Antifungal Prophylaxis with CD101 in Immunosuppressed Mouse Models of Candidiasis, Aspergillosis, and Pneumocystis Pneumonia (PCP)

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INTRODUCTION
Fungal infections cause significant morbidity and mortality. Disease- and treatment-related immunosuppression in patients with hematological diseases increase the risk of opportunistic infection caused by Candida spp., Aspergillus spp., and Pneumocystis spp.

Antifungal prophylaxis is an important consideration for this population. For example, lack of adequate prophylaxis increased risk of Pneumocystis pneumonia (PCP) to 15%-45%, and mortality rates due to PCP are high (48% to 70%) among HSCT recipients.1

Safety and tolerability, drug-drug interactions, and variable pharmacokinetics are among the complications encountered with antifungals currently used for prophylaxis, such as azoles for Candida spp. and Aspergillus spp. and trimethoprim/sulfamethoxazole (TMP/SMX) for PCP.2,3 Evidence of emerging resistance to TMP/SMX is also a concern.4,5 Unmet needs in antifungal prophylaxis remain.3

CD101, a novel echinocandin in phase 2 development, has demonstrated preclinical safety and efficacy in studies of invasive fungal infection. Whereas currently approved echinocandins are limited to once-daily IV dosing, CD101 stability and long half-life enable once-weekly IV dosing and subcutaneous (SC) administration,6,7 suggesting a potential for prophylaxis.

OBJECTIVES
To evaluate CD101 as antifungal prophylaxis in neutropenic mouse models of candidiasis, aspergillosis, and PCP, respectively.

MATERIALS & METHODS

Candidiasis model
ICR mice were rendered neutropenic by cyclophosphamide on days -4 and -1, and challenged with Candida albicans on day 0.

Aspergillosis model
ICR mice were rendered neutropenic by cpm on days -3, +1, and +4, then challenged with Aspergillus fumigatus on day 0.

RESULTS (cont’d)

PCP – Trophic Nuclei Counts
Clearance of trophic forms with CD101 is comparable to the active control TMP/SMX (ie, no nuclei detected) in the groups given CD101 20 mg/kg 1x or 3x/wk and 2 mg/kg 3x/wk. Trophic nuclei counts were significantly reduced in all CD101-treated groups (except 0.2 mg/kg 1x/wk) compared with the vehicle control.

RESULTS

Candidiasis (MIC=0.03 µg/mL) – Kidney CFU
CFU burden was completely cleared in all animals given 20 mg/kg except one (prophylaxis on day -3). No measurable CFU were seen in the groups given 10 mg/kg on day -3 or -1. Significant decreases in CFU were seen with 5 mg/kg given on day -3 or -1.

Aspergillosis (MEC=0.0078 µg/mL) – Survival
All animals in the 10 and 20 mg/kg groups survived regardless of prophylaxis day.

PCP – Asci/cyst Counts
Efficacy with CD101 was comparable to TMP/SMX in all but the lowest dose group (0.2 mg/kg 1x/wk), with no detectable asci. Asci counts were significantly reduced in all CD101 groups compared with vehicle.

REFERENCES

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