Of Mice and Men: Comparison of Rezafungin versus Micafungin Lung Exposures in Mouse and Potential Implications for Human ELF and Efficacy Studies

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INTRODUCTION

Rezafungin (RZF) is a novel echinocandin antifungal in Phase 3 clinical development for the treatment of candidemia and invasive candidiasis as well as for prevention of invasive fungal infections caused by *Candida, Aspergillus* and *Pneumocystis* spp.

RZF has in vitro activity against *Aspergillus fumigatus,* including azole-resistant isolates,[1] and the in vivo efficacy of RZF to treat and prevent aspergillosis has previously been established in neutropenic mouse infection models. To further substantiate the efficacy of rezafungin to prevent aspergillosis, RZF lung distribution (as measured by epithelial lung fluid; ELF) and prophylactic efficacy were compared with those of an approved echinocandin, micafungin (MCF), that is used in patients undergoing stem cell transplantation.

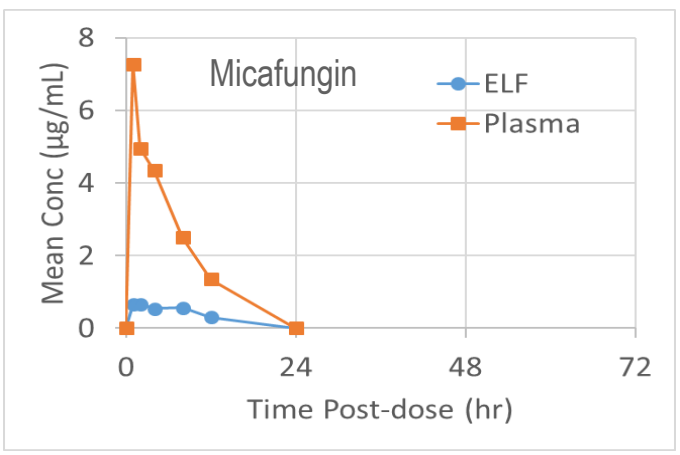
METHODS

ELF Distribution: Mice were given RZF (IP; 20 mg/kg, human 400 mg dose equivalent) or MCF (IP; 5 mg/kg, human treatment 100 mg dose equivalent). Plasma and bronchoalveolar lavage fluid (BALF) was collected between 0-72 hrs. Urea for plasma/BALF normalization for ELF volume were quantified using a commercially available, spectrophotometry-based assay whereas corresponding drug concentrations were measured by LC-MS/MS.

Prophylaxis Efficacy: Neutropenic ICR mice (6/grp) were given a single dose of RZF (IP; 10, 20 mg/kg) or MCF (IP; 2 mg/kg, human prophylaxis 50 mg dose equivalent) one day prior to *A. fumigatus* challenge (~10^5 CFU/mouse, intranasally) on Day 0. Survival was evaluated up to 7 days post-infection.

RESULTS

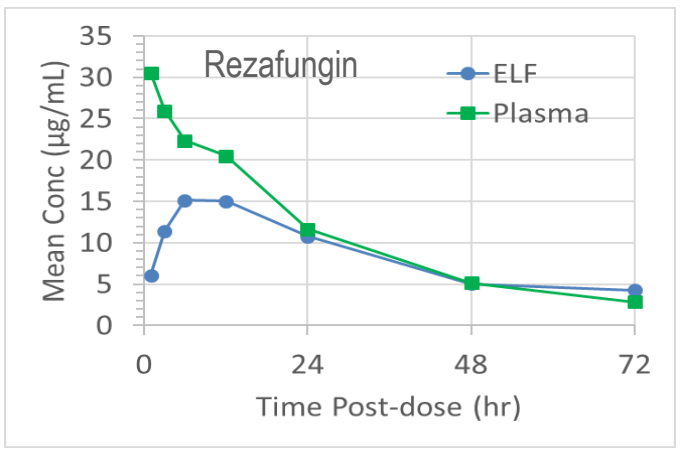
Following MCF 5 mg/kg (human treatment 100 mg dose equivalent), plasma C_{max} was 7.3 µg/mL at 1 hr post-dose, and declined with a $t_{1/2}$ of 4.7 hr. Maximum ELF concentration was 0.66 µg/mL at 2 hr postdose with a $t_{1/2}$ of 9.4 hr. Concentrations fell below the limit of quantitation (0.05 µg/mL, plasma; 0.01 µg/mL, BALF) at 24 hr postdose. MCF distribution into lung ELF, as measured by ELF/plasma AUC, is 0.15 and 0.21 based on AUC_{last} and AUC_{inf}, respectively.



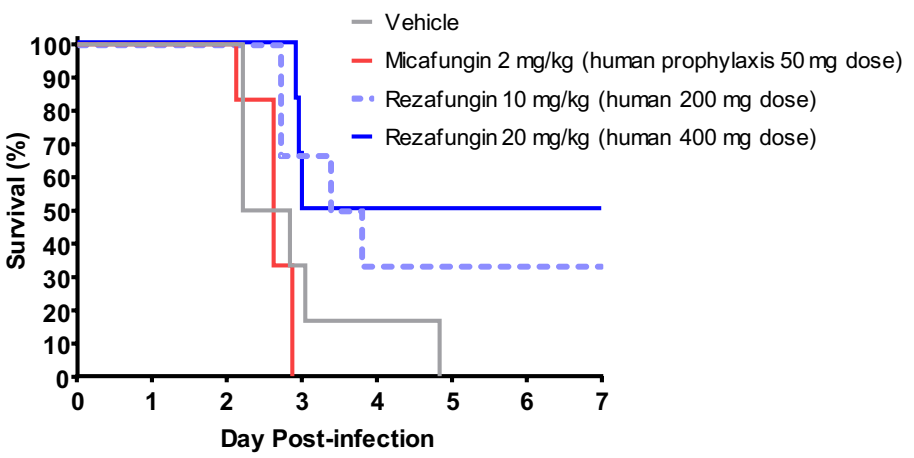
The observed mouse ELF/plasma ratio of ~0.2 based on AUC is comparable to values obtained for humans,[2,3] suggesting the mouse model may be predictive of human lung ELF distribution.

RESULTS (cont'd)

Following RZF 20 mg/kg (human 400 mg dose equivalent), plasma C_{max} was 30.5 µg/mL at 1 hr postdose ($t_{1/2}$ = 21 hr). Maximum ELF concentration was 15.1 µg/mL at 6 hr postdose ($t_{1/2}$ = 32 hr). Based on ELF/plasma AUC, RZF distribution into lung ELF is close to unity (0.80 and 0.95 based on AUC_{last} and AUC_{inf}, respectively).



In mouse prophylaxis efficacy, RZF at 10 or 20 mg/kg showed higher survival rates versus control or MCF at 2 mg/kg (human prophylaxis 50 mg dose equivalent) suggesting an advantage for RZF when dosed weekly at human equivalent doses of either 200 or 400 mg.



CONCLUSIONS

- Distribution of MCF into mouse ELF is comparable to reported human values suggesting the mouse model may be predictive of human lung distribution.
- ELF concentrations of RZF in the mouse remained >20-fold higher than the MEC_{90} (0.015 µg/mL)[4] against *A. fumigatus* and *A. flavus* in plasma (3 µg/mL) and ELF (4 µg/mL) after 3 days.
- As plasma half-life is 133 hrs in human vs. 21 hrs in mouse, it is reasonable to expect comparable plasma/ELF concentrations to be maintained after 1 week in humans.
- The higher lung ELF exposures and superior efficacy of RZF in aspergillosis reinforce the potential of RZF use as prophylaxis in immunocompromised patients.

REFERENCES

1. Wiederhold et al. *J Antimicrob Chemother.* Jul 2018. doi: 10.1093/jac/dky280.
2. Walsh et al. *Antimicrob Agents Chemother.* Aug 2010 (54)8, 3451-3459.
3. Nicolau et al. *Antimicrob Agents Chemother.* Mar 2009 (53)3, 1218-1220.
4. Pfaller et al. IDweek 2018. October 3-7, 2018; San Francisco, CA. Poster #2400.