Poster 3266

Scan to download a PDF of this poster. No personal information is collected.

Rezafungin Prevention of *Pneumocystis* Pneumonia and *Pneumocystis* Reactivation Using Different Doses and Durations of Prophylaxis in a Mouse Model

M. T. Cushion[1], A. Ashbaugh[1] and V. Ong[2]

University of Cincinnati College of Medicine and the Cincinnati VAMC, Cincinnati, OH, USA[1], and Cidara Therapeutics, San Diego, CA[2]

Voon Ong, PhD
Cidara Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121
vong@cidara.com

INTRODUCTION

Rezafungin is a novel echinocandin in development for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* species in patients undergoing blood and marrow transplantation.

Rezafungin has a favorable safety and tolerability profile and a low risk of drug-drug interactions. We previously demonstrated the efficacy of rezafungin in preventing *Pneumocystis* infection in an immunosuppressed mouse model [1-3].

The present study addressed whether *Pneumocystis* infection in a similar immunosuppressed mouse model could re-activate after 2 to 8 wks of prophylactic therapy using different dosing regimens of rezafungin.

METHODS

C3H/HeN mice were infected with *Pneumocystis murina* intranasally at 2 x 10^6/50 µL after immunosuppression with dexamethasone.

Mice were administered vehicle as a negative control (C/S), trimethoprim/sulfamethoxazole (T/S) as a positive control, caspofungin as a comparator echinocandin, or rezafungin intraperitoneally at the time of challenge.

Study drug administration was stopped at 2, 4, 6, and 8 weeks, at which time mice were immunosuppressed for an additional 6 weeks to allow any residual *P. murina* to re-activate.

Mice were then euthanized, and lungs were processed for analysis of nuclei and asci.

RESULTS

All rezafungin dose regimens at all timepoints significantly reduced both nuclei and asci burdens versus the C/S group (Fig. 1).

After 4 weeks of rezafungin prophylaxis (plus 6 weeks additional immunosuppression [Week 10 timepoint]; Fig. 1), both groups given rezafungin 20 mg/kg (3x/wk and 1x/wk) prevented *P. murina* organisms from activating infection.

After 6 and 8 weeks of rezafungin prophylaxis plus 6 weeks additional immunosuppression (Week 12 and 14 timepoints; Fig. 1), no re-activation of infection was present in any of the study groups.

After 2 and 4 weeks of prophylaxis (plus 6 weeks additional immunosuppression (Week 8 and 10 timepoints; Fig. 1), there was a significant reduction of nuclei and asci counts in all groups of rezafungin versus caspofungin.

After 2, 4, and 6 weeks of rezafungin prophylaxis plus 6 weeks additional immunosuppression, there was a significant reduction of nuclei and asci counts between all groups of rezafungin versus T/S 1x/week.

Significant benefit in survival was observed between rezafungin 20 mg/kg/3x/week and caspofungin 5 mg/kg/3x/week at week 14 (Fig. 2).

Color code: red=C/S, vehicle-treated negative control; green=rezafungin; pink=T/S, trimethoprim/sulfamethoxazole, blue=caspofungin.

Brackets (Weeks 8 and 10) denote groups with significant difference from Week 8 C/S group and caspofungin group. Capped lines (Weeks 12 and 14) indicate significant difference from Week 8 C/S group. P value ≤0.05.

Figure 1. Log_{10} mean nuclei and asci counts by total time (prophylaxis period + 6 weeks immunosuppression to allow reactivation)

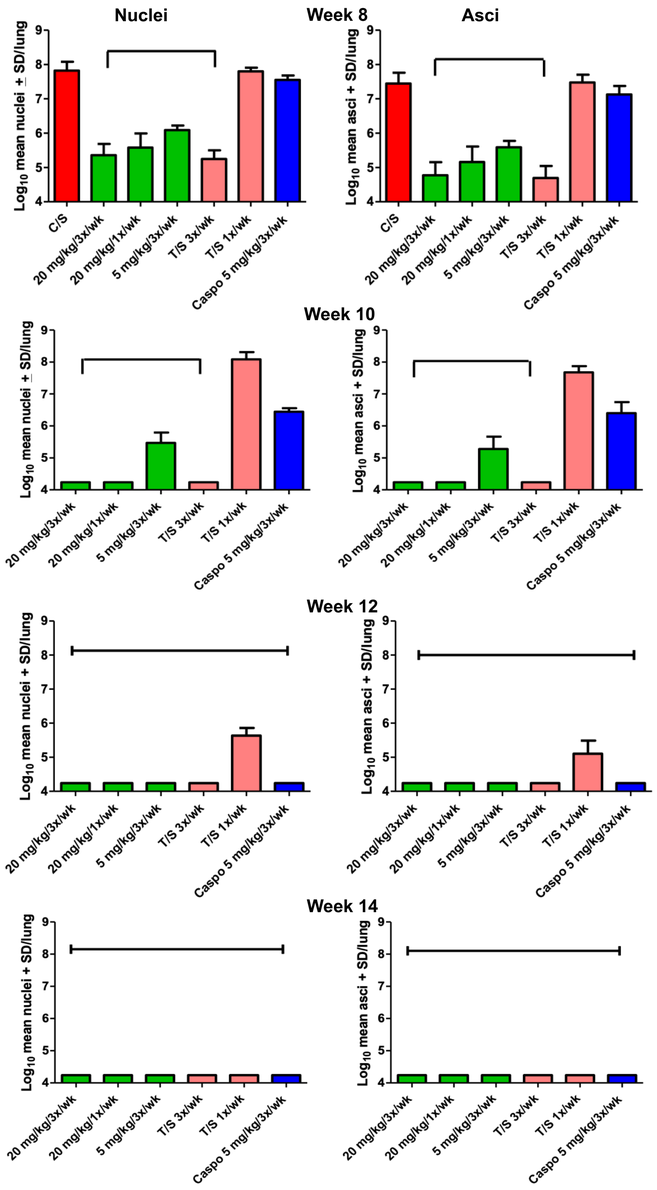
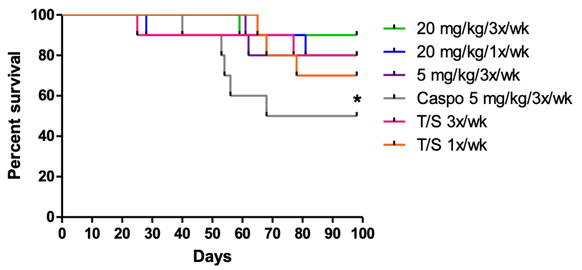


Figure 2. Survival curves at Week 14[a]



[a]Indicates survival following prophylaxis of 2–8 weeks and then 6 weeks of immunosuppression.
*Significant difference between RZF 20 mg/kg/3x/wk (green line) and caspofungin 5 mg/kg/3x/week (grey line) at week 14.

CONCLUSIONS

- Prophylaxis with rezafungin for durations as short as 4 weeks prevented *P. murina* organisms from developing infection after cessation of therapy and showed more efficacy than caspofungin.
- These results provide evidence that rezafungin can prevent *Pneumocystis* reactivation and that such regimens hold promise for prophylaxis against *Pneumocystis* in at-risk patients undergoing blood and marrow transplantation.

REFERENCES

1.Cushion MT and Ashbaugh A. TCT 2019; Houston, Texas. Poster 549.
2.Cushion MT, et al. ASH 2016; San Diego, CA; Poster 3396.
3.Cushion MT, et al. ASM Microbe 2016; Jun 16-20, 2016; Boston, MA.

DISCLOSURES / ACKNOWLEDGEMENTS

Author disclosures: M. Cushion (consultancy and research funding; Cidara Therapeutics), A. Ashbaugh (none), and V. Ong (employee, stockholder; Cidara Therapeutics). Editorial support was provided by T. Chung (Scribant Medical) with funding by Cidara Therapeutics.