ASM Microbe 2018
Friday-485

Activity of a Long-Acting Echinocandin Rezafungin (CD101) and Comparator Antifungal Agents Tested against Contemporary Invasive Fungal Isolates: SENTRY 2016

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Abstract

Background: Echinocandins are important agents for treating invasive fungal infections. We evaluated the activity of rezafungin (previously CD101), an echinocandin with extended half-life, and comparators using CLSI broth microdilution methods against 719 invasive fungal isolates collected worldwide during 2016.

Methods: Susceptibility (S) tests on 632 *Candida* spp. (6 species), 27 *C. neoformans* (CNEO), 12 *Aspergillus* section *Flavi* (AFL), 48 *A. fumigatus* (ASF) were conducted for rezafungin (RZF), 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: RZF inhibited 99.6% of *C. albicans* (CA) isolates ($MIC_{50/90}$, 0.03/0.06 µg/mL), 96.9% of *C. tropicalis* (CT) ($MIC_{50/90}$, 0.03/0.06 µg/mL), 97.0% of *C. glabrata* (CG) ($MIC_{50/90}$, 0.06/0.12 µg/mL), 100.0% of *C. krusei* (CK) ($MIC_{50/90}$, 0.03/0.06 µg/mL), and 100.0% of *C. dubliniensis* (CD) ($MIC_{50/90}$, 0.06/0.12 µg/mL) at ≤0.12 µg/mL. All *C. parapsilosis* (CP) isolates ($MIC_{50/90}$,1/2 µg/mL) were inhibited by RZF at ≤2 µg/mL. Resistance to fluconazole was detected among 5.9% of CG, 11.7% of CP, 3.1% of CT, and 0.4% of CA. The activity of RZF against these 6 *Candida* spp. was similar to that of the other echinocandins, the vast majority of which were susceptible/wild type (WT) using CBP/ECV. A total of 17 isolates (2 CA, 9 CG, 4 CK, and 2 CT) displayed 1 or more non-WT or resistant MIC values and were sequenced for *fks* HS mutations. HS mutations were detected in 9 isolates (CA [S645P], CG [2 S629P, 2 S663P, 1 P667H, 1 F658_del], CT [1 S654P and 1 F650S]). Fluconazole and other triazoles displayed good activity against CNEO, whereas echinocandins including RZF displayed limited activity against CNEO isolates. Echinocandins displayed good activity against ASF and AFL, and RZF activity was similar to that of anidulafungin, caspofungin, and micafungin. All isolates displayed WT MIC values for the mold-active azoles.

Conclusions: Rezafungin was as active as other echinocandins against common fungal organisms recovered from invasive fungal infections. The extended half-life and stability of rezafungin is very desirable for prevention and treatment, especially in patients who could be discharged on outpatient therapy.

Introduction

- Rezafungin (RZF, formerly CD101) is a novel echinocandin antifungal agent that possesses long-acting pharmacokinetics and displays chemical stability that allow for once-weekly dosing
- RZF demonstrates a low potential for resistance development and produces high, front-loaded plasma drug exposures that may reduce the potential for 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.
- RZF IV is being developed for once-weekly administration in the treatment of candidemia and other forms of invasive candidiasis (IC) and for prevention of invasive fungal infections, such as those caused by *Candida*, *Aspergillus*, and *Pneumocystis*.
- In the presented study, we compared RZF with the echinocandins anidulafungin, caspofungin, and micafungin, by testing a total of 719 *Candida* isolates (632 isolates; 6 species), *Cryptococcus neoformans* var. *grubii* (27 isolates), *Aspergillus fumigatus* (48 isolates), and *Aspergillus* section *Flavi* (12 isolates) obtained during the 2016 SENTRY Antifungal Surveillance Program

Materials and Methods

Fungal organisms

- A total of 719 non-duplicate fungal isolates prospectively collected during 2016 from 42 medical centers located in North America (239 isolates; 12 sites), Europe (325 isolates; 18 sites), the Asia-Pacific region (79 isolates; 6 sites), and Latin America (76 isolates; 6 sites) were evaluated (Figure 1)
- Isolates selected were from the following sources: bloodstream infections (498 isolates), pneumonia in hospitalized patients (95 isolates), intra-abdominal infections (7 isolates), skin and skin structure infections (27 isolates), and 92 were collected from other infection types

Species identification

- 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). CLSI clinical breakpoints were used for echinocandins against the 5 most common species of *Candida* (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*)
- Epidemiological cutoff values (ECVs) 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

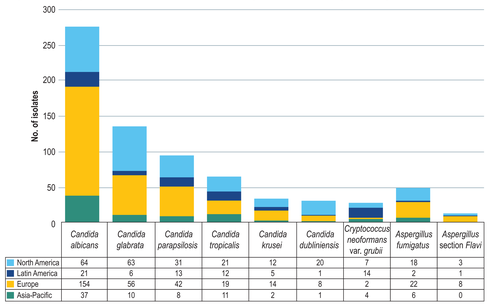
Screening for 1,3-β-D-glucan synthase mutations

- All *Candida* spp. isolates that were either resistant or non-wild type (NWT; MIC>ECV) to 1 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 719 fungal clinical isolates tested, 632 (87.9%) were *Candida* spp., 27 (3.8%) were *Cryptococcus neoformans var. grubii*, 12 (1.7%) were *Aspergillus* section *Flavi*, and 48 (6.7%) were *A. fumigatus*; see Figure 1 for the distribution of isolates by geographic region
- RZF ($MIC_{50/90}$, 0.03/0.06 µg/mL) inhibited 99.6% of 276 *C. albicans* isolates at ≤0.12 µg/mL (Table 1) and displayed similar activity to that of anidulafungin, caspofungin, and micafungin ($MIC_{50/90}$, 0.015/0.03, 0.015/0.03, and 0.015/0.015 µg/mL, respectively; Table 1)

Figure 1 Geographic distribution of main organisms and organism groups



	Candida albicans	*Candida glabrata*	*Candida parapsilosis*	*Candida tropicalis*	*Candida krusei*	*Candida dubliniensis*	*Cryptococcus neoformans var. grubii*	*Aspergillus fumigatus*	*Aspergillus* section *Flavi*
North America	64	63	31	21	12	20	7	18	3
Latin America	21	6	13	12	5	1	14	2	1
Europe	154	56	42	19	14	8	2	22	8
Asia-Pacific	37	10	8	11	2	1	4	6	0

Table 1 Antifungal activity of rezafungin, anidulafungin, caspofungin, and micafungin tested against the main organisms and organism groups of isolates tested using the CLSI method

Organism/organism group (no. of isolates) Antifungal agent	No. of isolates at MIC (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	>			
Candida albicans (276)															
Rezafungin	13 4.7	100 40.9	113 81.9	38 95.7	11 99.6	1 100.0								0.03	0.06
Anidulafungin	58 21.0	118 63.8	83 93.8	14 98.9	3 100.0									0.015	0.03
Caspofungin	19 6.9	220 86.6	34 98.9	1 99.3	1 99.6	0 99.6	0 99.6	1 100.0						0.015	0.03
Micafungin	67 24.3	185 91.3	22 99.3	1 99.6	0 99.6	0 99.6	0 99.6	1 100.0						0.015	0.015
Candida glabrata (135)															
Rezafungin	0 0.0	1 0.7	38 28.9	65 77.0	27 97.0	3 99.3	0 99.3	0 99.3	1 100.0					0.06	0.12
Anidulafungin	0 0.0	1 0.7	16 12.6	83 74.1	27 94.1	6 98.5	1 99.3	0 99.3	1 100.0					0.06	0.12
Caspofungin	1 0.7	24 18.5	92 86.7	14 97.0	2 98.5	1 99.3	0 99.3	1 100.0						0.03	0.06
Micafungin	6 4.4	97 76.3	24 94.1	2 95.6	5 99.3	0 99.3	0 99.3	1 100.0						0.015	0.03
Candida parapsilosis (94)															
Rezafungin					0 0.0	2 2.1	13 16.0	37 55.3	42 100.0					1	2
Anidulafungin						0 0.0	12 12.8	21 35.1	55 93.6	6 100.0				2	2
Caspofungin				0 0.0	5 5.3	56 64.9	32 98.9	1 100.0						0.25	0.5
Micafungin		0 0.0	1 1.1	0 1.1	1 2.1	0 2.1	16 19.1	71 94.7	5 100.0					1	1
Candida tropicalis (64)															
Rezafungin	3 4.7	20 35.9	24 73.4	12 92.2	3 96.9	0 96.9	0 96.9	1 98.4	1 100.0					0.03	0.06
Anidulafungin	3 4.7	26 45.3	22 79.7	9 93.8	2 96.9	0 96.9	0 96.9	2 100.0						0.03	0.06
Caspofungin	0 0.0	38 59.4	20 90.6	4 96.9	0 96.9	0 96.9	0 96.9	1 98.4	0 98.4	0 98.4	1 100.0			0.015	0.03
Micafungin	3 4.7	14 26.6	30 73.4	15 96.9	0 96.9	0 96.9	0 96.9	1 98.4	1 100.0					0.03	0.06
Candida krusei (33)															
Rezafungin	0 0.0	8 24.2	17 75.8	7 97.0	1 100.0									0.03	0.06
Anidulafungin	0 0.0	4 12.1	11 45.5	17 97.0	1 100.0									0.06	0.06
Caspofungin		0 0.0	2 6.1	16 54.5	13 93.9	2 100.0								0.06	0.12
Micafungin	0 0.0	1 3.0	2 9.1	21 72.7	9 100.0									0.06	0.12
Candida dubliniensis (30)															
Rezafungin		0 0.0	8 26.7	15 76.7	7 100.0									0.06	0.12
Anidulafungin	0 0.0	1 3.3	12 43.3	14 90.0	3 100.0									0.06	0.06
Caspofungin		5 16.7	25 100.0											0.03	0.03
Micafungin	0 0.0	6 20.0	23 96.7	1 100.0										0.03	0.03
Cryptococcus neoformans var. grubii (27)															
Rezafungin										0 0.0	14 51.9	13 100.0		8	>8
Anidulafungin									0 0.0	1 3.7	6 25.9	20 100.0		>8	>8
Caspofungin										0 0.0	2 7.4	25 100.0		>8	>8
Micafungin (27)								0 0.0	1 3.7	2 11.1	1 14.8	23 100.0		>8	>8
Aspergillus fumigatus (48)															
Rezafungin	26 54.2	20 95.8	2 100.0											≤0.008	0.015
Anidulafungin	22 45.8	24 95.8	2 100.0											0.015	0.015
Caspofungin	6 12.5	37 89.6	5 100.0											0.015	0.03
Micafungin	43 89.6	5 100.0												≤0.008	0.015
Aspergillus section *Flavi* (12)															
Rezafungin	3 25.0	7 83.3	2 100.0											0.015	0.03
Anidulafungin	8 66.7	2 83.3	2 100.0											≤0.008	0.03
Caspofungin	1 8.3	10 91.7	1 100.0											0.015	0.015
Micafungin	2 16.7	7 75.0	3 100.0											0.015	0.03

- RZF ($MIC_{50/90}$, 0.06/0.12 µg/mL) inhibited 131 (97.0%) of the *C. glabrata* isolates at ≤0.12 µg/mL (Table 1) with activity comparable to the activity of anidulafungin ($MIC_{50/90}$, 0.06/0.12 µg/mL) and caspofungin ($MIC_{50/90}$, 0.03/0.06 µg/mL) and 4-fold less than the activity of micafungin ($MIC_{50/90}$, 0.015/0.03 µg/mL; Table 1)
  - Fluconazole resistance was noted among 8 (5.9%) of *C. glabrata* isolates (data not shown)
- All *C. parapsilosis* isolates were inhibited by RZF ($MIC_{50/90}$, 1/2 µg/mL) at ≤2 µg/mL, the current CLSI susceptible breakpoint for the echinocandins tested against this *Candida* species (Table 1)
  - Fluconazole resistance was noted among 11 (11.7%) of *C. parapsilosis* isolates (data not shown)
- RZF ($MIC_{50/90}$, 0.03/0.06 µg/mL) inhibited 62 (96.9%) *C. tropicalis* isolates at ≤0.12 µg/mL (Table 1) with activity comparable to the activity of anidulafungin ($MIC_{50/90}$, 0.03/0.06 µg/mL), caspofungin ($MIC_{50/90}$, 0.015/0.03 µg/mL), and micafungin ($MIC_{50/90}$, 0.03/0.06 µg/mL; Table 1)
  - Fluconazole resistance was noted among 2 (3.1%) of the *C. tropicalis* isolates (data not shown)
- RZF ($MIC_{50/90}$, 0.03/0.06 µg/mL) was very active against 33 *C. krusei* isolates, and all *C. krusei* isolates were inhibited at ≤0.12 µg/mL (Table 1).
- The activity of RZF ($MIC_{50/90}$, 0.06/0.12 µg/mL; Table 1) against 30 *C. dubliniensis* isolates was comparable to those of anidulafungin ($MIC_{50/90}$, 0.06/0.06 µg/mL), caspofungin ($MIC_{50/90}$, 0.03/0.03 µg/mL), and micafungin ($MIC_{50/90}$, 0.03/0.03 µg/mL)
  - All but 1 isolate (NWT for fluconazole and voriconazole) were considered WT for azoles (data not shown)
- Echinocandins, including RZF, displayed limited activity against 27 *C. neoformans* var. *grubii* isolates ($MIC_{50/90}$, ≥8 µg/mL; Table 1)
  - Fluconazole and other triazoles displayed good activity against *C. neoformans* var. *grubii*, and $MIC_{50/90}$ values were 2/4 µg/mL for fluconazole, 0.03/0.12 µg/mL for voriconazole, and 0.12/0.25 µg/mL for posaconazole (data not shown)
- Echinocandins displayed good activity against *A. fumigatus*, and RZF ($MEC_{50/90}$, ≤0.008/0.015 µg/mL) activity was similar to that of anidulafungin ($MEC_{50/90}$, 0.015/0.015 µg/mL), caspofungin ($MEC_{50/90}$, 0.015/0.03 µg/mL), and micafungin ($MEC_{50/90}$, ≤0.008/0.015 µg/mL)
  - All isolates displayed WT MIC values for the mould-active triazoles (data not shown)

Table 2 Summary of *FKS* alterations detected

JMI collection no.	State and/or country	Organism	MIC according to CLSI method (µg/mL):				1,3-β-D-glucan synthase mutations:				
			Rezafungin	Anidulafungin	Caspofungin	Micafungin	*fks1* HS1	*fks1* HS2	*fks2* HS1	*fks2* HS2	Non-HS
984357	Ireland	*Candida albicans*	0.25	0.12	1	1	S645P	WT			*fks1* A1838P, *fks1* S1886T
978825	Turkey	*Candida albicans*	0.12	0.12	0.12	0.06	WT	WT	WT	WT	*fks1* S1886T
948247	USA	*Candida glabrata*	0.06	0.12	0.03	0.03	WT	WT	WT	WT	
949151	USA	*Candida glabrata*	0.03	0.06	0.06	0.12	WT	WT	WT	WT	*fks2* F30V
970382	USA	*Candida glabrata*	0.25	0.25	0.12	0.12	S629P	WT	WT	WT	
970397	USA	*Candida glabrata*	0.12	0.25	0.25	0.12	WT	WT	P667H	WT	*fks1* G14S
974239	USA	*Candida glabrata*	0.25	0.25	0.06	0.12	S629P	WT	WT	WT	*fks1* G14S
974249	USA	*Candida glabrata*	2	2	1	1	WT	WT	S663P	WT	
978819	Turkey	*Candida glabrata*	0.25	0.25	0.06	0.06	WT	WT	WT	WT	
983007	USA	*Candida glabrata*	0.12	0.5	0.06	0.12	WT	WT	F658 deletion	WT	
985673	USA	*Candida glabrata*	0.06	0.12	0.06	0.06	WT	WT	S663P	WT	
936285	Germany	*Candida krusei*	0.12	0.12	0.25	0.12	WT	WT			*fks1* L701M, *fks1* S274N
954660	Italy	*Candida krusei*	0.015	0.03	0.06	0.06	WT	WT			*fks1* L701M
975699	USA	*Candida krusei*	0.015	0.06	0.12	0.06	WT	WT			*fks1* L701M, *fks1* S274N
977046	Brazil	*Candida krusei*	0.015	0.015	0.06	0.06	WT	WT			*fks1* L701M, *fks1* S274N
970388	USA	*Candida tropicalis*	2	1	>8	2	S654P	WT			
977041	Brazil	*Candida tropicalis*	1	1	2	1	F650S	WT			

Abbreviations: WT, wild type; HS, hot spot

- Echinocandins displayed good activity against *A.* section *Flavi*, and RZF ($MEC_{50/90}$, 0.015/0.03 µg/mL) activity was similar to that of anidulafungin ($MEC_{50/90}$, ≤0.008/0.03 µg/mL), caspofungin ($MEC_{50/90}$, 0.015/0.015 µg/mL), and micafungin (0.015/0.03 µg/mL)
  - All isolates displayed WT MIC values for the mould-active triazoles (data not shown)
- Seventeen *Candida* spp. isolates displayed NWT or resistant echinocandin MIC values and were screened for *fks* mutations (Table 2)
- Two isolates were *C. albicans* and 1 carried *fks1* HS1 alterations (S645P; Table 2); RZF MIC values were ≤0.25 µg/mL for both isolates (Table 2)
- Nine isolates were *C. glabrata* and alterations in *fks* HS sequences were noted among 6 of those isolates (Table 2); 2 isolates carried *fks1* HS1 S629P alteration, 2 harbored *fks2* HS1 S663P, and the 2 remaining isolates carried the *fks2* HS1 alteration P667H or F658-deletion (Table 2)
  - Only 1 isolate harboring a mutation on S663P *fks2* HS1 exhibited resistant echinocandin MIC values and RZF MIC results at >0.25 µg/mL
- Two isolates were *C. tropicalis* and carried *fks1* HS1 alterations (S645P or F650S: RZF MIC values were elevated for both isolates (2 and 1 µg/mL, respectively; Table 2)
- Four *C. krusei* isolates displayed NWT echinocandin MIC values and none carried *fks* HS alterations; however, all 4 exhibited amino acid substitutions outside the HS regions on *fks1* (L701M, S274N; Table 2)

Conclusions

- The activity of RZF against common fungal species isolated from invasive clinical infections was comparable to currently available echinocandins, and variations of ±2-fold were noted for different species when RZF was compared to anidulafungin, caspofungin, and micafungin
- The prolonged half-life and high, front-loaded drug exposure of RZF coupled with its excellent potency and spectrum makes RZF a promising new antifungal candidate that may prove to be competitive with currently available echinocandins in prevention and treatment of invasive fungal infections
- Further evaluations of RZF against less common species of fungi is recommended and further development of this long-acting echinocandin is warranted

Acknowledgements

This study was funded by Cidara Therapeutics, Inc.

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