Evaluation of the Efficacy of CD101, a Novel Echinocandin, in the Treatment of Candida auris Infection Using a Murine Model of Disseminated Candidiasis

C. L. Hager1, L. Long1, E. L. Larkin1, and M. A. Ghannoum1

1Center for Medical Mycology, University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH

Abstract

Background: The first case in the Americas of an invasive infection caused by C. auris was reported in July of 2016. Multiple cases have since been reported with high mortality rates due to the multidrug-resistant nature of C. auris. Although C. auris shows increased susceptibility to the echinocandin class of antifungals, use of these drugs is restricted to multiple IV administrations. CD101 is a novel echinocandin with enhanced stability and pharmacokinetics, allowing for once weekly high dose administration.

Methods: Female 6- to 8-week-old CD-1 mice were inoculated with 3 x 10^7 C. auris blastospores via the lateral tail vein. Mice were randomized into 5 groups (n=5 for colony forming units (CFU) and n=10 for survival): CD101 20 mg/kg administered by intraperitoneal (IP) injection, fluconazole 20 mg/kg administered per os (PO), amphotericin B 0.3 mg/kg IP, and a vehicle control by IP. Treatments were administered 2 hours post-infection (day 1) and again on day 4 of the study for a total of 2 doses. Mice were monitored daily and a survival curve was generated. CFU were sacrificed on day 8 of the study. One kidney was removed from each mouse, homogenized, plated on potato dextrose agar (PDA), and incubated at 35°C for 2 days to determine CFU. The remaining survival mice were monitored until the end of the study (day 14).

Results: CD101 showed an average 3 log reduction in kidney CFU compared to fluconazole, amphotericin B, and vehicle-treated groups, which was statistically significant (P = 0.03, 0.03, and 0.04, respectively). At the end of the study, the percent survival of mice in CD101, fluconazole, amphotericin B, vehicle, and untreated groups was 80, 30, 20, and 0%, respectively (Figure 1).

Conclusions: Taken together, our findings show that CD101 possesses potent antifungal activity against C. auris infection in a disseminated model of candidiasis. Additionally, treatment with CD101 resulted in a significantly higher overall percent survival. Further investigation of this drug is warranted.

Materials & Methods

6- to 8-week-old female CD-1 mice were used in this study. Mice were inoculated with 3 x 10^7 C. auris blastospores via the lateral tail vein and randomized into 5 groups (n=5 for colony forming units (CFU) and n=10 for survival): CD101 20 mg/kg administered by intraperitoneal (IP) injection, fluconazole 20 mg/kg administered per os (PO), amphotericin B 0.3 mg/kg IP, and a vehicle control by IP.

A total of 2 treatment doses were administered: one 2 hours post-infection (day 1) and the other on day 4 of the study. Mice were monitored daily.

The survival mice were monitored until the end of the study (day 14) and a survival curve was generated. CFU groups were sacrificed on day 8 of the study. One kidney was removed from each mouse, homogenized, plated on potato dextrose agar (PDA), and incubated at 35°C for 2 days to determine CFU.

Figure 1 (Percent survival of mice in all groups):
- The untreated mice succumbed to the infection by day 5 of the study.
- Mice in the fluconazole-treated group showed 100% mortality by day 13 of the study.
- Percent survival for mice in the CD101-, amphotericin B-, and vehicle-treated groups were 80%, 30%, and 20%, respectively.
- CD101-treated mice had a significantly higher percent survival compared to mice treated with fluconazole, amphotericin B, and vehicle, as well as untreated mice (P = 0.0001, 0.01, 0.005, and <0.0001, respectively).

Figure 2 (Average log CFU from kidneys):
- Mice treated with CD101 showed significantly lower average log CFU in the kidneys compared to mice treated with fluconazole, amphotericin B, and vehicle (P = 0.03, 0.03, and 0.04, respectively).

Summary

CD101 showed superior efficacy in reducing fungal burden in the kidneys of C. auris infected mice.

Treatment with CD101 resulted in higher overall percent survival of mice.

Given this efficacy and the pharmacokinetics of CD101 allowing once weekly administration, it may be a more favorable treatment over currently available therapies.

Acknowledgments

This work was supported in part by Cidara Therapeutics