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Paper Poster Session I

News on antifungal prophylaxis and therapy

The novel fungal Cyp51 inhibitor VT-1129 demonstrates potent *in vivo* activity in mice against cryptococcal meningitis with a loading/maintenance dosing regimen

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Objectives: Cryptococcal meningitis (CM) is a significant invasive mycosis in immunocompromised patients, and morbidity and mortality remain unacceptably high even with appropriate therapy. VT-1129 is a novel fungal-specific Cyp51 inhibitor with potent *in vitro* and *in vivo* activity against *Cryptococcus* species (Najvar et al., Lockhart et al. 9th ICCC, 2014). Because of its long half-life in mice (>6 d), we evaluated the *in vivo* efficacy of a loading dose (LD)/maintenance dose (MD) strategy for VT-1129 against CM.

Methods: ICR mice were inoculated intracranially with *C. neoformans*. Treatment with oral VT-1129 (MIC 0.12 µg/mL, 100% inhibition), or placebo began 1 day later. Treatment consisted of three VT-1129 LD/MD groups: LD of 1, 3, or 30 mg/kg on day 1, followed by a MD of 0.15, 0.5, or 5 mg/kg once daily, respectively. A VT-1129 10 mg/kg QD only group was also included. In the fungal burden arm (N=20 mice/group), treatment continued for 14 days, and brains and plasma were collected on day 15. In the survival arm (N=20 mice/group), treatment continued until day 10 after which mice were monitored off-therapy until day 30. Fungal burden was assessed by colony-forming units per gram of brain tissue (CFU/g). VT-1129 plasma and brain concentrations were measured by LC/MS-MS. Survival was assessed by Kaplan-Meier analysis and differences in brain fungal burden were assessed for significance by ANOVA with Tukey's post-test for multiple comparisons. Non-linear regression analysis was used to assess the relationship between VT-1129 concentrations and fungal burden.

Results: Survival was significantly improved compared to placebo for each VT-1129 dose group (median survival >30 days vs. 12 days, $p \leq 0.0003$; percent survival 70-100% vs. 0%, $p \leq 0.0003$). VT-1129 at each dose significantly reduced brain fungal burden compared to placebo with day 15 CFU counts ranging between 0.46 to 4.57 log CFU/g compared to 6.41 log CFU/g for placebo ($p \leq 0.0004$). Mean trough plasma and brain concentrations on day 15 ranged from 0.187 to 5.70 mg/L and 0.533 to 13.99 mg/L, respectively, among the VT-1129 LD/MD groups. No significant differences in fungal burden were observed between the high LD/MD group and the 10 mg/kg QD group. Consistent with its long half-life, VT-1129 concentrations remained elevated on day 30, 20 days after therapy stopped, in the survival arm (range mean trough plasma and brain concentrations 0.135-0.736 mg/L and 0.238-3.31 mg/L, respectively, among the VT-1129 LD/MD groups). VT-1129 concentrations on day 15 inversely correlated with reductions in fungal burden (R^2=0.72).

Conclusions: The LD/MD strategy of VT-1129 demonstrated potent efficacy in this murine model of CM. Both reductions in brain tissue fungal burden and improvements in survival were observed. These data demonstrate the potential utility of VT-1129 in the treatment of CM, with the possible added advantage of a reduced maintenance dose.