Pharmacological Basis of CD101 Efficacy: Exposure Shape Matters

Elizabeth A. Lakota, Pharm.D., M.S.
Institute for Clinical Pharmacodynamics
242 Broadway
Schenectady, NY 12305
Telephone: (518) 631-8100/(518) 429-2600
E-mail: ELakota@ICPD.com

E.A. Lakota[1], C.M. Rubino[1], V. Ong[2], K. Bartizal[2], L. Miesel[3], S.M. Bhavnani[1], P.G. Ambrose[1],
[1]Institute for Clinical Pharmacodynamics, Schenectady, NY; [2]Cidara Therapeutics, San Diego, CA; [3]Eurofins Panlabs, Ltd., St. Charles, MO.

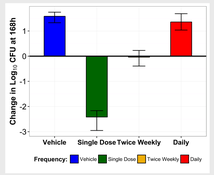
REVISED ABSTRACT

Introduction: All commercially available echinocandin antifungal agents are administered once daily, with efficacy driven by AUC. CD101 is a novel echinocandin with a concentration-dependent pattern of fungicidal activity *in vitro* and a long half-life (up to 150 h in humans, approximately 70-80 h in mice). Given these distinct characteristics, it is likely that the shape of the CD101 AUC greatly influences efficacy.

Methods: To test this hypothesis, the same total AUC was administered to groups of neutropenic ICR mice infected with *Candida albicans* (n=5) using 3 different schedules. A total CD101 dose of 2 mg/kg was administered as a single IV dose or in equal divided doses of either 1 mg/kg twice-weekly or 0.29 mg/kg/d over 7 days. The studies included a no-treatment control group. Animals were rendered neutropenic by 2 IP cyclophosphamide doses (150 and 100 mg/kg, administered 4 days and 1 day prior to infection, respectively) and inoculated with *C. albicans* R303 (1 x 10^3 CFU/mouse) 24 h prior to treatment. Animals were euthanized at 168 h following the start of treatment. Paired kidneys were harvested, homogenized, serially diluted, and plated for CFU determination.

Results: As shown in the figure, fungi grew well in the no-treatment control group with variable activity in treatment groups. When the CD101 $AUC_{0\text{-}168}$ was administered as a single dose, there was a >2 log_{10} CFU reduction from baseline at 168 h. When that same AUC was administered in 7 equal divided daily doses, there was an increase by >1 log_{10} CFU from baseline at 168 h.

Conclusions: These data support the hypothesis that the shape of the CD101 AUC greatly influences efficacy. CD101 was considerably more effective when given once per week compared to the same dose divided into twice-weekly or daily regimens.



INTRODUCTION

- CD101 is a novel echinocandin antifungal agent with activity against *Aspergillus* and *Candida* species, including azole- and echinocandin-resistant isolates.
- CD101 is a structural analog of anidulafungin, resulting in different physical and biological properties.
  - Reduced hepatotoxicity compared to anidulafungin.
  - Longer half-life (up to 150 hours in humans, approximately 70-80 hours in mice) compared to anidulafungin (~25 hours in humans).
- The ratio of the area under the concentration-time curve to the minimum inhibitory concentration (AUC:MIC ratio) is the pharmacokinetic-pharmacodynamic (PK-PD) index associated with CD101 efficacy [1].
- CD101's long half-life and the above-described PK-PD index associated with efficacy provide the opportunity to evaluate daily and extended interval dosing regimens.
  - Front loading drug exposure has resulted in better efficacy for other long half-life antimicrobials [2].
  - When considered in light of the long half-life of CD101, we hypothesized that the shape of the concentration-time profile would play a role in the efficacy.
- This theory was tested using data from an animal model in which the same total weekly dose was administered as a single dose, a twice-weekly regimen, or a daily regimen.

OBJECTIVE

- The objective of this study was to determine if the frequency of CD101 administration and associated effect on the shape of concentration-time curves influence efficacy in a neutropenic candidemia mouse model.

METHODS

Pharmacokinetic Study

- Healthy female ICR mice weighing 22 ± 2 g were given a single dose of CD101 via intraperitoneal (IP) injection.
  - The following doses were studied: 1, 4, and 16 mg/kg.
  - Three mice per dose were studied.
- CD101 plasma concentrations were determined at 0, 1, 3, 6, 12, 24, 48, 72, 96 hours post-dose using a validated LC/MS assay with a lower limit of quantification of 0.02 µg/mL.

Dose-Fractionation Study

- Male or female ICR mice (n=5 per regimen and observation time) weighing 22 ± 2 g were rendered neutropenic for the study by injecting the mice with cyclophosphamide treatment four days (- Day 4) (150 mg/kg IP) and one day (- Day 1) prior to infection at 100 mg/kg IP. Neutropenia was sustained for the duration of the study with cyclophosphamide doses (100 mg/kg IP) every 48 hours on days +1, +3, + 5 and + 7 after infection.
- Each animal was inoculated intravenously with 1 x 10^3 CFU of *Candida albicans* (Isolate R303, MIC=0.125 mg/L).
- CD101 (or vehicle) was administered 24 hours post-infection via IP injection. The doses studied are shown in **Table 1**.

Table 1. Summary of CD101 dosing regimens evaluated

Total Dose	Dosing Interval	Fractionated Doses
0.7 mg/kg	Single Dose	0.7 mg/kg x 1
	Twice Weekly	0.35 mg/kg x 2
	Daily	0.1 mg/kg x 7
2 mg/kg	Single Dose	2 mg/kg x 1
	Twice Weekly	1 mg/kg x 2
	Daily	0.29 mg/kg x 7
7 mg/kg	Single Dose	7 mg/kg x 1
	Twice Weekly	3.5 mg/kg x 2
	Daily	1 mg/kg x 7

- Mice were sacrificed 168 hours (7 days) following the start of treatment.
- Control arm mice were sacrificed 0, 24, and 48 hours post-administration of vehicle.
- Paired kidneys were aseptically harvested, homogenized, and plated for colony counts to determine the fungal burden (CFU/g).

Pharmacokinetic-Pharmacodynamic Analyses

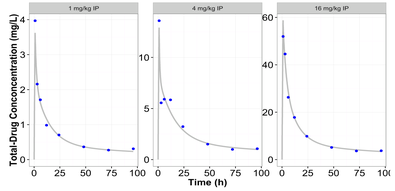
- Using the data collected from the PK study, a PK model was developed in S-ADAPT [3].
- Using the developed PK model, concentration-time profiles and $AUC_{0\text{-}168}$ values were computed for each dosing regimen administered in the dose-fractionation study.
  - Free-drug plasma concentrations were generated using a murine protein binding value of 99.1% [4].
- Relationships between the change in log_{10} CFU from baseline at 168 hours and $AUC_{0\text{-}168}$ were explored.

RESULTS

Pharmacokinetic Study

- CD101 exhibited linear PK over the dose ranged studied (1 to 16 mg/kg IP).
- A four-compartment model best described the PK data. Model fits are displayed in **Figure 1**.

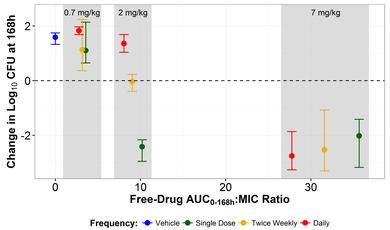
Figure 1. Observed (blue solid circles) and model fitted (lines) CD101 concentrations versus time following administration of single CD101 doses



Dose-Fractionation Study

- The results of the dose-fractionation study are displayed in **Figure 2**.
- Fungi grew well in the no-treatment control group.
- The magnitude of net change in log_{10} CFU from baseline at 168 hours was similar regardless of fractionation schedule within the CD101 0.7 and 7 mg/kg dosing groups.
- However, results within the CD101 2 mg/kg group varied by the fractionation schedule.

Figure 2. Mean (solid circles) and range (error bars) change in log_{10} CFU from baseline versus $AUC_{0\text{-}168}$:MIC ratio by fractionation schedule

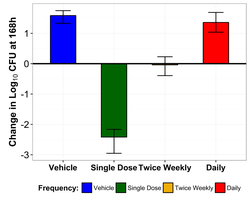


Note five mice died in the 0.7 mg/kg group prior to the end of the study.

- The change in log_{10} CFU reduction from baseline at 168 hours by fractionation schedule for the CD101 2 mg/kg group is displayed in **Figure 3**.
- When a total dose of 2 mg/kg was delivered daily (0.29 mg/kg/day), the magnitude of net change in log_{10} CFU from baseline at 168 hours was similar to the no-treatment control group.
- However, when 2 mg/kg is delivered as a single dose, there was a >2 -log_{10} CFU reduction from baseline at 168 hours.
- The 2 mg/kg x1 and 0.29 mg/kg daily x 7 regimens had similar cumulative CD101 exposures at 168 hours, as displayed in **Figure 2**. Despite having similar exposures, which influences efficacy, these regimens showed different effects.

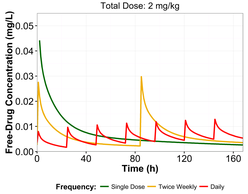
RESULTS

Figure 3. Mean (bar) and range (error bars) change in log_{10} CFU from baseline allowing administration of CD101 2 mg/kg grouped by fractionation schedule



- Free-drug plasma concentration-time profiles of the three fractionated CD101 2 mg/kg dosing regimens are displayed in **Figure 4**.
- All three regimens display different exposure profiles. In particular, the single dose regimen results in larger CD101 exposures early in therapy.
  - Free-drug plasma $AUC_{0\text{-}24}$ is 0.0654, 0.0303, and 0.00948 mg·h/L following administration of CD101 2 mg/kg as a single dose, twice-weekly, and daily regimen, respectively.
  - Further, administration of a single dose results in free-drug plasma concentrations which remain above those for the twice-weekly and daily regimens for 84 and 48 hours, respectively.

Figure 4. Simulated free-drug concentration time profiles for the fractionated CD101 2 mg/kg regimen



- Three CD101 regimens with similar total exposures, yet different exposure shapes, displayed considerably different magnitudes of net change in log_{10} CFU from baseline at 168 hours. This suggests that the shape of the CD101 AUC is a determinant of efficacy, with front loaded regimens demonstrating greater benefit.

CONCLUSIONS

- The magnitude of the net change in fungal burden was similar regardless of fractionation schedule within the CD101 0.7 and 7 mg/kg dosing groups, but differed within the 2 mg/kg group.
  - A 2 mg/kg dose was considerably more effective when given once per week compared to the same dose divided into twice-weekly or daily regimens.
- These data support the hypothesis that the shape of the CD101 AUC greatly influences efficacy.

REFERENCES

1. Rubino CM, Ong V, Thye D, Ambrose PG. Pharmacokinetics Pharmacodynamics (PKPD) of a Novel Echinocandin, CD101, in a Neutropenic Murine Disseminated Candidiasis Model. [Abstract # A-1292]. ICAAC. San Diego CA. September 17-21, 2015.
2. Ambrose PG, Drusano GL, Craig WA. In Vivo Activity of Oritavancin in Animal Infection Models and Rationale for a New Dosing Regimen in Humans. Clin Infect Dis 2012; Apr; 54 (S3):S220-8.
3. Bauer RJ. S-ADAPT/MCPEM User's Guide: Software for Pharmacokinetic, Pharmacodynamic and Population Data Analysis. Berkley, CA: 2006.
4. Cidara Therapeutics. Data on file.