Sunday, Poster 302

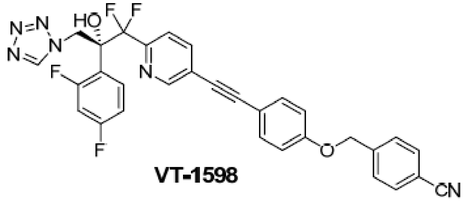
The Novel Fungal CYP51 Inhibitor VT-1598 Displays Fungicidal Activity *In Vivo*

Edward P. Garvey, Christopher M. Yates and Robert J. Schotzinger

Viamet Pharmaceuticals, Inc., Durham, North Carolina, USA

Intro and Objectives

Inhibitors of fungal CYP51 are typically fungistatic in short duration in vitro assays. However, fungistatic versus fungicidal distinctions can be dependent on length of in vitro assays, and is possibly complicated in vivo by immune effects. The novel fungal CYP51 inhibitor VT-1598 was tested in vitro and in vivo to further characterize its antifungal activity.



VT-1598

Materials & Methods

In vitro time-kill studies were conducted with 1X, 4X, and 16X MIC values of VT-1598 (with fluconazole (FLU) and amphotericin B (AMB) as controls) with *Candida albicans* 90028, and colony-forming units (CFUs) measured at 3, 6, 24, and 48 hr. Mouse pharmacokinetics were determined following an oral dose of 5 mg/kg VT-1598 formulated in 20% cremophor EL (N=3 animals). VT-1598 mouse plasma protein binding was determined by rapid-equilibrium dialysis. In a neutropenic murine model of invasive candidiasis, single oral doses of 20 mg/kg VT-1598 or 20 mg/kg FLU were administered 2 hr after tail-vein injection of *C. albicans* R303 (VT-1598 MIC = 0.0078 μg/ml). Kidney CFUs and plasma VT-1598 levels were determined at 22 hr post-dose.

In vitro time-kill and PK studies were performed at TCG Lifesciences Private Limited, Kolkata, India. In vivo invasive candidiasis studies were at done at Eurofins PanLabs Taiwan, Ltd., Taipei, Taiwan, with bioanalytical analyses at OpAns, LLC, Durham, North Carolina.

Results

Figure 1. VT-1598 Is fungistatic in vitro. Top: VT-1598 (MIC = 0.0078 μg/ml), Middle: FLU (MIC=0.25 μg/ml), Bottom: AMB (MIC=0.5 μg/ml)

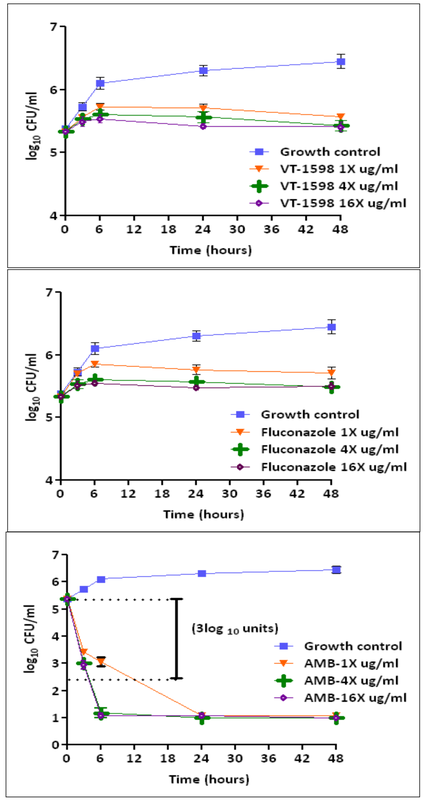


Figure 2. VT-1598 is orally available with a long PK half-life in mice.

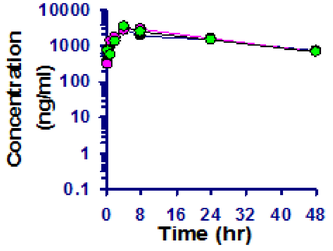


Table 1. VT-1598 PK parameters in mice (after a 5 mg/kg oral dose).

C_{max} (μg/ml)	T_{max} (hr)	AUC_{ltast} (μg*hr/ml)	$T_{1/2}$ (hr)	Cl_{app} (ml/min/kg)	%PPB
3.1	4.0	76.3	22.0	0.85	99.9

Table 2. VT-1598 is fungicidal in vivo in a neutropenic model of invasive candidiasis, reducing fungal burden measured at start of treatment.

Expt #	Kidney Fungal Burden, CFU/g				Plasma Level, μg/ml
	Vehicle Control		VT-1598*	FLU*	VT-1598
	2 hr	24 hr	24 hr	24 hr	24 hr
1	748	732000	121	6360	4.9
2	1180	235000	272	1230	7
3	916	171000	260	2692	7.3
4	1715	146000	40	-	5
5	931	292000	124	-	6.4
6	1849	246000	73	-	9.6
7	1404	275000	167	-	-
8	1440	361000	124	-	6.45
9	1440	361000	98	-	7.05
Average	**1291**	**313000**	**142****	**3427**	6.7
StDev	375	173000	79	2642	1.5

*Single oral dose of 20 mg/kg given 2 hr after inoculation. **P = 0.000038 vs. 2 hr vehicle control, by Student's T-test

Conclusions

- Similar to fluconazole, the novel fungal CYP51 inhibitor VT-1598 was fungistatic in vitro.
- In contrast, VT-1598 was fungicidal in vivo, reducing CFU/g measured at the start of treatment
- The in vivo fungicidal mechanism of VT-1598 is currently unknown, but likely not due to host immunity (model was in neutropenic mice) nor "unusual" plasma PK/PD [free VT-1598 C_{24h} (~0.0067 μg/ml) essentially the same as its MIC (0.0078 μg/ml)].
- These in vivo fungicidal data distinguish VT-1598 and strongly support clinical investigations.