The Tetrazole VT-1598 is Efficacious in a Murine Model of Invasive Aspergillosis with a PK/PD Expected of a Mold-Active CYP51 Inhibitor

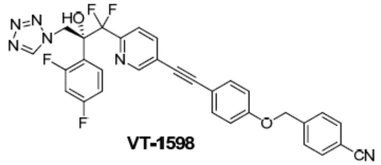
Edward P. Garvey[1], Andrew Sharp[2], Peter Warn[2], Christopher M. Yates[1], Robert J. Schotzinger[1]

[1]Viamet Pharmaceuticals, Inc., Durham, North Carolina, USA; [2]Evotec UK, Ltd., Manchester, England

Friday, Poster 1346

Introduction

VT-1598 is a novel fungal CYP51 inhibitor with potent in vitro activity against yeast, mold, and endemic pathogenic fungi (Wiederhold et al., JAC, 2017). Its tetrazole-based rational drug design imparts much greater selectivity versus human CYPs (Yates et al., BMCL, 2017), which could reduce human CYP-related side effects and DDIs. VT-1598 in vivo activity in murine models of cryptococcosis (Garvey et al., JAC, 2018), coccidioidomycosis (Wiederhold et al., AAC, 2018), and chronic mucocutaneous candidiasis (Break et al., JAC, 2018) have been reported. We report here its pharmacokinetic/pharmacodynamic (PK/PD) activity in an invasive aspergillosis (IA) model.



Materials & Methods

VT-1598 plasma PK was measured after 1 and 4 d of oral doses in neutropenic ICR mice without fungal inoculation, and mouse plasma protein binding was determined by rapid-equilibrium dialysis. In vivo antifungal activity was determined in a tail-vein IA model in neutropenic mice inoculated with A. fumigatus ATCC 204305 (N=6 per dose). VT-1598 MIC (0.25 μg/ml) was determined as outlined in CLSI M38-A2. Two separate studies were conducted, with oral VT-1598 treatment starting either 48 h prior (prophylaxis) or 5 h post-inoculation (delayed), with 4 days of post-inoculation dosing, and kidney fungal burden measured 1 d post last dose by both CFU and qPCR. Drug control was 10 mg/kg AmBisome i.v.

Table 1. VT-1598 PK Parameters in a Mouse Neutropenic Model of Invasive Aspergillosis

Dose Group	Day 1		Day 4		
	C_{max} (μg/ml)	$AUC_{0\text{-}inf}$ (μg*h/ml)	C_{max} (μg/ml)	$AUC_{0\text{-}inf}$ (μg*h/ml)	$t_{1/2}$ (h)
5 mg/kg once-daily	2.3	121	5.5	155	18
40 mg/kg once-daily	16.6	406	36.6	1033	22
40 mg/kg twice-daily	N.D	N.D.	47.3	1354	17

Figure 2. PD: Kidney Burden Dose Response Curve

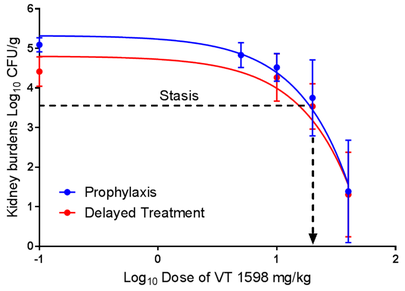
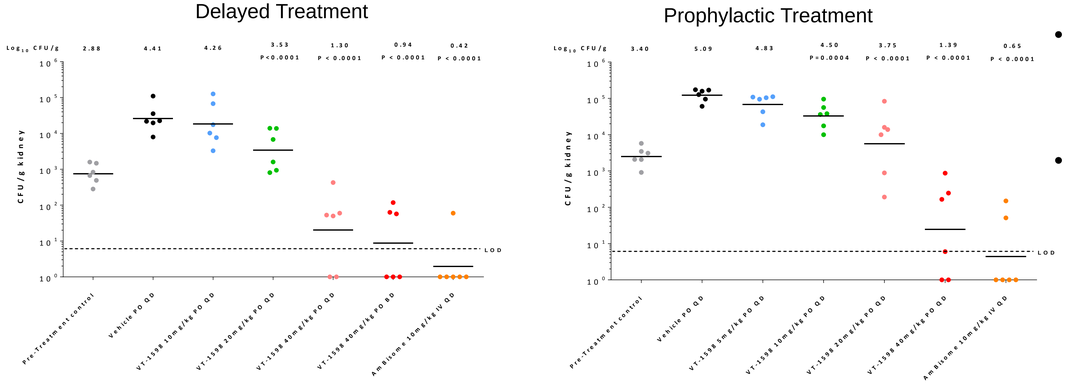


Figure 1. VT-1598 Dose-Dependent Fungal Burden Reductions in a Murine Neutropenic Model of Invasive Aspergillosis



Kidney fungal burden was also measured by qPCR, and described the same dose-dependency as CFU, i.e., no significant decrease in the low dose group, significant but partial decrease in the mid low group, and at or below LOD in the mid high and high dose groups (as well as in the AmBisome group).

Table 2. VT-1598 PK/PD in a Mouse Neutropenic Model of Invasive Aspergillosis

Study	Stasis Dose (mg/kg)	1-Log Killing Dose (mg/kg)	Stasis freeAUC/MIC[1]	1-Log freeAUC/MIC[1]	Posaconazole[2]		Isavuconazole[3]	
					Stasis free AUC/MIC	1-Log free AUC/MIC	Stasis free AUC/MIC	1-Log free AUC/MIC
Delayed	26	50	2.7	5.2	1.1	2.1	5.0	11
Prophylaxis	20	31	2.1	3.1	-	-	-	-

[1]freeAUC calculated by extrapolating AUC at the dose determined in Fig. 2, and then using VT-1598 protein binding of 99.9% in mouse plasma (i.e., multiplying AUC by 0.001), and finally by dividing by MIC of 0.25 μg/ml. [2]Lepak et al., ACC, January 2013; [3]Lepak et al., ACC, December 2013. Note, both literature studies used the IA aspiration pneumonia model.

Conclusions

- VT-1598 plasma exposure from oral doses in neutropenic mice was dose-dependent and displayed a long half-life.
- VT-1598 showed dose-dependent reduction in fungal burden in a murine IA model, with small but nonsignificant increases in efficacy when treatment started prior to infection.
- The PK/PD relationship derived from delayed treatment was similar to that described in the literature for clinically mold-active CYP51 inhibitors, posaconazole and isavuconazole, suggesting VT-1598 could have similar clinical efficacy in treating invasive aspergillosis.

Acknowledgement

This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Defense Medical Research and Development Program under Award No. W81XWH-15-2-0019. Opinions, interpretations, conclusions and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense. In conducting this research using animals, the investigators adhered to the laws of the United States and regulations of the Department of Agriculture.