Evaluation of CD101 Glucan Synthesis Inhibition, MIC Values and Mutant Prevention Concentrations Against Echinocandin-Susceptible and -Resistant Candida spp.

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ABSTRACT

Background: The aim of this study was to characterize the in vitro activity of CD101, a novel long half-life echinocandin, through assessment of enzymatic inhibition of wild-type and mutant β-(1,3)-glucan synthase (GS) from Candida albicans. CD101 was compared against echinocandin-susceptible and -resistant isolates and mutant prevention concentration (MPC) in Candida spp.

Methods: The kinetic inhibition parameter IC₅₀ (half-maximal inhibitory concentration) was determined for GS expressed in yeast (S. cerevisiae) and fungal cells. To determine the MICs, GS wild-type (WT) and mutant (ER) strains of Candida albicans were grown in RPMI 1640 medium for 24 h in the presence of 0 - 32 mg/L of CD101 or miconafungin (MCF). Serial dilutions of the samples were plated on YPD agar, and growth was monitored.

Results: Wild-type GS purified from C. albicans and C. glabrata were as sensitive to CD101 as MIC with mean IC₅₀ values of 2.57-14.5 and 0.45-15.69 nmol/L for CD101 and MCF, respectively. GS from echinocandin-resistant strains of C. albicans and C. glabrata, with enhanced enzyme activity and production, exhibited an IC₅₀ of either B1- or B2-like fold decrease in sensitivity to CD101 similar to MCF. D101 MIC values for all Candida spp. (range: 0.03-0.18 mg/L) were comparable to and demonstrated cross-resistance with MCF. For the MFC assay, a 3- to 5-fold decrease in CFUs was seen around the MICs for CD101 and MCF for C. albicans and C. glabrata. An advanced cell population persisted through their maximum inhibition and decreased at 16 – 32 mg/L. Thus, 16 mg/L was identified as the MPC for CD101 and MCF.

Conclusions: Overall, CD101 demonstrates comparable in vitro inhibition activity to MCF at the enzyme and cellular levels, as well as in MIC values for Candida spp., and warrants further analysis as a promising new glucan synthase inhibitor with unique pharmacokinetic properties.

INTRODUCTION

Echinocandins are the leading class of antifungal agents for the treatment of systemic fungal infections. There are two primary targets: glucan synthase (GS) and β-glucan synthase (BGS). Inhibition of the catalytic subunit of the β-(1,3)-glucan synthase complex encoded by the FKS and FKS gene in the Candida albicans pathogenic reaction is the primary event that correlates with clinical failure or poor response to therapy [1]. The three echinocandins approved by the Food and Drug Administration (FDA) for the treatment of invasive fungal infections (Liposomal, anidulafungin, and voriconazole) are used as second-line therapy for resistant Candida species. In order to determine the possible mechanism of resistance, we determined the MICs for CD101 in a novel long-acting echinocandin being developed as an extension to the standard of care in the treatment of fungal infections, for which there are currently no antifungal agents available. With the objective of characterizing this new compound, we assessed the effects of CD101, as well as published the MICs for CD101 in wild-type and mutant resistant isolates. CD101 was shown to have IC₅₀ values of 61 mg/L and ≤0.05 mg/L against echinocandin-susceptible and -resistant fungal strains, respectively. CD101 was able to inhibit the growth of a wide range of Candida species, including clinical isolates with reduced susceptibility to echinocandin-resistant isolates. The results indicate that CD101 is a promising new antifungal agent with a broad spectrum of activity against Candida spp.

RESULTS

IC₅₀ values for C. albicans and C. glabrata isolates. Inhibition curves for CD101 and MCF against the wild-type (WT) C. albicans isolates showed the typical pattern of β-(1,3)-glucan synthase inhibition by echinocandins. The FKS and FKS1 mutant strains displayed IC₅₀ fold-increase in IC₅₀ values for MCF and CD101, respectively. The C. glabrata FKS1 mutant strain displayed no significant reductions in activity after treatment with a high dose (10,000 ng/mL) of either MCF and CD101. The S636P mutant exhibited a lower IC₅₀ for CD101 compared to MCF. These data suggest that CD101 may be a potential agent for the treatment of echinocandin-resistant Candida spp.

CONCLUSIONS

In conclusion, CD101 is a potent inhibitor of glucan synthase with comparable activity to other echinocandins against both echinocandin-susceptible and -resistant isolates. CD101 is also effective against a wide range of Candida species, including clinical isolates with reduced susceptibility to echinocandin-resistant isolates. In vivo biofilm susceptibility testing of CD101 against isolates of Candida spp. proved results comparable to MCF.

The significance of MPICs for CD101 and MCF to overcome resistance is intriguing and warrants further investigation in in vivo model.

REFERENCES


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