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Activity of a Long-Acting Echinocandin (CD101) and Comparator Antifungal Agents Tested against Contemporary Invasive Fungal Isolates

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ABSTRACT

Background: Echinocandins are important agents for treatment of invasive fungal infections. We evaluated the activity of CD101, a once-weekly echinocandin with extended half-life, and comparators against 606 invasive fungal isolates collected worldwide during 2014 using CLSI broth microdilution methods.

Methods: 531 *Candida* spp. (7 species), 19 *C. neoformans* (CNEO) and 56 *A. fumigatus* (ASF) were susceptibility (S) tested for CD101, anidulafungin (ANF), caspofungin (CSF), micafungin (MCF) and azoles. CLSI clinical breakpoint (CBP) and epidemiological cutoff value (ECV) interpretive criteria were applied. Isolates displaying echinocandin MIC>ECV were sequenced for *fks* hot spot (HS) mutations.

Results: The activity of CD101 was similar to that of other echinocandins (**Table**). All *C. albicans* (CA), *C. tropicalis* (CTRO), *C. krusei* and *C. dubliniensis* (n=11) were inhibited by ≤0.12 µg/ml of CD101 and were S/wild-type to other echinocandins using CBP/ECV. Five *C. glabrata* (CGLA) displayed CD101 MIC >0.12 µg/ml (MIC, 1-4 µg/ml), elevated CSF (2->8 µg/ml), ANF (2-4 µg/ml) and MCF (2-4 µg/ml) results and carried mutations on *fks1* HS1 S629P (3 isolates/2 also had HS2 S663P), HS2 F659S (1) or S663P (3 isolates). *C. parapsilosis* (CPRP; n=92) and *C. orthopsilosis* (n=10) displayed higher MIC values (ranges 0.5-4 and 0.12-2 µg/ml, respectively), but similar results were observed for other echinocandins. Fluconazole resistance was noted among 11.0% of CGLA, 4.3% CPRP and 2.0% CA and CTRO. Echinocandins had limited activity against CNEO. CD101 activity against ASF was similar to that of MCF, two-fold greater than CSF, but less than ANF. These moulds displayed MIC values below ECVs for the mould-active azoles (itraconazole, voriconazole and posaconazole).

Conclusions: CD101 was as active as other echinocandins against common fungal organisms recovered from invasive fungal infections. The extended half-life profile is very desirable for prevention and treatment of serious fungal infections, especially in patients that can then be discharged.

Abstract Table

Organism (no. tested)	MIC/MEC$_{50/90}$ (µg/ml)			
	CD101	Anidulafungin	Caspofungin	Micafungin
C. albicans (251)	0.03/0.06	0.015/0.06	0.03/0.06	0.015/0.03
C. glabrata (100)	0.03/0.06	0.06/0.12	0.06/0.12	0.015/0.03
C. parapsilosis (92)	1/2	2/4	0.5/1	1/2
C. tropicalis (51)	0.015/0.06	0.015/0.03	0.03/0.06	0.03/0.06
C. krusei (16)	0.03/0.06	0.06/0.06	0.12/0.25	0.06/0.12
A. fumigatus (56)	0.015/0.015	≤0.008/0.015	0.03/0.03	0.015/0.015

INTRODUCTION

Despite the broad utilization of echinocandins to treat invasive candidiasis (IC) in critically ill hospitalized patients, clinical resistance to these agents remains uncommon, although both breakthrough infections and acquired resistance mutations in some species of *Candida* have been noted. Whereas the currently available echinocandins are highly efficacious and relatively easy to use in the treatment of IC and other invasive fungal infections (IFI), they must be administered daily by intravenous infusion, potentially prolonging the hospitalization of patients undergoing therapy and limiting their use to the inpatient setting. The availability of an echinocandin with activity that is comparable to those presently in use but with a pharmacokinetic (PK) profile that allows for less frequent administration, would alter the standard-of-care therapy (e.g., echinocandin therapy) to be more easily administered in both inpatient and outpatient settings.

CD101 IV is a novel echinocandin antifungal agent that displays chemical stability in plasma, aqueous solution, and at elevated temperature as well as possessing a long-acting PK. CD101 IV is being developed for once-weekly IV administration for the treatment and prevention of serious fungal infections. Less frequent administration while maintaining high exposure would alter hospital stays, improve compliance for outpatients and provide more convenient outpatient prophylaxis or maintenance treatment regimens.

In the presented study, we determined the activity and potency of CD101 and comparator antifungal agents tested against 606 clinical fungal isolates collected worldwide from IFI (2014).

MATERIALS AND METHODS

Fungal organisms. A total of 606 non-duplicate prospectively collected fungal isolates from 38 medical centers located in North America (161 isolates; 10 sites), Europe (294; 17), the Asia-Pacific Region (82; 6) and Latin America (69; 5) were evaluated. Isolates selected were from the following sources: bloodstream, (379 strains), normally sterile body fluids, tissues or abscesses (22 strains), respiratory tract specimens (96 strains) and 109 were collected from other or non-specified body sites.

Species identification. Yeast isolates were subcultured and screened using CHROMagar *Candida* (Becton Dickinson, Sparks, Maryland USA) to ensure purity and to differentiate *Candida albicans/Candida dubliniensis, Candida tropicalis* and *Candida krusei.* Isolates suspected to be either *C. albicans* or *C. dubliniensis* (green colonies on CHROMagar) were incubated at 45°C. All other yeast isolates were submitted to Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) using the MALDI Biotyper according to the manufacturer's instructions (Bruker Daltonics, Billerica, Massachusetts USA). Isolates that were not identified by either phenotypic or proteomic methods were identified using sequencing-based methods as previously described.

Antifungal susceptibility testing. All isolates were tested by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) methods outlined in documents M27-A3 and M38-A2. Frozen-form panels used RPMI 1640 broth supplemented with MOPS (morpholinepropane sulfonic acid) buffer and 0.2% glucose and inoculated with 0.5 to 2.5 X 10^3 cells/ml suspensions. MIC/MEC values were determined visually, after 24, 48 or 72 hours of incubation at 35°C, as the lowest concentration of drug that resulted in ≥50% inhibition of growth relative to the growth control or complete (100%) inhibition. CLSI clinical breakpoints were used for the five most common species of *Candida* (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*) for echinocandins, fluconazole and voriconazole. Epidemiological cutoff values (ECV) were applied when available.

Quality control was performed as recommended in CLSI documents M27-A3 and M38-A2 using strains *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *A. flavus* ATCC 204304 and *A. fumigatus* MYA-3626.

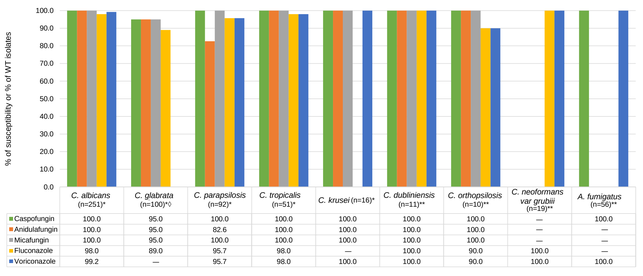
RESULTS

- CD101 (MIC$_{50/90}$, 0.03/0.06 µg/ml) inhibited all 251 *C. albicans* isolates at ≤0.12 µg/ml (**Table 1**). This compound displayed activity most similar to that of caspofungin (MIC$_{50/90}$, 0.03/0.06 µg/ml).
- CD101 (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/ml) inhibited 95 (95.0%) of the *C. glabrata* isolates at ≤0.12 µg/ml (**Table 1**). The activity of this investigational echinocandin was two-fold greater when compared to anidulafungin or caspofungin (MIC$_{50}$ and MIC$_{90}$, 0.06 and 0.12 µg/ml for both compounds) and two-fold less than the activity of micafungin (MIC$_{50}$ and MIC$_{90}$, 0.015 and 0.03 µg/ml; **Table 1**).
- All *C. parapsilosis* isolates were inhibited by CD101 (MIC$_{50}$ and MIC$_{90}$, 1 and 2 µg/ml) at ≤4 µg/ml (**Table 1**). CD101 displayed similar activity to that of micafungin (MIC$_{50/90}$, 1/2 µg/ml), slightly greater activity when compared to anidulafungin (MIC$_{50/90}$, 2/4 µg/ml) and was two-fold less active than caspofungin (MIC$_{50/90}$, 0.5/1 µg/ml; **Table 1**).
- *C. tropicalis* isolates (n=51) were considered susceptible to the clinically available echinocandins and CD101 (MIC$_{50/90}$, 0.015/0.06 µg/ml) inhibited all isolates at ≤0.06 µg/ml (**Table 1**).
- CD101 (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/ml) was very active against 16 *C. krusei* and all isolates were inhibited at ≤0.06 µg/ml (**Table 1**).
- The activity of CD101 (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/ml; **Table 1**) against *C. dubliniensis* isolates was comparable to that of caspofungin (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/ml).
- CD101 (MIC$_{50}$ and MIC$_{90}$, 0.5 and 1 µg/ml) activity against *C. orthopsilosis* was similar to the activity of anidulafungin and micafungin (MIC$_{50/90}$, 0.5/1 µg/ml for both). Caspofungin was two-fold more active against *C. orthopsilosis* isolates (MIC$_{50}$ and MIC$_{90}$, 0.25 and 0.5 µg/ml; **Table 1**) when compared to other echinocandins.
- The echinocandins, including CD101, had limited activity against *C. neoformans var. grubii* isolates (n=19; **Table 1**); all isolates had MIC values at ≥8 µg/ml for these compounds.
- Echinocandins displayed good activity against *A. fumigatus;* CD101 (MEC$_{50}$ and MEC$_{90}$, 0.015 and 0.015 µg/ml) activity was two-fold greater than that of caspofungin (MEC$_{50/90}$, 0.03/0.03 µg/ml) and similar to that of micafungin. Anidulafungin (MEC$_{50/90}$, ≤0.008/0.015 µg/ml; **Table 1**) was slightly more active than the other compounds from the same class.
- Among the five *C. glabrata* isolates displaying resistant MIC results for clinically available echinocandins, one harbored a mutation on *fks1* HS1 encoding alteration S629P and another two carried alterations on *fks2* HS1 F659S or S663P. The two remaining isolates were collected from the same patient in Edmonton, Canada and both strains carried alterations on *fks1* HS1 S629P and *fks2* HS1 S663P conferring elevated caspofungin MIC results (>8 µg/ml) and MIC results of 2-4 µg/ml for CD101, anidulafungin and micafungin (**Table 2**).
- The activity of comparator agents tested against organisms/organism groups is displayed in **Figure 1**. Fluconazole resistance was noted among 2.0% of *C. albicans* and *C. tropicalis*, 11.0% of *C. glabrata* and 4.3% of *C. parapsilosis*. All *C. neoformans var. grubii* and *A. fumigatus* isolates were considered wild-type for the azoles.

Table 1. Antifungal activity of echinocandins against organisms/organism groups tested using the CLSI reference method.

Organism species/groups (no. tested)/Agent	Number (cumulative %) of isolates inhibited at MIC/MEC (µg/ml)												MIC/MEC (µg/ml)	
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	50%	90%
Candida albicans (251)														
CD101	17 (6.8)	107 (49.4)	91 (85.7)	28 (96.8)	8 (100.0)								0.03	0.06
Anidulafungin	69 (27.5)	101 (67.7)	54 (89.2)	22 (98.0)	5 (100.0)								0.015	0.06
Caspofungin	4 (1.6)	76 (31.9)	135 (85.7)	34 (99.2)	2 (100.0)								0.03	0.06
Micafungin	17 (6.8)	171 (74.9)	63 (100.0)										0.015	0.03
Candida glabrata (100)														
CD101		3 (3.0)	59 (62.0)	29 (91.0)	4 (95.0)	0 (95.0)	0 (95.0)	1 (96.0)	3 (99.0)	1 (100.0)			0.03	0.06
Anidulafungin	1 (1.0)	0 (1.0)	11 (12.0)	62 (74.0)	21 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	3 (98.0)	2 (100.0)			0.06	0.12
Caspofungin			38 (38.0)	51 (89.0)	6 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	2 (97.0)	0 (97.0)	3 (100.0)		0.06	0.12
Micafungin	1 (1.0)	73 (74.0)	21 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	3 (98.0)	2 (100.0)			0.015	0.03
Candida parapsilosis (92)														
CD101						22 (23.9)	35 (62.0)	34 (98.9)	1 (100.0)				1	2
Anidulafungin						4 (4.3)	28 (34.8)	44 (82.6)	16 (100.0)				2	4
Caspofungin					31 (33.7)	49 (87.0)	11 (98.9)	1 (100.0)					0.5	1
Micafungin						10 (10.9)	57 (72.8)	25 (100.0)					1	2
Candida tropicalis (51)														
CD101	2 (3.9)	27 (56.9)	16 (88.2)	6 (100.0)									0.015	0.06
Anidulafungin	5 (9.8)	27 (62.7)	18 (98.0)	1 (100.0)									0.015	0.03
Caspofungin		12 (23.5)	23 (68.6)	15 (98.0)	1 (100.0)								0.03	0.06
Micafungin	1 (2.0)	15 (31.4)	27 (84.3)	8 (100.0)									0.03	0.06
Candida krusei (16)														
CD101		3 (18.8)	11 (87.5)	2 (100.0)									0.03	0.06
Anidulafungin		1 (6.2)	6 (43.8)	9 (100.0)									0.06	0.06
Caspofungin				4 (25.0)	10 (87.5)	2 (100.0)							0.12	0.25
Micafungin				8 (50.0)	8 (100.0)								0.06	0.12
Candida dubliniensis (11)														
CD101			6 (54.5)	4 (90.9)	1 (100.0)								0.03	0.06
Anidulafungin		1 (9.1)	3 (36.4)	7 (100.0)									0.06	0.06
Caspofungin		1 (9.1)	5 (54.5)	5 (100.0)									0.03	0.06
Micafungin		3 (27.3)	8 (100.0)										0.03	0.03
Candida orthopsilosis (10)														
CD101					1 (10.0)	3 (40.0)	1 (50.0)	4 (90.0)	1 (100.0)				0.5	1
Anidulafungin						3 (30.0)	2 (50.0)	4 (90.0)	1 (100.0)				0.5	1
Caspofungin				1 (10.0)	3 (40.0)	3 (70.0)	3 (100.0)						0.25	0.5
Micafungin					2 (20.0)	2 (40.0)	3 (70.0)	3 (100.0)					0.5	1
Cryptococcus neoformans var. grubii (19)														
CD101											6 (31.6)	13 (100.0)	>8	>8
Anidulafungin												19 (100.0)	>8	>8
Caspofungin											4 (21.1)	15 (100.0)	>8	>8
Micafungin												19 (100.0)	>8	>8
Aspergillus fumigatus (56)														
CD101	23 (41.1)	29 (92.9)	4 (100.0)										0.015	0.015
Anidulafungin	30 (53.6)	21 (91.1)	5 (100.0)										≤0.008	0.015
Caspofungin		18 (32.1)	35 (94.6)	3 (100.0)									0.03	0.03
Micafungin	16 (28.6)	38 (96.4)	2 (100.0)										0.015	0.015

Figure 1. Activity of comparator antifungal agents against isolates tested in this study. CLSI clinical breakpoints were applied for *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* where available. ECVs were applied for the remaining species or organism groups.



"—" = criteria is not available.
*CLSI clinical breakpoints were applied.
^Fluconazole % corresponds to susceptible dose dependent (SDD).
**Epidemiological cutoff values (ECV) were applied.

Table 2. Activity of CD101 compared to other echinocandins for *Candida* spp. isolates harboring FKS alterations detected in this study.

State and/or country	Organism	MIC according to CLSI method (µg/ml):				1,3-β-D-glucan synthase mutations[a]:			
		CD101	ANF	CSF	MCF	*fks1* HS1	*fks1* HS2	*fks2* HS1	*fks2* HS2
Israel	*C. glabrata*	1	2	2	2	WT	WT	F659S	WT
CA, USA	*C. glabrata*	2	2	8	2	S629P	WT	WT	WT
NY, USA	*C. glabrata*	2	2	2	2	WT	WT	S663P	WT
Canada	*C. glabrata*	4	4	>8	4	S629P	WT	S663P	WT
Canada	*C. glabrata*	2	4	>8	4	S629P	WT	S663P	WT

Abbreviations: ANF = Anidulafungin; CSF = Caspofungin, MCF = Micafungin.
a. WT= wildtype.

CONCLUSIONS

- The activity of CD101 tested by reference methods against common fungal species isolated from invasive infections worldwide during 2014 was comparable to currently available echinocandins.
- Further evaluation of CD101 against less common species is recommended, and expanded clinical development of this long-acting echinocandin is warranted.

ACKNOWLEDGEMENT

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