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

MA PFALLER, SA MESSER, PR RHOMBERG, SE COSTELLO, M CASTANHEIRA
JMI Laboratories, North Liberty, IA, USA

Mariana Castanheira, PhD
JMI Laboratories
335 Beaver Kreek Centre
North Liberty, Iowa 52317
Phone: (319) 665-3370
mariana-castanheira@jmilabs.com

Abstract

Background: CD101 is a novel echinocandin displaying exceptional chemical stability and a long-acting pharmacokinetics. This compound has being developed for once-weekly IV administration for the treatment of invasive candidiasis and candidemia. We evaluated the activity of CD101 and comparators against 713 invasive fungal isolates collected worldwide during 2015 using CLSI broth microdilution methods.

Methods: 589 *Candida* spp. (6 species), 14 *C. neoformans* (CNEO), 13 *A. flavus* (ASFL) and 97 *A. fumigatus* (ASF) were tested for susceptibility (S) to 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. tropicalis* (CTRO), *C. krusei* and *C. dubliniensis* (CDU; n=12), 99.7% of *C. albicans* (CA) and 98.3% of *C. glabrata* (CGLA) were inhibited by ≤0.12 µg/ml of CD101 and were S/wild-type to other echinocandins using CBP/ECV. Two CGLA displayed CD101 MIC >0.12 µg/ml (MIC, 0.25 and 1 µg/ml), elevated CSF (>0.5 µg/ml), ANF (0.25-0.5 µg/ml) and MCF (0.12-0.25 µg/ml) results and possessed HS mutations in *fks1*/*fks2*. *C. parapsilosis* (CPRP) displayed higher MIC values (range 0.25-2 µg/ml), but similar results were observed for other echinocandins. Fluconazole resistance was noted among 6.6% of CGLA, 3.6% CPRP and 0.0% CA, CDU and CTRO. Echinocandins had limited activity against CNEO. CD101 activity against ASF and ASFL (MEC, ≤0.03 µg/ml) was comparable to the other echinocandins (MEC, ≤0.03 µg/ml). 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 since less frequent dosing of this agent should facilitate shorter and cost effective hospital stays, improve compliance for outpatients and provide more convenient outpatient prophylaxis.

	MIC/MEC$_{50/90}$ (µg/ml)			
Organism (no. tested)	CD101	Anidulafungin	Caspofungin	Micafungin
C. albicans (304)	0.03/0.06	0.015/0.03	≤0.008/0.015	≤0.008/0.015
C. glabrata (121)	0.03/0.12	0.06/0.12	0.03/0.06	≤0.008/0.015
C. parapsilosis (83)	1/2	2/2	0.25/0.5	1/1
C. tropicalis (55)	0.03/0.06	0.015/0.03	0.015/0.03	0.015/0.03
C. krusei (14)	0.03/0.06	0.03/0.12	0.12/0.25	0.06/0.12
A. fumigatus (97)	0.015/0.03	≤0.008/0.03	0.015/0.03	≤0.008/0.015
A. flavus (13)	≤0.008/0.03	0.015/0.015	0.015/0.03	0.015/0.015

Introduction

CD101 (formerly SP 3025; Cidara Therapeutics, Inc.) is a novel echinocandin antifungal agent that displays chemical stability in plasma, aqueous solution, and at elevated temperature as well as long-acting pharmacokinetics. CD101 is in development as a once-weekly IV formulation for the treatment of candidemia and other forms of invasive candidiasis (IC; infection of normally sterile body fluids and tissues). Less frequent dosing of this agent may facilitate shorter and cost-effective hospital stays, provide more convenient (eg, outpatient) prophylaxis or maintenance treatment regimens and support outpatient compliance.

CD101 demonstrates a low potential for resistance development, and the CD101 dosing regimen produces high initial plasma drug exposures that may reduce the potential for the emergence of resistance during therapy. This long-acting echinocandin exhibits comparable potency and spectrum to that of other echinocandins against both wild-type (WT) and echinocandin resistant *Candida* spp.

In the present study, we performed a broad assessment of CD101 in comparison with currently approved echinocandins (anidulafungin, caspofungin and micafungin) by testing a total of 713 isolates of *Candida* (589 isolates; 6 species), *Cryptococcus neoformans* var. *grubii* (14 isolates), *Aspergillus fumigatus* sensu stricto (97 isolates) and *Aspergillus* section Flavi (13 isolates) obtained during the 2015 SENTRY Antifungal Surveillance Program.

Methods

Fungal organisms. A total of 713 non-duplicate fungal isolates prospectively collected during 2015 from 47 medical centers located in North America (228 isolates; 14 sites), Europe (329 isolates; 18 sites), the Asia-Pacific Region (84 isolates; 7 sites) and Latin America (72 isolates; 8 sites) were evaluated (**Figure 1**). Isolates selected were from the following sources: bloodstream infections (427 isolates), pneumonia in hospitalized patients (180), intra-abdominal infections (14), skin and skin structure infections (17), and 75 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. MIC/MEC values were determined visually, after 24, 48 or 72 hours of incubation at 35ºC, with MIC defined as the lowest concentration of drug that resulted in ≥50% inhibition of growth relative to the growth control and MEC defined as the lowest concentration resulting in a change in hyphal morphology. CLSI clinical breakpoints were used for the five most common species of *Candida* (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*). 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, *Aspergillus flavus* ATCC 204304 and *A. fumigatus* MYA-3626.

Screening for 1,3-ß-D-glucan synthase mutations. All isolates of *Candida* spp. that were either resistant or non-wild-type (NWT; MIC > ECV) to one or more of the echinocandins were characterized for the presence or absence of a mutation in the hot spot (HS) regions of *fks1* and *fks2* (*C. glabrata* only) as described previously.

Results

- Among the 713 fungal clinical isolates tested, 589 (82.6%) were *Candida* spp., 14 (1.9%) *C. neoformans* var. *grubii*, 13 (1.8%) *A. flavus* species complex and 97 (13.6%) were *A. fumigatus*. The distribution of isolates according to the geographic regions is displayed in **Figure 1**.
- CD101 (MIC$_{50/90}$, 0.03/0.06 µg/mL) inhibited 99.7% of 304 *C. albicans* isolates at ≤0.12 µg/mL (**Table 1**). This compound displayed similar activity to that of anidulafungin and caspofungin (MIC$_{50/90}$, 0.015/0.03 and ≤0.008/0.015 µg/mL, respectively; **Table 1**).
- CD101 (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.12 µg/mL) inhibited 119 (98.3%) of the *C. glabrata* isolates at ≤0.12 µg/mL (**Table 1**). The activity of this investigational echinocandin was comparable to the activity of anidulafungin (MIC$_{50}$ and MIC$_{90}$, 0.06 and 0.12 µg/mL) and caspofungin (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/mL) and eight-fold less than the activity of micafungin (MIC$_{50}$ and MIC$_{90}$, ≤0.008 and 0.015 µg/mL; **Table 1**).
- All *C. parapsilosis* isolates were inhibited by CD101 at ≤2 µg/mL, the current CLSI susceptible breakpoint for the approved echinocandins tested against this *Candida* species (**Table 1**). CD101 (MIC$_{50}$ and MIC$_{90}$, 1 and 2 µg/mL) displayed similar activity to that of micafungin (MIC$_{50/90}$, 1/1 µg/mL) and anidulafungin (MIC$_{50/90}$, 2/2 µg/mL) and was four-fold less active than caspofungin (MIC$_{50/90}$, 0.25/0.5 µg/mL).
- *C. tropicalis* (55 isolates) were considered susceptible to the clinically available echinocandins, and CD101 (MIC$_{50/90}$, 0.03/0.06 µg/mL) inhibited all isolates at ≤0.12 µg/mL (**Table 1**).
- CD101 (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/mL) was very active against 14 *C. krusei* and all isolates were inhibited at ≤0.12 µg/mL (**Table 1**). These isolates were susceptible to anidulafungin (MIC$_{50/90}$, 0.03/0.12 µg/mL), caspofungin (MIC$_{50/90}$, 0.12/0.25 µg/mL) and micafungin (MIC$_{50/90}$, 0.06/0.12 µg/mL) according to the CLSI breakpoint criteria.
- 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 those of anidulafungin (MIC$_{50}$ and MIC$_{90}$, 0.03 and 0.06 µg/mL), caspofungin (MIC$_{50}$ and MIC$_{90}$, 0.015 and 0.03 µg/mL) and micafungin (MIC$_{50}$ and MIC$_{90}$, 0.015 and 0.015 µg/mL).
- Echinocandins, including CD101, displayed limited activity (MIC ≥8 µg/mL) against *C. neoformans* var. *grubii* isolates (n=14; **Table 1**).
- Echinocandins displayed good activity against *A. fumigatus* and CD101 (MEC$_{50}$ and MEC$_{90}$, 0.015 and 0.03 µg/mL) activity was similar to that of anidulafungin (MEC$_{50}$ and MEC$_{90}$, ≤0.008/0.03 µg/mL), caspofungin (MEC$_{50/90}$, 0.015/0.03 µg/mL) and micafungin (≤0.008/0.015 µg/mL).
- Echinocandins displayed good activity against *A. flavus* species complex and CD101 (MEC$_{50}$ and MEC$_{90}$, ≤0.008 and 0.03 µg/mL) activity was similar to that of anidulafungin (MEC$_{50}$ and MEC$_{90}$, 0.015/0.015 µg/mL), caspofungin (MEC$_{50/90}$, 0.015/0.03 µg/mL) and micafungin (0.015/0.015 µg/mL).
- Four *Candida* spp. isolates displayed non-wild-type echinocandin MIC values and were screened for *fks* mutations (**Table 2**). Three isolates were *C. glabrata* and only one isolate displaying resistant MIC results for these clinically available echinocandins (according to the current CLSI breakpoints) carried *fks1* HS1 alteration (F625S). One *C. albicans* was resistant to both caspofungin and micafungin (MIC, 1 µg/mL) and displayed an *fks1* HS1 alteration S645P.

Figure 1. Geographic distribution of main organisms and organism groups as part of this study.

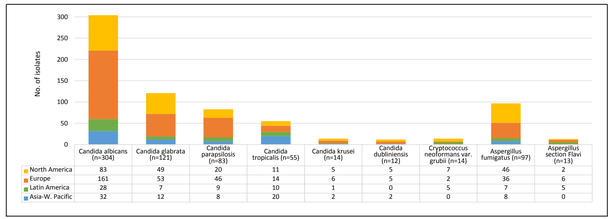

Table 1. Antimicrobial activity of CD101, anidulafungin, caspofungin, and micafungin tested against isolates included in this study.

Organisms / Organism Groups	No. of isolates at MIC/MEC (µg/mL; cumulative %)												MIC$_{50}$	MIC$_{90}$
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
***Candida albicans* (304)**														
CD101	56 (18.4)	81 (45.1)	125 (86.2)	33 (97.0)	8 (99.7)	1 (100.0)							0.03	0.06
Anidulafungin	96 (31.6)	135 (76.0)	65 (97.4)	5 (99.0)	2 (99.7)	1 (100.0)							0.015	0.03
Caspofungin	160 (52.6)	122 (92.8)	19 (99.0)	2 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)					≤0.008	0.015
Micafungin	213 (70.1)	86 (98.4)	4 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)					≤0.008	0.015
***Candida glabrata* (121)**														
CD101		3 (2.5)	69 (59.5)	22 (77.7)	25 (98.3)	1 (99.2)	0 (99.2)	1 (100.0)					0.03	0.12
Anidulafungin		1 (0.8)	38 (32.2)	43 (67.8)	37 (98.3)	1 (99.2)	0 (99.2)	1 (100.0)					0.06	0.12
Caspofungin	4 (3.3)	44 (39.7)	59 (88.4)	12 (98.3)	1 (99.2)	0 (99.2)	0 (99.2)	1 (100.0)					0.03	0.06
Micafungin	68 (56.2)	43 (91.7)	8 (98.3)	0 (98.3)	1 (99.2)	1 (100.0)							≤0.008	0.015
***Candida parapsilosis* (83)**														
CD101						1 (1.2)	11 (14.5)	35 (56.6)	36 (100.0)				1	2
Anidulafungin							5 (6.0)	20 (30.1)	53 (94.0)	5 (100.0)			2	2
Caspofungin				1 (1.2)	9 (12.0)	54 (77.1)	19 (100.0)						0.25	0.5
Micafungin							30 (36.1)	48 (94.0)	5 (100.0)				1	1
***Candida tropicalis* (55)**														
CD101	6 (10.9)	15 (38.2)	24 (81.8)	8 (96.4)	2 (100.0)								0.03	0.06
Anidulafungin	6 (10.9)	29 (63.6)	16 (92.7)	4 (100.0)									0.015	0.03
Caspofungin	17 (30.9)	30 (85.5)	6 (96.4)	2 (100.0)									0.015	0.03
Micafungin	7 (12.7)	34 (74.5)	12 (96.4)	2 (100.0)									0.015	0.03
***Candida krusei* (14)**														
CD101		2 (14.3)	10 (85.7)	1 (92.9)	1 (100.0)								0.03	0.06
Anidulafungin			7 (50.0)	5 (85.7)	2 (100.0)								0.03	0.12
Caspofungin				4 (28.6)	5 (64.3)	5 (100.0)							0.12	0.25
Micafungin				10 (71.4)	4 (100.0)								0.06	0.12
***Candida dubliniensis* (12)**														
CD101			6 (50.0)	5 (91.7)	1 (100.0)								0.03	0.06
Anidulafungin		1 (8.3)	9 (83.3)	1 (91.7)	1 (100.0)								0.03	0.06
Caspofungin		8 (66.7)	3 (91.7)	1 (100.0)									0.015	0.03
Micafungin	2 (16.7)	10 (100.0)											0.015	0.015
***Cryptococcus neoformans* var. *grubii* (14)**														
CD101											5 (35.7)	9 (100.0)	>8	>8
Anidulafungin												14 (100.0)	>8	>8
Caspofungin												14 (100.0)	>8	>8
Micafungin												14 (100.0)	>8	>8
***Aspergillus fumigatus* (97)**														
CD101	45 (46.4)	41 (88.7)	11 (100.0)										0.015	0.03
Anidulafungin	55 (56.7)	32 (89.7)	10 (100.0)										≤0.008	0.03
Caspofungin	14 (14.4)	61 (77.3)	21 (99.0)	1 (100.0)									0.015	0.03
Micafungin	87 (89.7)	9 (99.0)	1 (100.0)										≤0.008	0.015
***Aspergillus* section Flavi (13)**														
CD101	7 (53.8)	4 (84.6)	2 (100.0)										≤0.008	0.03
Anidulafungin	6 (46.2)	6 (92.3)	1 (100.0)										0.015	0.015
Caspofungin	2 (15.4)	6 (61.5)	5 (100.0)										0.015	0.03
Micafungin	4 (30.8)	8 (92.3)	1 (100.0)										0.015	0.015

Table 2. FKS alterations detected in *Candida spp.* isolates displaying non-wild-type echinocandin MIC values.

State, Country	Organism	MIC according to CLSI method (µg/mL):				1,3-ß-D-glucan synthase mutations[a]:			
		CD101	ANID	CASP	MICA	fks1 HS1	fks1 HS2	fks2 HS1	fks2 HS2
NY, USA	*Candida albicans*	0.25	0.25	1	1	S645P	WT	NT	NT
TX, USA	*Candida glabrata*	0.25	0.25	0.06	0.03	WT	WT	WT	WT
CA, USA	*Candida glabrata*	1	1	1	0.25	F625S	NT	WT	WT
VA, USA	*Candida glabrata*	0.12	0.12	0.06	0.12	WT	WT	WT	WT

a. WT=wildtype
Abbreviations: ANID = Aniduladungin; CASP = Caspofungin; MICA = Micafungin.

Conclusions

- The activity of CD101 against common fungal species isolated from invasive infections was comparable to clinically available echinocandins and variations of ±two-fold were noted for different species when CD101 was compared to anidulafungin, caspofungin and micafungin.
- The chemical stability and prolonged half-life of CD101, coupled with the excellent potency and spectrum determined herein, makes CD101 a promising new antifungal agent that may prove to be competitive with currently approved echinocandins for improved prophylactic and treatment efficacy of invasive candidiasis.

Acknowledgements

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