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Activity of a Long-Acting Echinocandin Rezafungin Tested against Invasive Fungal Isolates Collected Worldwide

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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
- Rezafungin demonstrates a low potential for resistance development and produces high front-loaded plasma drug exposures that may reduce the potential for resistance emerging during therapy
- This long-acting echinocandin exhibits comparable potency and spectrum to other echinocandins against both wild-type (WT) and echinocandin-resistant *Candida* spp.
- Intravenous rezafungin 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 this study, we examined the activity of rezafungin and comparator agents tested against 719 clinical fungal isolates collected during 2017 from sterile body sites, respiratory tract infections, skin and skin structure infections, and bloodstream infections as part as the SENTRY Antifungal Surveillance Program worldwide

Materials and Methods

Fungal organisms

- A total of 719 non-duplicate fungal isolates prospectively collected during 2017 from 49 medical centers located in North America (217 isolates; 18 sites), Europe (317 isolates; 19 sites), the Asia-Pacific region (89 isolates; 8 sites), and Latin America (96 isolates; 4 sites) were evaluated (Figure 1)
- Isolates selected were from the following sources: bloodstream infections (485 isolates), pneumonia in hospitalized patients (100 isolates), intra-abdominal infections (7 isolates), skin and skin structure infections (33 isolates), and 88 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

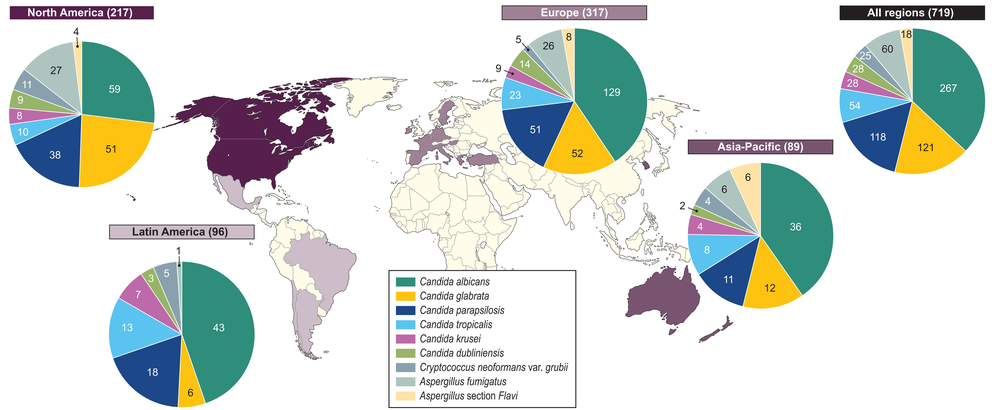
Antifungal susceptibility testing

- All isolates were tested by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) documents (M27, M38, M60, M61)
- 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*) (M27, M60)
- Epidemiological cutoff values (ECVs) were applied when available (M59)
- Quality control (QC) was performed as recommended in CLSI documents M27 and M38 by using strains *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *Aspergillus flavus* ATCC 204304, and *Aspergillus fumigatus* MYA-3626
  - No rezafungin QC ranges have been published by CLSI; however, proposed QC values for *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were used in this survey

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

Figure 1 Main organisms and organism groups stratified by geography



Results

- Among the 719 fungal clinical isolates tested, 616 (85.7%) were *Candida* spp., 25 (3.5%) were *Cryptococcus neoformans* var. *grubii*, 18 (2.5%) were *Aspergillus* section *Flavi*, and 60 (8.3%) were *A. fumigatus*; see Figure 1 for the distribution of isolates by geographic region
- Rezafungin inhibited 100.0% of 267 *C. albicans* ($MIC_{50/90}$, 0.03/0.06 µg/mL), 28 *C. dubliniensis* ($MIC_{50/90}$, 0.06/0.12 µg/mL), and 28 *C. krusei* ($MIC_{50/90}$, 0.03/0.12 µg/mL) isolates at ≤0.12 µg/mL
- Rezafungin inhibited 93.4% of 121 *C. glabrata* ($MIC_{50/90}$, 0.06/0.12 µg/mL) and 96.3% of 54 *C. tropicalis* ($MIC_{50/90}$, 0.03/0.12 µg/mL) isolates at ≤0.12 µg/mL
- Rezafungin inhibited 98.3% of 118 *C. parapsilosis* isolates ($MIC_{50/90}$, 1/2 µg/mL) at ≤2 µg/mL, the current CLSI susceptible breakpoint for the echinocandins tested against this *Candida* species (Table 1)
- Echinocandins, including rezafungin, displayed limited activity against 25 *C. neoformans* var. *grubii* isolates ($MIC_{50/90}$, >4 µg/mL; Table 1)
  - Fluconazole and other triazoles displayed good activity against *C. neoformans* var. *grubii*
- Echinocandins, including rezafungin ($MEC_{50/90}$, 0.015/0.015 µg/mL), displayed good activity against *A. fumigatus*
  - All isolates displayed WT MIC values for the mould-active triazoles (data not shown)
- Echinocandins displayed good activity against *Aspergillus* section *Flavi*, and rezafungin ($MEC_{50/90}$, 0.015/0.015 µg/mL) activity was similar to that of anidulafungin ($MEC_{50/90}$,0.015/0.03 µg/mL)
- Thirteen *Candida* spp. isolates displayed NWT or resistant echinocandin MIC values and were screened for *fks* mutations (Table 2)
  - Alterations in *fks* HS sequences were noted among 7 of the 10 *C. glabrata* isolates (Table 2)
    - 2 isolates carried *fks1* HS1 alteration (S629P or F625S); 1 of them also harbored *fks2* HS1 R665G alteration
    - 3 isolates harbored *fks2* HS1 S663P
    - 2 remaining isolates carried *fks2* HS1 alterations F658Y with a deletion at Y657 (Table 2)
    - Isolates harboring a mutation on S663P *fks2* HS1 exhibited resistant echinocandin MIC values and rezafungin MIC results at 0.25, 1, and 2 µg/mL
  - 3 isolates were *C. tropicalis* and none carried *fks* HS alterations (Table 2)

Table 1 Antifungal activity of rezafungin, anidulafungin, caspofungin, and micafungin tested against the main organisms and organism groups (CLSI)

Organism/organism group (no. of isolates)	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	> a				
Candida albicans (267)															
Rezafungin	12 4.5	83 35.6	96 71.5	66 96.3	10 100.0									0.03	0.06
Anidulafungin	48 18.0	90 51.7	100 89.1	25 98.5	4 100.0									0.015	0.06
Caspofungin	22 8.2	164 69.7	69 95.5	12 100.0										0.015	0.03
Micafungin	67 25.1	177 91.4	23 100.0											0.015	0.015
Candida glabrata (121)															
Rezafungin		0 0.0	33 27.3	60 76.9	20 93.4	2 95.0	3 97.5	2 99.2	1 100.0					0.06	0.12
Anidulafungin	0 0.0	1 0.8	6 5.8	61 56.2	43 91.7	3 94.2	2 95.9	3 98.3	1 99.2	1 100.0				0.06	0.12
Caspofungin	0 0.0	18 14.9	71 73.6	23 92.6	3 95.0	2 96.7	3 99.2	0 99.2	1 100.0					0.03	0.06
Micafungin	16 13.2	82 81.0	13 91.7	4 95.0	1 95.9	2 97.5	2 99.2	1 100.0						0.015	0.03
Candida parapsilosis (118)															
Rezafungin	0 0.0	1 0.8	0 0.8	0 0.8	0 0.8	0 0.8	2 2.5	14 14.4	48 55.1	51 98.3	2 100.0			1	2
Anidulafungin	0 0.0	1 0.8	0 0.8	0 0.8	0 0.8	0 0.8	2 2.5	5 6.8	25 28.0	77 93.2	8 100.0			2	2
Caspofungin	0 0.0	1 0.8	0 0.8	0 0.8	3 3.4	63 56.8	47 96.6	3 99.2	1 100.0					0.25	0.5
Micafungin	0 0.0	1 0.8	0 0.8	0 0.8	1 1.7	1 2.5	12 12.7	94 92.4	9 100.0					1	1
Candida tropicalis (54)															
Rezafungin	0 0.0	11 20.4	19 55.6	17 87.0	5 96.3	2 100.0								0.03	0.12
Anidulafungin	1 1.9	8 16.7	30 72.2	10 90.7	4 98.1	1 100.0								0.03	0.06
Caspofungin	1 1.9	20 38.9	25 85.2	4 92.6	3 98.1	1 100.0								0.03	0.06
Micafungin	3 5.6	14 31.5	27 81.5	8 96.3	2 100.0									0.03	0.06
Candida krusei (28)															
Rezafungin	0 0.0	3 10.7	12 53.6	10 89.3	3 100.0									0.03	0.12
Anidulafungin		0 0.0	10 35.7	9 67.9	9 100.0									0.06	0.12
Caspofungin			0 0.0	10 35.7	13 82.1	4 96.4	1 100.0							0.12	0.25
Micafungin		0 0.0	2 7.1	17 67.9	9 100.0									0.06	0.12
Candida dubliniensis (28)															
Rezafungin	0 0.0	1 3.6	9 35.7	11 75.0	7 100.0									0.06	0.12
Anidulafungin	0 0.0	3 10.7	14 60.7	5 78.6	6 100.0									0.03	0.12
Caspofungin	0 0.0	5 17.9	21 92.9	2 100.0										0.03	0.03
Micafungin	0 0.0	14 50.0	14 100.0											0.015	0.03

Organism/organism group (no. of isolates)	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	> a				
Cryptococcus neoformans var. *grubii* (25)															
Rezafungin									0 0.0	7 28.0	18 100.0			>4	>4
Anidulafungin								0 0.0	2 8.0	5 28.0	18 100.0			>4	>4
Caspofungin									0 0.0	2 8.0	23 100.0			>4	>4
Micafungin									0 0.0	5 20.0	20 100.0			>4	>4
Aspergillus fumigatus (60)															
Rezafungin		25 41.7	29 90.0	6 100.0										0.015	0.015
Anidulafungin		16 26.7	26 70.0	18 100.0										0.015	0.03
Caspofungin		2 3.3	26 46.7	30 96.7	2 100.0									0.03	0.03
Micafungin		42 70.0	17 98.3	1 100.0										≤0.008	0.015
Aspergillus section *Flavi* (18)															
Rezafungin		8 44.4	10 100.0											0.015	0.015
Anidulafungin		2 11.1	14 88.9	2 100.0										0.015	0.03
Caspofungin		1 5.6	2 16.7	15 100.0										0.03	0.03
Micafungin		1 5.6	13 77.8	4 100.0										0.015	0.03

a Greater than the highest dilution tested.

Table 2 Summary of *fks* alterations detected in strains with elevated echinocandin MIC values as part of SENTRY Surveillance Program

Isolate	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
997524	Mexico	*Candida glabrata*	0.5	0.5	0.25	0.06	F625S	Wild type	Wild type	Wild type
999721	Italy	*Candida glabrata*	0.06	0.06	0.06	0.06	Wild type	Wild type	Wild type	Wild type
1015009	Spain	*Candida glabrata*	0.5	1	0.5	0.25	Wild type	Wild type	Y657 deletion, F658Y	Wild type
1020535	United States	*Candida glabrata*	0.25	0.25	0.12	0.06	Wild type	Wild type	Wild type	Wild type
1021070	France	*Candida glabrata*	1	2	0.5	0.5	Wild type	Wild type	S663P	Wild type
1025460	United States	*Candida glabrata*	0.5	1	0.5	1	S629P	Wild type	R665G	Wild type
1026179	Spain	*Candida glabrata*	1	1	0.25	0.25	Wild type	Wild type	Y657 deletion, F658Y	Wild type
1034513	Ireland	*Candida glabrata*	2	4	2	0.5	Wild type	Wild type	S663P	Wild type
1034514	Ireland	*Candida glabrata*	0.25	0.5	0.12	0.12	Wild type	Wild type	S663P	Wild type
1034803	United States	*Candida glabrata*	0.12	0.12	0.06	0.06	Wild type	Wild type	Wild type	Wild type
1034763	Turkey	*Candida tropicalis*	0.06	0.06	0.25	0.12	Wild type	Wild type	NT	NT
1034766	Turkey	*Candida tropicalis*	0.12	0.25	0.03	0.06	Wild type	Wild type	NT	NT
1041544	Greece	*Candida tropicalis*	0.06	0.06	0.03	0.12	Wild type	Wild type	NT	NT

NT, not tested.

Conclusions

- Rezafungin activity against common fungal species isolated from invasive clinical infections was comparable to currently available echinocandins, and variations of ±2- to 4-fold were noted for different species when rezafungin was compared to anidulafungin, caspofungin, and micafungin
- The prolonged half-life and high front-loaded drug exposure of rezafungin coupled with its excellent potency and spectrum makes rezafungin a promising new antifungal candidate that may prove to be competitive with currently available echinocandins in preventing and treating invasive fungal infections
- Further evaluation of rezafungin against less common species of fungi is recommended and further development of this long-acting echinocandin is warranted

Acknowledgements

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