Rezafungin: Efficacious Against Invasive Aspergillosis Caused by Azole-Resistant Aspergillus fumigatus Harboring the TR34/L98H Mutation

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ABSTRACT

Background: Invasive aspergillosis (IA) caused by azole-resistant A. fumigatus is of increasing concern. Isolates harboring the TR34/L98H mutation in the CYP51A gene are often pan-azole-resistant, can be found in the environment, and can cause invasive disease in patients without previous azole exposure. Rezafungin (formerly CD101) is an investigational echinocandin with a long half-life (130 h in humans) and potent in vitro activity against A. fumigatus, including azole-resistant A. fumigatus (Wiederhold et al. J Antimicrob Chemother 2018). Our objective was to evaluate the in vivo efficacy of intermittent dosing of rezafungin against IA caused by A. fumigatus harboring the TR34/L98H mutation.

Methods: A clinical isolate of A. fumigatus harboring a confirmed TR34/L98H mutation was used (rezafungin MIC 0.06 μg/mL, posaconazole MIC 1 μg/mL). Male ICR mice were rendered neutropenic with cyclophosphamide (200 mg/kg IP) and 5-fluorouracil (5 mg/mouse) both administered 1 day prior to inoculation. Mice were inoculated via the lateral tail vein. Rezafungin was administered 1 day after inoculation with vehicle control (dextrose 0.15% in saline) or supratherapeutic, therapeutic, or subtherapeutic rezafungin (1, 4, or 16 mg/kg IP on days 1, 4, and 7, respectively). Colony-forming units (CFUs) were enumerated by colony forming units (CFU). Survival was assessed by Kaplan-Meier analysis and fungal burden by qPCR. Outcome measures included survival and fungal burden as measured by colony-forming units (CFUs) and quantitative real-time PCR (qPCR).

RESULTS (continued)

Figure 2. Fungal burden on day 8 post-inoculation (fungal burden arm) in neutropenic mice with invasive aspergillosis caused by an azole-resistant A. fumigatus isolate harboring a TR34/L98H mutation. As measured by CFUs (A) or qPCR (B).

Figure 3. Fungal burden in the survival arm on day 12 post-inoculation in neutropenic mice with invasive aspergillosis caused by an azole-resistant A. fumigatus isolate harboring a TR34/L98H mutation. As measured by CFUs (A) or qPCR (B).

CONCLUSIONS

Extended interval dosing of rezafungin was associated with improved outcomes in this mouse model of invasive aspergillosis caused by azole-resistant A. fumigatus due to the TR34/L98H mutation. Improvements in survival and reductions in fungal burden as measured by qPCR were observed compared to vehicle control. Further studies are warranted to assess the potential benefits of extended interval dosing of rezafungin for the treatment of aspergillosis caused by azole-resistant A. fumigatus.

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MATERIALS AND METHODS

Isolate & Inoculation

- Aspergillus fumigatus clinical isolate UTHSCSA D15-116 (rezafungin MEC 0.06 μg/mL, posaconazole MIC 1 μg/mL) was used
- Male ICR mice were rendered neutropenic with cyclophosphamide (200 mg/kg IP) and 5-fluorouracil (5 mg/mouse) both administered 1 day prior to inoculation
- Mice were inoculated via the lateral tail vein

Antifungal Treatment

- Antifungal therapy began 1 day post-inoculation and continued through day 7
- Treatment groups consisted of: 1) Vehicle Control, 2) rezafungin 1, 4, or 16 mg/kg administered by IP injection on days 1, 4, and 7, and 3) posaconazole 20 mg/kg PO BID

RESULTS (continued)

Figure 1. Survival curves in a neutropenic mouse model of invasive aspergillosis caused by an azole-resistant A. fumigatus isolate harboring a TR34/L98H mutation.

OBJECTIVE

- Our objective was to evaluate the in vivo efficacy of rezafungin for the treatment of azole-resistant invasive aspergillosis
- A clinical isolate of A. fumigatus harboring a TR34/L98H mutation was used to establish invasive disease in a neutropenic murine model
- Outcome measures included survival and fungal burden as measured by colony-forming units (CFUs) and quantitative real-time PCR (qPCR)

BACKGROUND

- Invasive aspergillosis caused by azole-resistant A. fumigatus is of increasing concern
- Isolates harboring the TR34/L98H mutation in the CYP51A gene are of particular concern as they are often pan-azole resistant
- Isolates harboring the TR34/L98H mutation have now been found in numerous countries around the world
- Rezafungin (formerly CD101) is an investigational echinocandin with a long half-life (130 hours in humans), high plasma exposure and tissue concentrations, and potent in vitro activity against A. fumigatus, including azole-resistant A. fumigatus (Wiederhold et al. J Antimicrob Chemother 2018;73:3063-3067)
- This long half-life translates into high exposures, and thus may allow for less frequent dosing compared to other echinocandins (Lepak et al. Antimicrob Agents Chemother 2018;62:e01572-18; Zhao et al. Antimicrob Agents Chemother 2017;61:e01009-17)