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

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C. L. Hager[1], L. Long[1], E. L. Larkin[1], and M. A. Ghannoum[1]
[1]Center for Medical Mycology, University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH

Email Emily Larkin at Emily.larkin@uhhospitals.org
or Dr. Mahmoud Ghannoum at mag3@case.edu

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. In this study, we evaluated the efficacy of CD101 in the treatment of disseminated *C. auris* infection using a murine model of disseminated candidiasis.
Methods: Female 6-8 week old CD-1 mice were immunosuppressed with cyclophosphamide (200 mg/kg) 3 days prior to infection and 150 mg/kg 1 day post-infection. On the day of infection, 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 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. 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, 0, 30, 20, and 0%, respectively (Figure 1).
Conclusion: 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.

Background

- The first case in the Americas of an invasive infection caused by *C. auris* was reported in July of 2016.
- *C. auris* is often multidrug-resistant leading to high mortality.
- The echinocandin class of antifungals appears to be the most effective class against *C. auris* infection.
- Current echinocandins require multiple IV administration to complete a course of therapy.
- CD101 is a novel echinocandin with enhanced stability and pharmacokinetics, allowing for high plasma drug exposure and once weekly administration.
- In this study, we evaluated the efficacy of CD101 in the treatment of disseminated *C. auris* infection using a murine model of disseminated candidiasis.

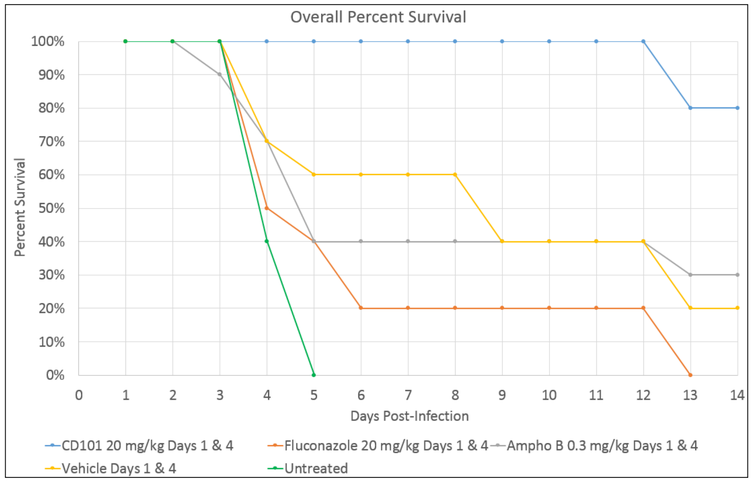

Figure 1: Survival curve of mice in all treatment groups after 14 days.

Materials & Methods

- 6- to 8-week–old female CD-1 mice were used in this study
- Mice were immunosuppressed with cyclophosphamide 3 days prior to infection at 200 mg/kg and 1 day post-infection at 150 mg/kg.
- 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.

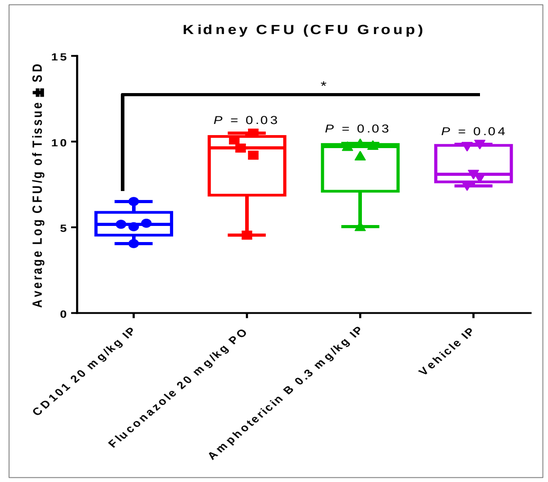

Figure 2: Average log CFU ± SD of kidneys one day after the last treatment

Results

Figure 1 (Percent survival of mice in all groups):
- The untreated mice succumbed to the infection with 100% mortality 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

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