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A Single-Dose, Subcutaneous (SC) Prophylaxis CD101 Administration Prevents Fungal Infection in Mouse Models of Candidiasis and Aspergillosis

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ABSTRACT

CD101 is a novel echinocandin that has shown robust preclinical efficacy. Its differentiated PK profile may offer the potential for intermittent dosing and extend utility to include inpatient and outpatient prophylaxis. Mouse (neutropenic and non-neutropenic) models of disseminated candidiasis and aspergillosis were used to evaluate the efficacy of single subcutaneous (SC) CD101 doses as antifungal prophylaxis.

Candidiasis: ICR mice (5/grp) were rendered neutropenic by cyclophosphamide (CP) on day -4/-1 (150/100 mg/kg), then infected with *C. albicans* SC5314 (IV, 100 µL, 10^5 CFU/mouse) on day 0. Mice were given one SC CD101 dose (5, 10, or 20 mg/kg) on day -5, -3 or -1 prior to infection. At 24 h post infection, kidneys were removed for CFU enumeration.

Aspergillosis: ICR mice (6/grp) were rendered neutropenic by CP on days -3/+1/+4 (300/100/100 mg/kg), then infected with *A. fumigatus* 13073 (IV, 100 µL, 10^4 CFU/mouse) on day 0. Prior to infection, mice were given one SC CD101 dose (5, 10 or 20 mg/kg) on day -5, -3, or -1. Survival was monitored for 14 days. The same models (using CD101 3, 10, or 30 mg/kg) were also studied in non-neutropenic DBA mice.

In the neutropenic mouse candidiasis model, CFU reduction correlated with increasing CD101 dose and with prophylaxis closer to fungal challenge. No detectable CFU was found in all but 1 animal when 20 mg/kg (400 mg human equivalent) was given up to 5 days before infection. No detectable CFU was found in all animals with 10 mg/kg dosed up to 3 days before infection. At 5 mg/kg, CFU reduction was observed when given 1 day before infection whereas CFU increase was observed when given on day -3 or -5. In non-neutropenic mice, the CFU reduction was more robust. At ≥10 mg/kg, no detectable CFU was found in all animals dosed up to 5 days before infection. At 3 mg/kg, a net stasis was achieved when given on day -3.

In the neutropenic mouse aspergillosis model, CD101 5, 10, or 20 mg/kg on day -5, -3 or -1 showed >50% increases in survival compared with vehicle. There was 100% survival regardless of prophylactic treatment day with doses ≥10 mg/kg. The 5 mg/kg group showed increased survival when prophylaxis was given closer to challenge. Comparable survival results were observed in the non-neutropenic model.

A single CD101 dose was protective against fungal infection when given up to 5 days prophylactically in mice suggesting prolonged CD101 tissue residence times to complement a long plasma half-life. CD101 SC may be a new agent/route for even less frequent (possibly every 1-2 wks) echinocandin prophylaxis in humans, who have 3X longer plasma half-life than mice.

INTRODUCTION

Fungal infections pose a significant public health burden with high morbidity and mortality. Immunocompromised patients continue to be at risk for opportunistic infections caused by fungal pathogens, such as *Candida* spp. and *Aspergillus* spp.

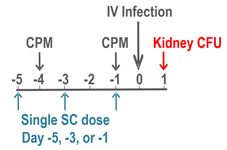
CD101 is a novel echinocandin that has demonstrated robust preclinical efficacy and is differentiated from currently available echinocandins by a long-acting pharmacokinetic profile, allowing for once-weekly intravenous dosing, and exceptional stability and solubility, enabling formulating for subcutaneous (SC) administration.

The potential for intermittent SC administration may extend the practical utility of CD101 beyond that of other echinocandins, to include antifungal treatment and prophylaxis in the outpatient setting.

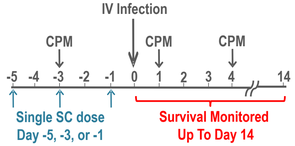
Neutropenic (cyclophosphamide-induced) as well as non-neutropenic (normal) mouse models of candidiasis and aspergillosis were used to evaluate the in vivo efficacy of single SC doses of CD101 for the prevention of fungal infections.

MOUSE PROPHYLAXIS MODELS

Candidiasis model: ICR mice (5/grp) were rendered neutropenic by cyclophosphamide (CPM) on day -4 (150 mg/kg) and day -1 (100 mg/kg), then challenged (day 0) with *C. albicans* ATCC SC5314 via IV (100 µL, 10^5 CFU/mouse). Prior to infection, mice were given one SC dose (5, 10, or 20 mg/kg) of CD101 on day -5, -3, or -1. Kidneys were removed for CFU enumeration at 24 hours post-infection. Non-neutropenic DBA mice were also studied using a similar design.

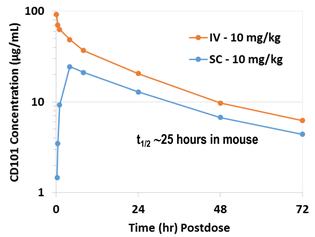


Aspergillosis model: ICR mice (6/grp) were rendered neutropenic by cyclophosphamide on days -3 (6 mg/mouse), +1 and +4 (2 mg/mouse). Challenge with *A. fumigatus* ATCC 13073 via IV (100 µL, 10^4 CFU/mouse) occurred on day 0. Prior to challenge, mice were given one SC dose (5, 10 or 20 mg/kg) of CD101 on day -5, -3, or -1. Survival was monitored for 14 days. Non-neutropenic DBA mice (10^6 CFU/ mouse challenge) were also studied using a similar design.



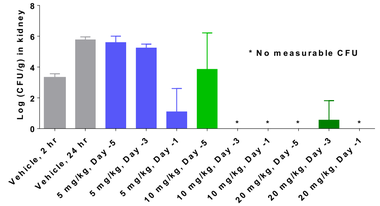
MOUSE PHARMACOKINETICS

The PK profile of CD101 in mice (3/group) following a 10-mg/kg IV or SC dose shows a half-life of ~25 hrs and SC bioavailability of ~50%[1].

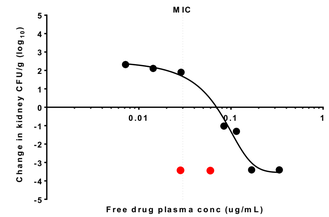


RESULTS

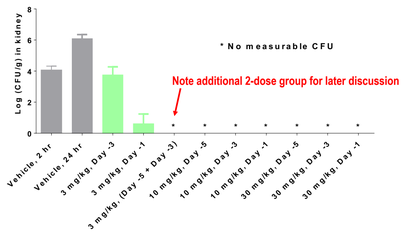
In neutropenic mouse candidiasis (MIC=0.03 µg/mL), complete kidney CFU clearance was observed in all but one animal receiving 20 mg/kg on day -3 and all animals receiving 10 mg/kg at days -3 and -1. At doses of 5 or 10 mg/kg, prophylaxis with CD101 demonstrated a significant decrease in CFU at day -3 and -1.



Good correlation was noted between free drug plasma concentration at time of infection with CFU reduction with exceptions: Red symbols correspond to 10 and 20 mg/kg (day -3 and -5, respectively) and indicate an apparent hysteresis where effective prophylaxis occurs despite low plasma conc, likely due to slower clearance from tissues.

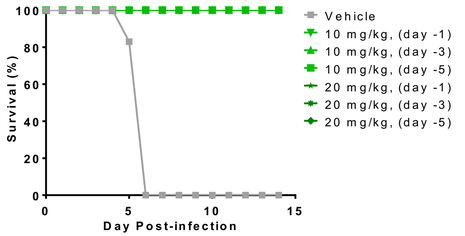


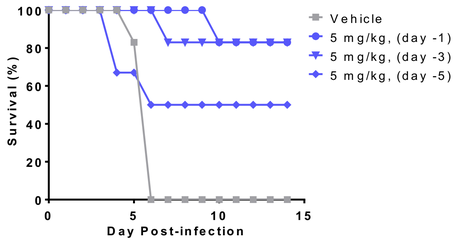
In non-neutropenic mouse candidiasis (same strain/inoculum), more dramatic CFU reduction was observed at a lower dose (3 mg/kg). Doses of ≥10 mg/kg were completely protective regardless of day of prophylaxis.



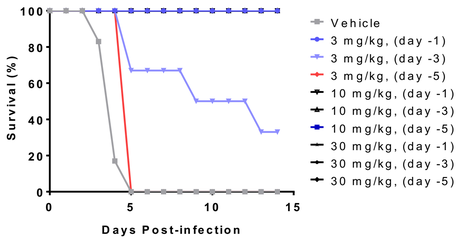
RESULTS (cont'd)

In neutropenic mouse aspergillosis (MEC=0.0078 µg/mL), survival was monitored for 14 days after challenge. All animals in the 10 and 20 mg/kg groups survived regardless of prophylactic treatment day. The 5 mg/kg group showed increased survival when prophylaxis was given closer to challenge.





In non-neutropenic mouse aspergillosis (same strain/inoculum), all animals given >10 mg/kg survived regardless of prophylactic treatment day. Similar to previous neutropenic model, the 3 mg/kg group showed increased survival when prophylaxis was given closer to challenge.



DISCUSSION / CONCLUSION

CD101, a novel echinocandin, was found to be protective against fungal infection in mice when administered as a single SC dose of ≥10 mg/kg (roughly ≥200 mg human IV dose) at up to 5 days (or about 5 mouse $t_{1/2}$) prior to infection challenge.

Additionally, results in the study with non-neutropenic or normal DBA mice suggested that two smaller doses (3 mg/kg) given within the same 5 days prior to infection challenge (on days -5 and -3) in mouse offer the same protection as a larger single dose (10 mg/kg on day -5).

As has been shown for caspofungin[2] and micafungin[3] in similar studies, tissue residence time likely plays an important role in CD101 prophylaxis efficacy. Tissue residence time for CD101 has been noted to be especially long-lasting by Perlin and colleagues using MALDI Imaging mass spectrometry[4].

Though it remains to be studied, it is reasonable to anticipate that the protective effect in human may encompass a longer duration than in mouse as the $t_{1/2}$ of CD101 in human ($t_{1/2}$ >90 hours) is >3x longer than in mouse. We estimate that the prophylactic effect from a single dose in mouse given 5 days (~5-times mouse $t_{1/2}$) prior to infection challenge should translate to similar prophylactic effect from a single dose given to humans for up to at least 2.5 weeks (~5-times human $t_{1/2}$).

These results suggest that CD101 may be a potential new agent for intermittent outpatient echinocandin treatment and prophylaxis of *Aspergillus* and *Candida*.

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DISCLOSURES

V.O., K.B.: employees of Cidara Therapeutics, Inc.
S.R.L., L.M.: None.