**ABSTRACT**

Background: Because currently marketed echinocandins are administered by daily intravenous (IV) infusion, their usage is often limited to inpatient settings. A safe and effective echinocandin with physicochemical and pharmacokinetic (PK) properties enabling less frequent and alternate routes of administration is desired.

Methods: Structural modifications of different echinocandin scaffolds were made by rational design and synthesis. Test articles were evaluated by reversed-phase chromatography. Efficacy was evaluated in a candidiasis mouse model. The most promising candidates were further evaluated based on PK after IV administration in dogs, that article concentrations were determined by quantitative LC/MS/MS from extracted plasma and comparison to a standard curve. PK parameters were calculated using noncompartmental analysis.

Results: At the pharmacophore sites modified, scaffolds were intolerant of the large substituents, and in vitro activity diminished with increasing bulk. Smaller hemispherical ether and substituted amine derivatives at C5-amine resulted in some compounds displaying enhanced efficacy. Permanently charged, pH-dependent, and charge-neutral analogues produced up to 4-log reductions of fungal burden in mice. Half-lives of the most efficacious compounds varied up to 4-46 h (2 to 3 h in dogs). The compound with the most desirable combination of efficacy and PK (CD101) was selected for nonclinical development.

Conclusions: CD101 is a novel echinocandin with unique modifications of the cephalosporin B, C, and D ring systems. The compounds for the study were made by an iterative process of multiple iterations and were synthesized. Test articles were made by rational design and synthesis. Test articles were harvested, homogenized, and assayed for fungal burden. The single-dose pharmacokinetics of test agents were compared in beagle dogs. Levels of test article in the plasma samples were measured by quantitative LC/MS/MS analysis compared to a calibration curve and an internal standard.

**RESULTS (cont’d)**

Compounds were discovered with activity and/or other properties similar to or superior to those of known comparators using the iterative process summarized in Figure 1.

**CONCLUSIONS**

- CD101 and some other novel echinocandins displayed activity comparable or superior to that of anidulafungin in a mouse model of disseminated candidiasis.

- Promising candidates included charged, chargeable, and charge-neutral moieties.

- CD101 has an unusually long half-life in the dog, an observation that has also been observed in the mouse, rat, and cynomolgus monkey, and chimpanzees.

- CD101 has desirable tissue penetration, which could be beneficial for invasive infections.

- Both the hemispherical ether and ammonium moieties of the choline group contribute to the stability and PK advantage of CD101. Structurally similar compounds featuring only one of these moieties did not exhibit the same beneficial PK.

- The properties of CD101 may enable more flexible dosing schedules and alternate routes of administration, thereby enabling utilization for indications not amenable to daily infusion therapies.

- The strong antifungal activity of CD101 coupled with high exposures and safety margin afforded by its unique PK profile may prove helpful in overcoming antifungal-resistant organisms.

**REFERENCES**


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**METHODS**

The compounds for the study were made by an iterative process of rational design and synthesis followed by reversed-phase HPLC and purification.

Female CD-1 mice were rendered neutropenic with cyclophosphamide and were inoculated with C. albicans R303. Test articles were administered intraperitoneally 2 h after infection. After 24 h, kidneys were harvested, homogenized, and assayed for fungal burden. The single-dose pharmacokinetics of test agents were compared in beagle dogs. Levels of test article in the plasma samples were measured by quantitative LC/MS/MS analysis compared to a calibration curve and an internal standard.

**RESULTS**

Compounds were discovered with activity and/or other properties similar to or superior to those of known comparators using the iterative process summarized in Figure 1.

**CONCLUSIONS**

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