Poster 568

Rezafungin (CD101) Prophylactic Dose Rationale for Prevention of *Aspergillus*, *Candida*, and *Pneumocystis* infections

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INTRODUCTION

Currently, the standard of care for prophylaxis following hematopoietic stem cell transplantation (HSCT) is to use one antifungal agent to prevent infections with *Candida* and *Aspergillus* and an additional antimicrobial agent to prevent PCP. Management of antifungal prophylaxis in this patient group is challenged by factors of the underlying disease and treatment, immunosuppression, and risks of drug-drug interactions. For the first time, a single antifungal drug is being proposed as prophylaxis against invasive fungal infections (IFIs) including *Pneumocystis carinii* pneumonia (PCP).

Rezafungin (previously, CD101) is a novel echinocandin that demonstrates a broad spectrum antifungal activity profile, inclusive but not limited to *Candida*, *Aspergillus*, and *Pneumocystis* species. The echinocandin class has demonstrated safety and tolerability, as well as low DDI potential. Rezafungin has a more stable molecular structure compared to the other currently approved echinocandins, resulting in a reduction in the formation of toxic metabolites and an increase in the duration of exposure to active drug. This stability further translates into an improved safety profile as demonstrated in both nonclinical and clinical studies, as well as a unique PK profile that allows for high dose, front-loaded exposures for enhanced fungal killing and once-weekly IV dosing. These characteristics of rezafungin may be particularly useful in antifungal prophylaxis. Both in vitro and in vivo data have demonstrated the potency and efficacy of rezafungin for prophylaxis against candidemia and disseminated candidiasis, pulmonary and disseminated aspergillosis, and PCP. A Phase 3 study of rezafungin in IFI prophylaxis is planned. In addition, in vitro and in vivo data have demonstrated the efficacy of rezafungin in treatment of candidiasis and aspergillosis and there is an ongoing Phase 2 double-blind, randomized, controlled trial comparing 2 dose regimens of rezafungin against caspofungin in the treatment of candidemia and/or invasive candidiasis. Results are expected prior to the initiation of the Phase 3 study in IFI prophylaxis.

Here, we compared the clinical pharmacokinetics of rezafungin to measures of nonclinical *in vitro* susceptibility and *in vivo* efficacy to guide dose selection for the prevention of fungal infections.

METHODS

Protein Binding. Protein binding of rezafungin in human plasma was assessed using an ultracentrifugation approach where free compound is separated from protein-bound compound by sedimentation of the plasma proteins using high g forces, and analyzed with LC-MS/MS. Pooled mixed gender plasma (K_2EDTA) was used. Back-calculated concentrations for rezafungin were performed with each concentration tested, in replicates of 4.

Antifungal Activity. Minimal inhibitory and minimal effective concentrations (MIC and MEC, respectively) were determined according to CLSI broth microdilution methodology (M27-A3, M38-A2), as noted in Pfaller, et al 2017a, and 2017b.

PK/PD. Mean unbound rezafungin plasma concentrations following a single dose of 200 mg or 400 mg rezafungin acetate in healthy Phase 1 subjects were obtained by calculation using percentage free-drug results from ex vivo experiments described above, across all time points. Resultant concentrations were compared to measures of in vitro antifungal activity against representative pathogens.

RESULTS

Protein Binding

In general, rezafungin appears to show lower protein binding in human plasma than in mouse plasma (Table 1). There does not appear to be concentration-dependence in the protein binding of rezafungin.

Like previous echinocandins, protein binding of rezafungin is high (>95%). The range of mean protein binding values was 96.4% to 98.0%. Median plasma protein binding across all concentrations is 97.4% in human plasma, with a corresponding percent free-drug value of 2.6%, as compared to a free-drug value of 0.8% in mice.

Table 1: Rezafungin protein binding in human and mouse plasma

Concentration (µg/mL)	% Free (Mean ± SD)	% Protein Binding
Human		
7	2.0 ± 0.2	98.0
10	3.6 ± 0.6	96.4
20	2.3 ± 0.1	97.7
30	2.6 ± 0.6	97.4
60	2.6 ± 0.4	97.4
Mouse		
7	0.7 ± 0.05	99.3
10	0.8 ± 0.1	99.2
20	0.8 ± 0.1	99.2
30	0.8 ± 0.04	99.2
60	0.7 ± 0.1	99.3

Antifungal Activity

The in vitro activity of rezafungin was previously evaluated as part of the JMI Laboratories international SENTRY Antimicrobial Surveillance Program (Pfaller, et al 1998). Published results from the 2014 and 2015 surveys (Pfaller, et al 2017a and b), and unpublished results of the 2016 survey were used to select targets for prophylaxis. Potent rezafungin activity was seen against *Aspergillus fumigatus* (MEC_{90}= 0.015 µg/mL) and *Candida albicans* (MIC_{90}= 0.06 µg/mL) clinical isolates. Although standard in vitro MIC testing is not possible for *Pneumocystis* spp., rezafungin prevented PCP by blocking formation of both trophic and cyst/asci forms in mice at human equivalent doses of <50 mg, with results similar to standard of care (trimethoprim/sulfamethoxazole) (Cushion, et al 2016).

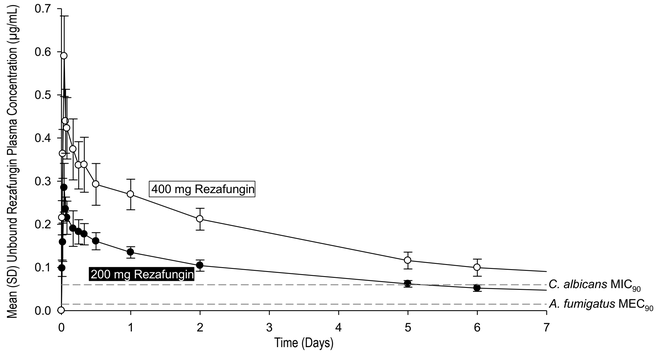

Figure 1: Unbound Rezafungin Plasma Concentrations in Healthy Adults Relative to Antifungal Activity

RESULTS (cont'd)

PK/PD

Mean unbound rezafungin plasma concentrations in Phase 1 subjects following a single dose of 400 mg were above the MIC_{90} for *C. albicans* for 7 days, and rezafungin plasma concentrations for both 400 mg and 200 mg were above the MEC_{90} for *A. fumigatus* for 7 days (Figure 1). Due to expected accumulation given rezafungin's long half-life of 133 hours, trough concentrations would exceed both MIC_{90} and MEC_{90} even for the 200 mg dose from the 2nd dose on, or from the first dose if a loading dose of 400 mg was used (Table 2).

Table 2. Anticipated Prophylaxis Coverage by Rezafungin Dose Regimen

Rezafungin Dose Regimen	Pathogen	Prophylaxis Coverage During Entire Dosing Interval	
		First Dose	≥ 2 Doses
400 mg once weekly	*Aspergillus*	Yes	Yes
	Candida	Yes	Yes
	Pneumocystis	Yes	Yes
400 mg loading and 200 mg once weekly	*Aspergillus*	Yes	Yes
	Candida	Yes	Yes
	Pneumocystis	Yes	Yes
200 mg once weekly	*Aspergillus*	Yes	Yes
	Candida	No	Yes
	Pneumocystis	Yes	Yes

CONCLUSION

Rezafungin at clinical doses of 400 mg or 200 mg once-weekly, will likely be effective in preventing 3 common classes of fungal infections.

REFERENCES

Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. Antimicrob Agents Chemother. 2017a;61(3):e02045-16.
Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. Internat J Antimicrob Agents 2017b;50:352–358.
Cushion M, Ashbaugh A, Lynch K, Linke MJ, Bartizal K. Blood. 2016;128:3396.
Pfaller MA, Jones RN, Doern GV, Sader HS, Hollis RJ, Messer SA. J Clin Microbiol. 1998;36(7):1886-9.

DISCLOSURES

All authors are employed by and own shares in Cidara Therapeutics, Inc.