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Efficacy of CD101, a Novel Echinocandin, in Mouse Models of Aspergillosis and Azole-Resistant Disseminated Candidiasis

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AMENDED ABSTRACT

Background: CD101 is a novel echinocandin with long-acting pharmacokinetics and exceptional stability in development for prevention and treatment of serious fungal infections. The in vivo efficacy of CD101 was evaluated using neutropenic mouse models of azole-resistant candidiasis and aspergillosis.

Methods: An azole-resistant strain of *Candida albicans* (R357; resistant to fluconazole [Flu], voriconazole, and posaconazole but susceptible to amphotericin B [AmB] and echinocandins) isolated from human blood was used for the mouse candidiasis model. A test strain of *Aspergillus fumigatus* (ATCC 13073) was used for the mouse aspergillosis model. Mice were rendered neutropenic by cyclophosphamide and then infected by injections of *C. albicans* (10^5 CFU/mouse) or *A. fumigatus* (10^4 CFU/mouse) into the tail vein. Test articles were administered starting 2 hours after infection. In the mouse candidiasis model, groups of 5 mice each received one dose of AmB (3 mg/kg IV), Flu (20 mg/kg orally), or CD101 (3, 10 or 30 mg/kg by intraperitoneal administration [IP]). After 72 hours postinfection, mice were euthanized and *C. albicans* counts in kidney tissue (CFU/g) were measured. In the mouse aspergillosis model, groups of 10 mice each received one dose of AmB (3 mg/kg IP) or CD101 (2 mg/kg IV and IP). Survival was monitored daily for 10 days. Differences between vehicle and test article groups were assessed for significance by one-way ANOVA followed by Dunnett's test and Fisher's Exact test in the candidiasis and aspergillosis models, respectively.

Results: One dose of CD101 3 mg/kg produced a >99.9% (or > 3log; P<0.001) reduction in *C. albicans* CFU compared with vehicle through at least 72 hours postdose following a single IP dose. AmB showed similar, albeit less robust, efficacy (>99% or >2log reduction in CFU; P<0.05), whereas fluconazole was less efficacious (83.9% or <2log reduction in CFU). In the aspergillosis model, CD101 administered 2 mg/kg IV or IP showed similar efficacy to that of AmB 2 mg/kg IP, both with significantly longer survival than vehicle (P<0.05; Figure).

Conclusions: A single dose of CD101 3 mg/kg produced significant reduction in *C. albicans* burden compared with vehicle (P<0.001) in the neutropenic mouse model of azole-resistant candidiasis, demonstrating efficacy comparable, if not better, to that of AmB at the same dose. One dose of CD101 also demonstrated efficacy in the mouse model of aspergillosis. These data support the continued development of CD101 for treatment of serious infections caused by *Candida*, including azole resistant strains, and *Aspergillus* spp.

INTRODUCTION

- Patients undergoing treatment for hematological malignancies are at increased risk for invasive, potentially fatal, fungal infections, such as candidiasis, aspergillosis, and *Pneumocystis* pneumonia.
- The increasing prevalence of infections caused by non-albicans species and resistance to azole antifungals are serious concerns, particularly as widespread use of fluconazole for antifungal prophylaxis continues (1-3).
- CD101 is a novel echinocandin with potent in vitro activity against *Candida* spp. and *Aspergillus fumigatus*, similar to that of other echinocandins (4,5), and demonstrated in vivo efficacy (6,7)
- CD101 is differentiated by exceptional stability and long-acting pharmacokinetics that support longer-term dosing intervals and potential routes of administration beyond once-daily intravenous infusion (8,9)
- Here we evaluated the potential efficacy of CD101 against azole-resistant candidiasis and aspergillosis using disseminated mouse infection models.

METHODS

Mice

- In both models, Institute for Cancer Research (ICR) mice were rendered neutropenic by cyclophosphamide (cpm)

Inoculum

- Azole-resistant *C. albicans* R357 (10^5 CFU/mouse): a human blood isolate resistant to fluconazole, voriconazole, and posaconazole, and susceptible to amphotericin B and echinocandins (Table)
- Conidia of *A. fumigatus* ATCC 13073 (2x10^4 CFU/mouse)

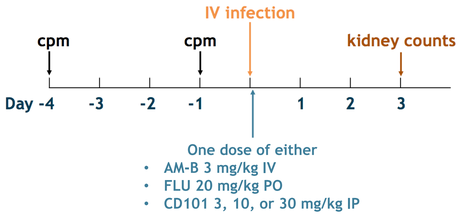
Susceptibility of azole-resistant *C. albicans* R357

Antifungal agent	Endpoint (% inhibition)	MIC (µg/mL)	Susceptibility (CLSI)
Fluconazole	50%	>64	R
Voriconazole	50%	>64	R
Posaconazole	50%	>64	
Amphotericin B	100%	0.5	S
Caspofungin	50%	0.25	S
CD101	50%	0.125	

METHODS (cont'd)

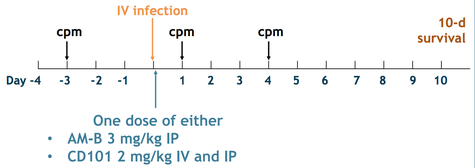
Azole-resistant disseminated candidiasis model

- Neutropenic mice inoculated with *C. albicans* R357 into tail vein
- Test articles administered 2 h after infection



Disseminated aspergillosis model

- Neutropenic mice inoculated with *A. fumigatus* ATCC 13073 into tail vein
- Test articles administered 1 h after infection



AM-B = amphotericin B; cpm = cyclophosphamide; FLU = fluconazole; IP = intraperitoneal; IV = intravenous; PO = oral.

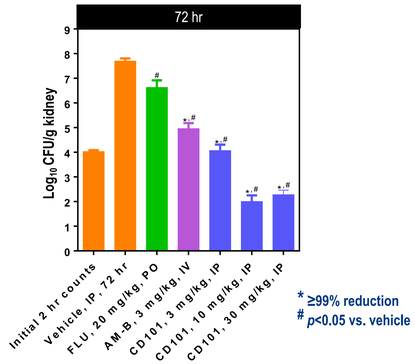
Analyses

- Outcomes
  - *C. albicans* counts (CFU/g) in kidney tissue 72 hours post-infection
  - Daily survival monitoring x 10 days in the aspergillosis model
- Differences between vehicle and test article groups were assessed for significance by one-way ANOVA followed by Dunnett's test and Fisher's Exact test in the candidiasis and aspergillosis models, respectively.

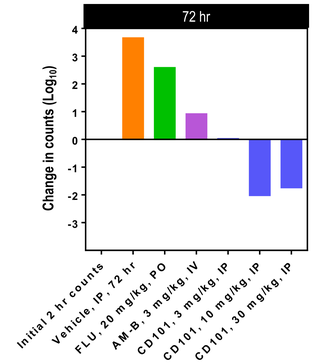
RESULTS

Azole-resistant candidiasis model

- CD101 at all 3 tested doses demonstrated ≥99% reduction in *C. albicans* counts (log_{10} CFU/g kidney) 72 h after infection



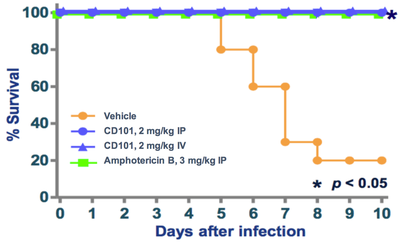
- Among the articles tested, CD101 (10 mg/kg and 30 mg/kg) was the only treatment to demonstrate a reduction (fungicidal) in fungal burden at 72 h compared with pretreatment counts (initial 2 h counts)



RESULTS (cont'd)

Disseminated aspergillosis model

- CD101 (2 mg/kg IP and IV) demonstrated similar rates of survival to that of amphotericin B (3 mg/kg IP)
- CD101-treated mice had better survival outcomes than did controls



CONCLUSIONS

- CD101 administered IP and IV was efficacious in neutropenic mouse models of disseminated candidiasis and aspergillosis
  - Significantly greater fungal burden reduction and rates of survival than vehicle
  - Outcomes comparable to those of AM-B at the same doses used in each respective model
- CD101 efficacy persisted 72 h after infection, consistent with its long-acting pharmacokinetics
- These data demonstrate the potential of CD101 in humans and support its continued development for treatment and prevention of serious infections caused by *Candida*, including azole-resistant strains, and *Aspergillus* spp.

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