INTRODUCTION

C. albicans is an azole-resistant human blood isolate. Fluconazole (MIC90 = 0.06 μg/mL) and voriconazole (MIC90 = 0.01 μg/mL) are approved echinocandins, CD101 is fungicidal against C. albicans. Unlike previously approved echinocandins, CD101 has a uniquely stable structure enabling it to be formulated for topical administration and developed for treatment of VVC.

CD101 was designed to be a highly stable molecule and has shown robust efficacy in mouse infection models of disseminated Candida/Aspergillus. CD101 has an excellent nonclinical safety and toxicology profile enabling high concentration, front-loaded doses, and is currently in Phase 2 clinical trials for candidemia and vulvovaginal candidiasis (VVC). Topical formulations of CD101 were optimized and found to be efficacious using a rat VVC model. Initial rat VVC studies were performed using an azole-susceptible C. albicans strain (ATCC 44858). We have since developed mouse disseminated and rat VVC infection models using an azole-resistant C. albicans strain (R357). The results of these studies are presented and discussed in this poster.

METHODS

Mouse disseminated infection model
- Neutropenic ICR Mice (n = 5/group)
- Cyclophosphamide on Days -4 (-150 mg/kg) and -1 (-100 mg/kg)
- Infection – Day 0, C. albicans R357, 10^5 CFU/mouse
- Treatment with a single dose, 2 hr after infection
  - Vehicle or CD101, intranasal (IP)
  - Amphotericin B – intravenous (IV)
- Flucloxacillin – Oral (PO)
- Kidney CFU – 48, 72 hr after infection

Rat VVC model
- Oopho hysterectomyized Wistar Rats (n = 5/group)
- 17β-estradiol (10 mg/kg) 3 days before infection and 4 mg/kg/week
- Deamethasone (2 mg/L) added to drinking water
- Vaginal Infection – Day 0, C. albicans (ATCC 44858 or R357)
  10^5 CFU/vaginal wash
- Treatment starts 2 days after infection for 3 days, Days 2 to 4
- Vaginal lavage/CFU from separate groups – Days 5 to 12 after infection (1 to 8 days after treatment cessation)

Vaginal infection
- Vaginal lavage CFU on days 5 to 12

RESULTS

C. albicans strain R357 is an azole-resistant human blood isolate.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Endpoint (1/% inhibition)</th>
<th>MIC (μg/mL)</th>
<th>Susceptibility (CLSI)</th>
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<tbody>
<tr>
<td>Fluconazole</td>
<td>50% =64 R</td>
<td></td>
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</tr>
<tr>
<td>Voriconazole</td>
<td>50% =64 R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>100% = 0.5 S</td>
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<tr>
<td>Caspofungin</td>
<td>50% = 0.25 S</td>
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<tr>
<td>CD101</td>
<td>100% = 0.125 S</td>
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With a long systemic half-life, CD101 was previously shown to be highly effective against azole-resistant C. albicans (R357) for at least 72 hrs following a single dose. Plots below show difference relative to initial counts.

RESULTS (cont’d)

In earlier rat VVC studies, topical CD101 gel given 2BID eradicated azole-susceptible C. albicans (ATCC 44858) up to at least 1 week after treatment cessation. Flucloxacillin given orally showed modest improvement whereas topical miconazole (2% cream) showed fungal rebound less than 1 week after treatment cessation.

With optimization, a slower release gel formulation of CD101 was developed that enabled once daily (QD) topical administration. This slower release CD101 gel formulation was found to be highly effective in the rat VVC model of azole-resistant C. albicans (R357). The vaginal lavage CFU showed that topical CD101 cleared the vaginal infection and reduced fungal burden for at least 1 week after treatment cessation. Nystatin (2.3% or 100,000 USP/g), a polyene antifungal, did not appear to reduce vaginal CFU as effectively on day 5 compared to CD101.

RESULTS (cont’d)

CD101 also showed comparable cidality in vaginal tissue CFU reduction.

CONCLUSIONS

CD101 is a novel, stable and long-acting echinocandin, demonstrated efficacy in mouse disseminated infection as well as rat VVC models of azole-resistant Candida. The CFU reduction in these tested models shows that CD101 is fungicidal in vivo against C. albicans.

REFERENCES

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