); cross-resistance MIC measurements used RPMI medium (CLSI M27-A3). **Specific data shown in Figure 1 and Table 2.

Figure 1. Resistance Passage and Stability for CA 24433. Shaded areas in stability curves represent WT MIC values.

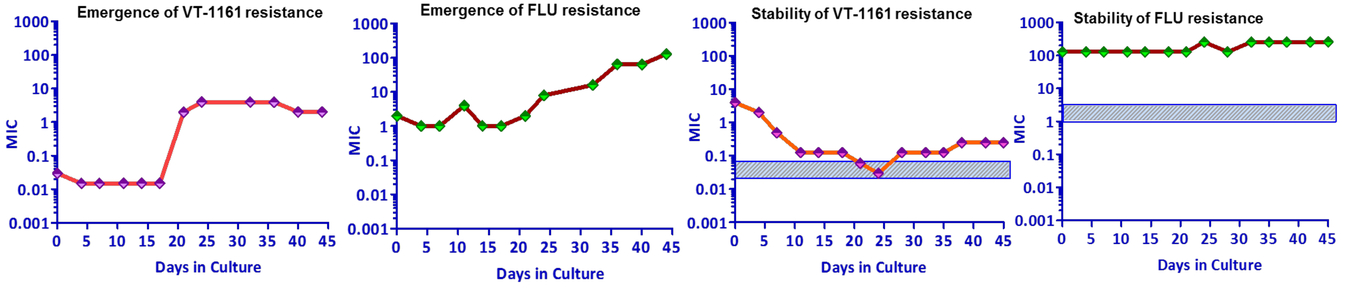

Table 2. Cross Resistance Profile of Isolates from CA 24433 Resistance Passage Study

CA 24433 strain	MIC*, μg/ml				
	VT-1161	FLU	VOR	AMB	CAS
Parental	0.007	0.25	0.015	1.0	0.12
FLU resistant	16	256	16	2.0	0.25
VT-1161 resistant	0.03**	0.25	0.03	2.0	0.12

*MICs measured in RPMI medium (CLSI M27-A3). **4-fold elevation of MIC less pronounced in RPMI medium than in YNB medium (133-fold, see Figure 1).

Conclusions

- Emergence of stable, cross-resistant elevation of VT-1161 MICs occurred in only 1/5 *Candida* spp. in tissue-culture passage studies.
- In contrast, emergence of stable, cross-resistant elevation of fluconazole MICs occurred in 3/5 species examined.
- In conjunction with the initial study using CA 36082, VT-1161 has displayed a relatively low *in vitro* potential for emergence of resistance.