Activity of a Long-Acting Echinocandin, Rezafungin, and Comparator Antifungal Agents Tested against Contemporary Invasive Fungal Isolates: SENTRY 2018

Michael A. Pfaller, Cecilia Carvalhaes, Shawn A. Messer, Paul R. Rhomberg, Mariana Castanheira
JMI Laboratories, North Liberty, Iowa, USA

Introduction

- Echinocandins are first-line treatment of candidemia and have been used as empirical and prophylactic therapy in patients who are at risk of invasive candidiasis, aspergillosis, and pneumocystis
- Rezafungin is a novel long-acting echinocandin with improved pharmacokinetics when compared to currently available echinocandins, providing front-loaded drug exposure and extensive distribution to sites of infection that are critical to antifungal efficacy
- Rezafungin is in Phase 3 development as a once-weekly, intravenous therapy for the treatment of candidemia/invasive candidiasis and is being developed for the prevention of infections caused by *Candida*, *Aspergillus,* and *Pneumocystis* spp. in patients undergoing blood and marrow transplantation
- We evaluated the activity of rezafungin and comparators using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods against 767 invasive fungal isolates collected as part of the 2018 SENTRY Antifungal Surveillance Program worldwide

Materials and Methods

Bacterial isolates

- A total of 767 non-duplicate fungal isolates were collected prospectively (1/patient) from 37 medical centers located in North America (13 sites), Europe (13), the Asia-Pacific region (6), and Latin America (5)
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program
- Isolates were recovered from patients with bloodstream infections (BSIs, 477 isolates), intra-abdominal infections (IAIs, 18 isolates), skin and skin structure infections (SSSIs, 46 isolates), urinary tract infections (UTIs, 24 isolates), or pneumonia while hospitalized (PIHP, 111 isolates), and 91 isolates were collected from non-specified sites (Figure 1)

Susceptibility testing

- Susceptibility tests on 656 *Candida* spp. (6 species), 21 *Cryptococcus neoformans* var. *grubii*, and 90 *Aspergillus* spp. were conducted for rezafungin, anidulafungin, caspofungin, micafungin, and azoles according to CLSI documents M27 (2017) and M38 (2017)
- CLSI clinical breakpoint and epidemiological cutoff value (ECV) interpretive criteria were applied (CLSI M60, 2017; M59, 2018)
- Minimal effective concentration (MEC) values were read for echinocandins against *Aspergillus* spp.
- Quality control (QC) was performed as recommended by CLSI using the following strains: *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258, *Aspergillus flavus* ATCC 204304, and *Aspergillus fumigatus* ATCC MYA-3626
- Isolates displaying echinocandin MIC>ECV were sequenced for *fks* hot spot mutations by MiSeq Sequencer (Illumina)
- Each sample was assembled using a reference-guided assembly in DNASTAR SeqMan NGen v.14.0 (Madison, Wisconsin, USA) and compared to sequences available in the literature

Results

- Rezafungin inhibited 99.7% of *Candida albicans* isolates ($MIC_{50/90}$, 0.015/0.06 µg/mL), 98.7% of *Candida tropicalis* ($MIC_{50/90}$, 0.03/0.06 µg/mL), 96.6% of *Candida glabrata* ($MIC_{50/90}$, 0.03/0.06 µg/mL), 100.0% of *C. krusei* ($MIC_{50/90}$, 0.015/0.12 µg/mL), and 100.0% of *Candida dubliniensis* ($MIC_{50/90}$, 0.03/0.12 µg/mL) at ≤0.12 µg/mL (Table 1)
- All (117/117 [100.0%]) *C. parapsilosis* isolates ($MIC_{50/90}$, 1/2 µg/mL) were inhibited by rezafungin at ≤2 µg/mL (Table 1)
- Fluconazole resistance was detected among 9.3% of *C. glabrata*, 15.4% of *C. parapsilosis*, and 2.6% of *C. tropicalis*
- The activity of rezafungin against these *Candida* spp. was similar to that of the other echinocandins, the vast majority of which were susceptible/wild type (WT; 98.8%; 648/656) using clinical breakpoints or ECV criteria
- A total of 8 isolates (6 *C. glabrata* and 2 *C. tropicalis*) displayed 1 or more non-WT or resistant echinocandin MIC values; however, mutations on *fks* hot spots were detected only in 4 *C. glabrata* isolates (Table 2)
- Fluconazole and other azoles displayed good activity against *C. neoformans* whereas echinocandins, including rezafungin, displayed limited activity against *C. neoformans* isolates (Table 1)
- Echinocandins displayed good activity against 75 *A. fumigatus* (rezafungin $MEC_{50/90}$, 0.015/0.03 µg/mL) and 15 *Aspergillus* section *Flavi* (rezafungin $MEC_{50/90}$, 0.008/0.008 µg/mL), and rezafungin activity was similar to that of anidulafungin (Table 1), caspofungin, and micafungin
- All but 4 *A. fumigatus* isolates (3 non-WT MICs for itraconazole ≥2 µg/mL and 1 non-WT for voriconazole ≥2 µg/mL) displayed WT MIC values for the mould-active azoles
- Rezafungin showed good activity against *Candida* spp. regardless of the infection type; interestingly, MIC_{90} values for echinocandins including rezafungin were lower against isolates recovered from IAI than from other infections, despite similar species distribution (Figures 2 and 3)
- Rezafungin displayed similar activity as other echinocandins against *Candida* spp. isolates regardless of the geographic region

Conclusions

- Rezafungin was as active as other echinocandins against frequently recovered *Candida* spp. and *Aspergillus* spp. from invasive fungal infections
- Activity of rezafungin against *Candida* spp. isolates was similar in different geographic regions
- Limited activity was observed for all echinocandins against *C. neoformans* isolates
- These *in vitro* data of rezafungin against *Candida* spp. and *Aspergillus* spp. contribute to accumulating research demonstrating rezafungin potential for the treatment and prevention of invasive fungal infections

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Figure 1 Characteristics of the fungal isolates recovered from the worldwide 2018 SENTRY Antifungal Surveillance Program

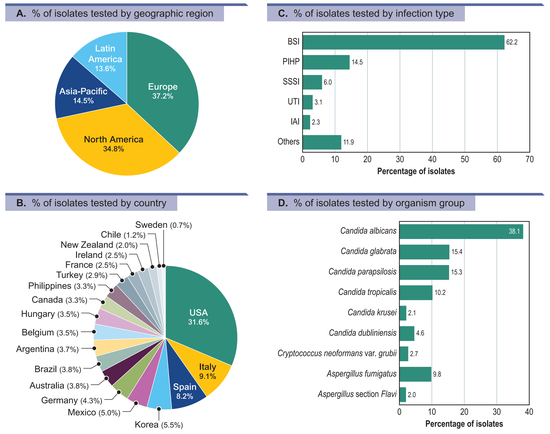
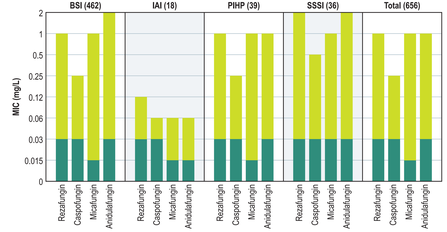


Figure 2 Activity of rezafungin and other echinocandins against *Candida* spp. recovered from the 2018 SENTRY Antifungal Surveillance Program by infection type



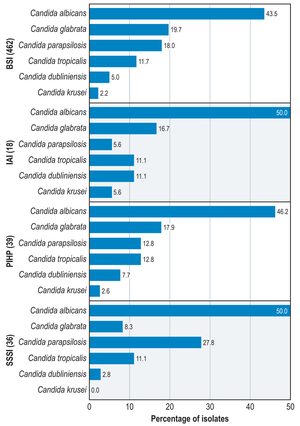
Abbreviations: BSI, bloodstream infection; IAI, intra-abdominal infection; PIHP, pneumonia in hospitalized patients; SSSI, skin and skin structure infection

Table 2 Summary of Fks alterations detected in *Candida spp.* strains as part of the 2018 SENTRY Antifungal Surveillance Program

Isolate	Site code	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
1051621	A	Hungary	*Candida tropicalis*	0.25	0.25	0.12	0.12	Wild type	Wild type	NT	NT
1051641	A	Hungary	*Candida glabrata*	1	1	1	0.5	Wild type	Wild type	F659_del	Wild type
1053234	B	Canada	*Candida glabrata*	0.12	0.12	0.06	0.06	Wild type	Wild type	Wild type	Wild type
1075570	C	Belgium	*Candida glabrata*	0.06	0.12	0.06	0.06	Wild type	Wild type	Wild type	Wild type
1078854	D	NY, USA	*Candida glabrata*	0.06	0.06	0.06	0.06	Wild type	Wild type	F659_del	Wild type
1078861	D	NY, USA	*Candida glabrata*	2	2	1	1	Wild type	Wild type	S663P	Wild type
1085740	E	Spain	*Candida tropicalis*	0.06	0.06	0.06	0.12	Wild type	Wild type	NT	NT
1087598	F	VA, USA	*Candida glabrata*	2	4	4	4	Wild type [a]	Wild type [a]	S663P	Wild type

NT, not tested.
[a] Deletion outside *fks1* hot spot (HS) 1 and HS2 was observed.

Figure 3 Distribution of *Candida* spp. by infection type



Abbreviations: BSI, bloodstream infection; IAI, intra-abdominal infection; PIHP, pneumonia in hospitalized patients; SSSI, skin and skin structure infection; UTI, urinary tract infection

Table 1 MIC distribution of rezafungin and anidulafungin tested against fungal isolates from the 2018 SENTRY Antifungal Surveillance Program worldwide

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC/MEC (µg/mL) of:															MIC50	MIC90
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	> [b]				
Candida albicans																	
Rezafungin (292)	11 3.8	6 5.8	45 21.2	87 51.0	100 85.3	35 97.3	7 99.7	1 100.0								0.015	0.06
Anidulafungin (292) [a]	0 0.0	30 10.3	96 43.2	82 71.2	72 95.9	10 99.3	2 100.0									0.015	0.03
Candida glabrata																	
Rezafungin (118)	1 0.8	0 0.8	0 0.8	4 4.2	65 59.3	37 90.7	7 96.6	1 97.5	0 97.5	1 98.3	2 100.0					0.03	0.06
Anidulafungin (118) [a]			0 0.0	2 1.7	32 28.8	66 84.7	15 97.5	0 97.5	0 97.5	1 98.3	1 99.2	1 100.0				0.06	0.12
Candida parapsilosis																	
Rezafungin (117)						0 0.0	1 0.9	1 1.7	35 31.6	49 73.5	31 100.0					1	2
Anidulafungin (117) [a]						0 0.0	1 0.9	1 1.7	9 9.4	43 46.2	57 94.9	6 100.0				2	2
Candida tropicalis																	
Rezafungin (78)		0 0.0	9 11.5	21 38.5	32 79.5	12 94.9	3 98.7	1 100.0								0.03	0.06
Anidulafungin (78) [a]	0 0.0	2 2.6	13 19.2	25 51.3	28 87.2	6 94.9	3 98.7	1 100.0								0.015	0.06
Candida krusei																	
Rezafungin (16)			0 0.0	11 68.8	2 81.2	0 81.2	3 100.0									0.015	0.12
Anidulafungin (16) [a]				0 0.0	12 75.0	2 87.5	2 100.0									0.03	0.12
Candida dubliniensis																	
Rezafungin (35)	1 2.9	0 2.9	1 5.7	3 14.3	13 51.4	13 88.6	4 100.0									0.03	0.12
Anidulafungin (35)		0 0.0	1 2.9	4 14.3	19 68.6	10 97.1	1 100.0									0.03	0.06
Cryptococcus neoformans var. *grubii*																	
Rezafungin (21)											0 0.0	2 9.5	19 100.0			>4	>4
Anidulafungin (21)										0 0.0	1 4.8	5 28.6	15 100.0			>4	>4
Aspergillus fumigatus																	
Rezafungin (75)	0 0.0	3 4.0	13 21.3	39 73.3	20 100.0											0.015	0.03
Anidulafungin (75)	0 0.0	4 5.3	19 30.7	44 89.3	8 100.0											0.015	0.03
Aspergillus section *Flavi*																	
Rezafungin (15)		0 0.0	5 33.3	9 93.3	1 100.0											0.008	0.008
Anidulafungin (15)		0 0.0	5 33.3	10 100.0												0.008	0.008

[a] CLSI susceptibility criteria published at M60 (2017): green shadow, susceptible; yellow shadow, intermediate; red shadow, resistant.
[b] Greater than the highest concentration tested.

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Contact

Cecilia Carvalhaes, MD, PhD, D(ABMM)
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: cecilia-carvalhaes@jmilabs.com

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