P0173

High and Sustained Lung Epithelial Lining Fluid (ELF)-to-Plasma Exposure Ratio from a Single Dose of Rezafungin (CD101): Efficacy Comparison to Posaconazole and Micafungin in a Mouse Pulmonary Aspergillosis Infection Model

Voon Ong, Ph.D.
Cidara Therapeutics, Inc.
6310 Nancy Ridge Dr., Suite 101
San Diego, CA 92121 USA
vong@cidara.com

V. Ong[1], G. Hough[1], S. Flanagan[1], K. Bartizal[1], A. Sattar[2], A. Sharp[2], P. Thommes[2],T. Murphy[3]
[1]Cidara Therapeutics, San Diego, CA; [2]Evotec, Manchester, UK; [3]NeoSome Life Sciences, Lexington, MA

INTRODUCTION AND PURPOSE

Disease- and treatment-related immune-suppression in patients with hematological diseases increase the risk of opportunistic fungal infections caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii*, and thus antifungal prophylaxis is a requirement in this population. However, there remain unmet needs in antifungal prophylaxis. Safety/tolerability, drug-drug interactions, and variable PK complicate antifungal prophylaxis options, such as the azoles for *Candida* spp. and *Aspergillus* spp.

Rezafungin (previously CD101) is a novel echinocandin in clinical development that has demonstrated robust preclinical efficacy and is differentiated from currently available echinocandins by its long-acting pharmacokinetic profile that allows for once-weekly dosing. Whereas currently approved echinocandins are limited to once-daily IV dosing, the potential for intermittent administration may extend the practical utility of rezafungin to include antifungal prophylaxis and treatment in the outpatient setting.

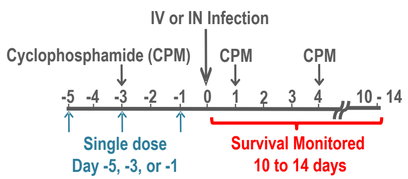
Rezafungin shows potent in vitro minimum inhibitory/effective concentration (MIC/MEC) against a variety of fungi[1]. The translatability of in vitro potency to in vivo efficacy was investigated by measuring rezafungin in mouse lung epithelial lining fluid (ELF). Subsequently, neutropenic mouse models of disseminated *Candida*, *Aspergillus*, or *Pneumocystis* infections were used to confirm prophylactic efficacy by rezafungin[2]. This presentation will highlight comparative prophylaxis treatments in a mouse model of pulmonary aspergillosis.

METHODS

Rezafungin (20 mg/kg IP; human 400 mg AUC equivalent dose) was measured in lung ELF of CD-1 mice. After dosing, 3 mice/timepoint were euthanized for plasma and bronchoalveolar lavage fluid (BALF) collection with 2 x 0.5 mL flushes of saline at 0, 1, 3, 6, 12, 24, 48, and 72 hours post-dose. Urea levels for plasma/BALF normalization for lung ELF volume were measured using spectrophotometry. Rezafungin concentrations in plasma/BALF samples were measured by LC-MS/MS.

Disseminated aspergillosis: Neutropenic (by cyclophosphamide, CPM) ICR mice (6/grp) were challenged with *A. fumigatus* ATCC 13073 (IV, 10^4 CFU/mouse) on day 0. Treatment (2 hr after infection) with rezafungin was given as a single dose. Survival was monitored for 14 days. The same model was used for prophylaxis except rezafungin (SC; 5, 10, or 20 mg/kg) was dosed on days -1, -3 or -5 prior to infection.

Pulmonary (intranasal, IN) aspergillosis: Neutropenic (CPM-induced) ICR mice (10/grp) were challenged with *A. fumigatus* AF293 (IN, 10^5 CFU/mouse) on day 0. Prophylactic rezafungin was given as a single dose (IP; 5, 10, or 20 mg/kg) 1 day prior to infection. Survival was monitored for 10 days.

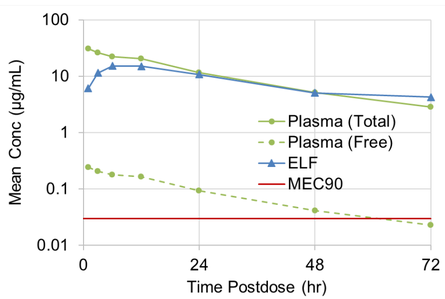


RESULTS

Rezafungin exhibited potent in vitro activity against 97 clinical *A. fumigatus* isolates with MEC_{50}, MEC_{90} and MEC range values of 0.015, 0.03, and ≤0.0078-0.03 µg/mL, respectively (from 2015)[1].

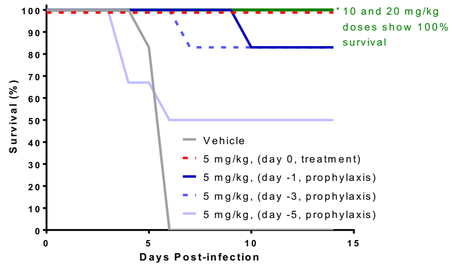
Drug	MEC_{50}	MEC_{90}	Range
Rezafungin	0.015	0.03	≤0.008 - 0.03
Anidulafungin	≤0.008	0.03	≤0.008 - 0.03
Caspofungin	0.015	0.03	≤0.008 - 0.06
Micafungin	≤0.008	0.015	≤0.008 - 0.03
Itraconazole	0.5	1	0.25 - 1
Posaconazole	0.25	0.5	0.12 - 0.5
Voriconazole	0.5	0.5	0.12 - 1
Amphotericin B	1	2	0.25 - 2

Following dose administration, rezafungin concentrations in ELF reached a maximum by 4 hr and was comparable between plasma and ELF at ≥24 hr post-dose based on total-drug with an ELF/Plasma AUC ratio of 0.80. If plasma concentrations were corrected for protein binding (99.2%), the ELF/Plasma AUC ratio would be 100.

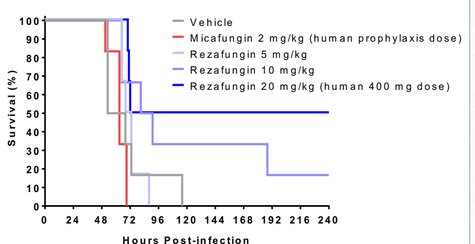


RESULTS (con't)

In disseminated aspergillosis, all animals in the 10 and 20 mg/kg groups survived regardless of prophylaxis day. The 5 mg/kg groups showed increased survival when prophylaxis was given closer to challenge (or 100% survival when given as treatment on day 0).

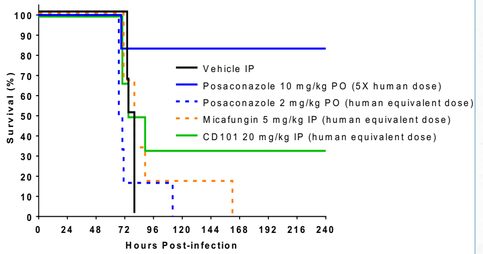


In pulmonary aspergillosis, dose-dependent increases in survival were observed with the dose of 20 mg/kg in mice showing the most pronounced increase in survival relative to vehicle. Micafungin did not appear to be efficacious when tested at its human (50 mg) AUC equivalent dose approved for prophylaxis in hematopoietic stem cell transfer (HSCT) patients.



RESULTS (con't)

A subsequent study with rezafungin, micafungin, and posaconazole at their respective human AUC equivalent doses suggests an advantage for rezafungin with higher survival relative to micafungin or posaconazole. Only posaconazole at 5x higher (10 mg/kg) than human AUC showed a statistically significant increase in survival.



CONCLUSION

Good in vitro potency and lung ELF distribution coupled with a long $t_{1/2}$ translated to enduring efficacy for rezafungin in mouse aspergillosis models. Additionally, as rezafungin human $t_{1/2}$ (133 hr) is 5x longer than mouse (25 hr), protection from a single prophylaxis dose in mouse given 1 day prior to fungal challenge should translate to similar protection from a single prophylactic dose in humans for up to 1 week. Rezafungin may potentially be a new agent for intermittent outpatient echinocandin treatment and prophylaxis of aspergillosis in a clinical setting.

REFERENCES

1. Pfaller et al., International Journal of Antimicrobial Agents 50 (2017) 352–358
2. 22nd Congress of the European Hematology Association, 2017, Poster P645