Efficacy of CD101, a novel echinocandin antifungal, in a mouse model of disseminated aspergillosis

Y. Ong1, K. Bartizal1, L. Miesl1, H-H. Huang2, and W-T. You2
1Cidara Therapeutics, Inc., San Diego, CA, USA; 2Eurofins Panlabs, Ltd., Taipei, Taiwan

Abstract

Purpose: CD101, a novel echinocandin with long-acting pharmacokinetics and chemical stability, is being developed as an IV, once-weekly administered antifungal for serious fungal infections. CD101 IV is currently in clinical development for the treatment of candidemia. Given the potent in vitro activity of CD101 against A. fumigatus, this study was conducted to evaluate the in vivo efficacy of CD101 IV for treatment of aspergillosis using a disseminated infection model in neutropenic mice.

Methods: The susceptibility of the A. fumigatus test strain ATCC 13073 was evaluated by measuring the minimal effective concentration (MEC) for changes in the hyphal morphology (CLSI protocol M38-A2). The in vivo efficacy was assessed using a mouse model of disseminated aspergillosis in which neutropenic animals were infected by injecting a suspension of A. fumigatus strain ATCC 13073 into the tail vein with an inoculum size of 10⁶ CFU/mouse. Test article and vehicle were administered to groups of 10 mice twice daily by IV injection starting 2 h after infection for five days (bid × 5). Survival was monitored for 10 days after infection. The Fisher's exact test was performed to assess the significance of the differences between the test article and vehicle treatment groups.

Results: CD101 demonstrated potent in vitro activity against A. fumigatus strain ATCC 13073 with an MEC value of 0.0078 µg/mL. CD101 administered IV to infected neutropenic mice at 0.2, 1, and 5 mg/kg bid for 5 days was associated with a significant increase in 10-day survival compared to vehicle group (p < 0.05; Figure). Amphotericin B was used as the positive control treatment at 0.3 mg/kg for 5 days. Animal survival rate of CD101 at the lowest dose tested, 0.2 mg/kg, was comparable to amphotericin B at 0.3 mg/kg.

Conclusion: CD101 IV was shown to be effective when administered by the IV route, using a mouse model of disseminated A. fumigatus infection. The efficacy supports the utility of CD101 IV for the treatment of aspergillosis.

Introduction

• Echinocandins have potent antifungal properties against Aspergillus species.
• CD101 is a novel echinocandin with excellent stability and long-acting pharmacokinetics with potent in vitro activity against A. fumigatus that is similar to the marketed echinocandins (1-3).

The objective of this study was to evaluate the potential efficacy for treatment of disseminated aspergillosis in a mouse model.

In vitro susceptibility

Aspergillus fumigatus clinical isolates (n=64) (4)

<table>
<thead>
<tr>
<th>MEC (µg/mL)</th>
<th>Caspofungin</th>
<th>Anidulafungin</th>
<th>Micafungin</th>
<th>CD101</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>0.008</td>
<td>0.015</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

Methods

A. fumigatus in vitro susceptibility

The susceptibility of A. fumigatus ATCC 13073 was tested with the microdilution method of CLSI M38-A2. RPMI medium was seeded with 1-5 x 10⁵ CFU/mL of conidia. Assay plates were incubated at 28°C for 48 hours then inspected for growth inhibition and alterations of hyphal morphologies. The Minimum Inhibitory Concentration, MIC, of amphotericin B was the lowest concentration that resulted in complete inhibition of visual growth. The Minimum Effective Concentration, MEC, of echinocandins was defined as the lowest concentration that produced small rounded hyphal forms.

A. fumigatus disseminated infection model, mouse

Animals: Female ICR mice were immunosuppressed by three intraperitoneal injections of cyclophosphamide (cpm): 6 mg/mouse on Day -3, then 2 mg/mouse on Days +1 and +4.

Infection: Animals were inoculated by IV injection with conidia of strain ATCC 13073, 2 x 10⁸ CFU per mouse, on Day 0.

Drug formulation and administration: CD101 was formulated in 10% DMSO, 1% Tween 20 in 0.9% NaCl. Amphotericin B was formulated in 0.9% NaCl. CD101 was administered by intravenous (IV) injection and amphotericin B was administered by intraperitoneal (IP) injection.

Outcome measure: Survival was monitored daily for 10 days. Significance was assessed with the Fisher's Exact test.

Results

(A) A. fumigatus ATCC 13073 in vitro susceptibility

<table>
<thead>
<tr>
<th>Amphotericin B</th>
<th>Caspofungin</th>
<th>Anidulafungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC (µg/mL)</td>
<td>Caspofungin</td>
<td>Anidulafungin</td>
<td>Micafungin</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0.008</td>
<td>0.008</td>
</tr>
</tbody>
</table>

(B) A. fumigatus disseminated infection model, mouse 5 day dosing

CD101 administered twice daily (bid) for five days showed efficacy similar to amphotericin B.

- CD101 – 0.2, 1 and 5 mg/kg, IV, bid five days
- Amphotericin B – 0.3 mg/kg, IP, bid five days
- Started 1 and 7 hr after infection

(C) A. fumigatus disseminated infection model, mouse one dose

CD101 administered once showed efficacy similar to amphotericin B.

- CD101 – 2 mg/kg, IV and IP
- Amphotericin B – 2 mg/kg, IP
- Administered 1 hr after infection

CONCLUSIONS

• CD101 demonstrated efficacy against disseminated A. fumigatus infection in mice using IV and IP administration.

• There was a positive dose response for the 3 CD101 doses tested.

• One 2 mg/kg dose showed efficacy similar to that of amphotericin B.

• CD101 may offer a promising treatment for disseminated aspergillosis in humans.

References


Animal welfare

The studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC, 2011). Experiments were performed in the Eurofins Panlabs AAALAC-accredited vivarium with the oversight of veterinarians in compliance with the Eurofins Panlabs IACUC regulations to assure the humane treatment of laboratory animals.

Acknowledgements

We thank K.Y. Lin, Jui-Chieh Chien, Ingrid Yang, and Hsiang-Yu Lee for contributions to this study. This study was funded by a research grant from Cidara Therapeutics, Inc.