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Abstract (poster session)

Efficacy and reproducibility of the novel fungal Cyp51 inhibitor VT-1161 against invasive candidiasis caused by resistant Candida albicans

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Objective: Candida albicans is a major cause of invasive mycoses. With resistant Candida, treatment options are limited. Our initial experiments have demonstrated potent in vitro and in vivo activity against C. albicans isolates that are resistant to both fluconazole (FLC) and caspofungin (CFG) (Fothergill et al. ICAAC 2011 & Najvar et al. ISHAM 2012). Our objective was to evaluate the robustness of the in vivo efficacy of VT-1161 against invasive candidiasis caused by a resistant C. albicans isolate. Methods: Immunocompetent ICR mice were inoculated intravenously with C. albicans 43001 (VT-1161, fluconazole [FLC] & caspofungin [CAS] MICs =< 0.03, 32, and 2 mcg/mL, respectively). Therapy with placebo, VT-1161 (5, 20, & 40 mg/kg PO QD), FLC (20 mg/kg PO BID), or CAS (10 mg/kg IP QD) began 1 day post-challenge and continued through day 7. Mice were followed off therapy until day 21 to assess survival. Kidneys were collected on day 8, and on the days that the mice succumbed to infection or on day 21, and fungal burden was assessed by colony-forming units (CFU). The infection models were conducted in duplicate with each isolate. Results: The survival advantage and reductions in kidney fungal burden were highly reproducible between the two experiments. Each dose of VT-1161 resulted in significant improvements in the median survival (>21 days for each dose in each experiment) and percent survival (range 70 - 100%) compared to animals administered placebo and CAS (Table 1). In addition, each dose of VT-1161 resulted in significant reductions in fungal burden within the kidneys on day 8 (range 3.40 - 3.98 log CFU/g) compared to placebo and CAS. These results were also highly reproducible as the results at each dose differed by < 0.5 log CFU/g between the experiments. Fungal burden remained low at day 21, 14 days after therapy with VT-1161 was stopped. FLC also resulted in significant reductions in fungal burden on day 8 and improvements in median survival. However, significant regrowth was observed in the survival arm with FLC, and the percent survival was not significantly different than placebo. Conclusions: VT-1161 consistently demonstrated potent in vivo efficacy against resistant C. albicans. Improvements in survival and reductions in fungal burden were highly reproducible and were significantly greater than observed with placebo and CAS. These data reinforce the potential utility of this agent against resistant C. albicans infections.

Table 1. Survival and fungal burden results for the experiments conducted in duplicate.

Group	**Placebo**	**VT-1161 5 mg/kg QD**	**VT-1161 20 mg/kg QD**	**VT-1161 40 mg/kg QD**	**FLC 20 mg/kg BID**	**CAS 10 mg/kg QD**
Experiment 1 (Infecting Inoculum 7.5 x 10^5 cells/mouse)						
Median Survival	12.8 days	>21 days*,§	>21 days*,§	>21 days*,§	20.5 days*,§	10.5 days
Percent Survival	10%	100%*,§	100%*,§	90%*,§	40%	0%
Mean $\log_{10}$ CFU/g (day 8)	6.39 (0.22)	3.45*,§ (0.36)	3.40*,§ (0.25)	3.98*,§ (1.05)	3.57*,§ (0.71)	6.86 (0.26)
Mean $\log_{10}$ CFU/g (day 21)	7.01 (0.57)	5.01*,§,# (0.59)	2.84*,§,# (0.56)	2.96*,§,# (1.75)	6.51 (0.48)	6.92 (0.36)
Experiment 2 (Infecting Inoculum 1.1 x 10^6 cells/mouse)						
Median Survival	5.5 days	>21 days*,§	>21 days*,§	>21 days*,§	19.5 days*,§	6 days
Percent Survival	0%	70%*,§	80%*,§	70%*,§	30%	0%
Mean $\log_{10}$ CFU/g (day 8)	6.39 (0.24)	3.59*,§ (0.34)	3.43*,§ (0.25)	3.55*,§ (0.94)	3.68*,§ (0.35)	6.34 (0.20)
Mean $\log_{10}$ CFU/g (day 21)	6.88 (0.52)	5.55 (0.81)	3.48*,§,# (1.44)	3.71*,§,# (1.94)	6.65 (0.29)	6.51 (0.31)

*p-value <0.05 vs. Placebo; §p-value <0.05 vs. CAS; #p-value <0.05 vs. FLC