Poster #P54

Rezafungin *In Vitro* Activity against *Candida* spp. Causing Invasive Infections in Hematology/Oncology and Transplant Units Worldwide (2014–2021)

To obtain a PDF of this poster, scan the QR code or visit https://www.jmilabs.com/data/posters/ICHS2022_Rezafungin.pdf.

Cecilia G. Carvalhaes[1], Paul R. Rhomberg[1], Gregory J. Strand[1], Taylor Sandison[2*], Mariana Castanheira[1]

[1] JMI Laboratories, North Liberty, Iowa, USA

*[2] Cidara Therapeutics, San Diego, California, USA; * Presenting author*

Taylor Sandison, MD, MPH
Cidara Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 101
San Diego, CA, USA
tsandison@cidara.com

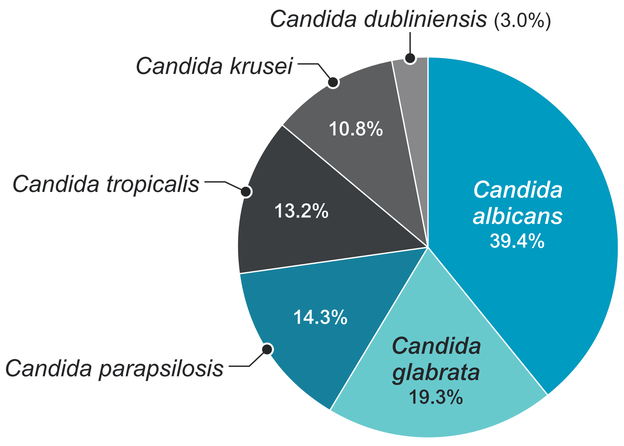
INTRODUCTION

- Patients undergoing hematologic, oncologic, and/or transplant therapy are at risk for invasive candidiasis (IC) and require antifungal treatments that are efficacious, safe, and compatible with other medications.
- Echinocandins are the mainstay treatment for IC in both neutropenic and non-neutropenic patients as well as critically ill patients.
- Rezafungin is a new echinocandin with long half-life and front-loaded drug exposure that allows for once-weekly intravenous administration instead of the once-daily intravenous administration required by anidulafungin, caspofungin, and micafungin.
- The *in vitro* activity of rezafungin and comparator agents was evaluated against *Candida* spp. isolates causing IC in patients from onco-hematology and transplant units (HTU) worldwide.

METHODS

- Out of 5229 *Candida* spp. isolates collected as part of the SENTRY Antifungal Surveillance Program from 2014 to 2021, 462 isolates were from HTU patients.
- Only isolates determined to be significant by local criteria as the reported probable cause of IC were included in the program.
- A single isolate per patient was collected from 48 medical centers located in Europe (48.1% of isolates; 20 sites in 12 countries), North America (29.7%; 17 sites in 2 countries), Asia-Pacific (18.6%; 7 sites in 4 countries), and Latin America (3.7%; 4 sites in 3 countries).
- Fungal isolates were identified by MALDI-TOF MS (Bruker Daltonics, MA, USA) or by DNA sequencing analysis when an acceptable identification was not achieved by mass spectrometry.
- Antifungal susceptibility testing was performed by broth microdilution following CLSI M27 (2017) guidelines for all isolates.
  - Panels were made by dispensing 10 µL of a 20x drug stock solution into wells that contained 90 µL of RPMI and then mixing.
- CLSI interpretative criteria and epidemiological cutoff value (ECV) criteria from the M57S (2022) and M27M44S (2022) documents were applied, including the recently approved rezafungin provisional ECVs and susceptible breakpoints against *Candida* spp. (Table 1).

Figure 1. Distribution of *Candida* spp. causing IC worldwide in patients from HTUs



IC, invasive candidiasis; HTUs, onco-hematology and transplant units.

Table 1. Rezafungin CLSI provisional ECVs and clinical breakpoint criteria

Organism	Rezafungin CLSI criteria [a] (mg/L)	
	Epidemiological cutoff value	Susceptible breakpoint
C. albicans	0.06	≤0.25
C. glabrata	0.12	≤0.5
C. parapsilosis	4	≤2
C. krusei	0.12	≤0.25
C. tropicalis	0.12	≤0.25
C. dubliniensis	0.12	≤0.12
C. auris	0.5	≤0.5

[a] ECV and BP criteria published in CLSI M57S (2022) and M27M44S (2022), respectively. Values are considered tentative for one year from the document publication date and are open for comment.

Table 2. Antimicrobial activity of rezafungin and comparator agents tested against *Candida* spp.

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI [a]		
			%S	%I	%R
C. albicans (*n*=182)					
Rezafungin	0.03	0.06	100.0	—	—
Anidulafungin	0.015	0.06	100.0	0.0	0.0
Caspofungin	0.015	0.03	99.5	0.0	0.5
Micafungin	0.015	0.03	99.5	0.0	0.5
Fluconazole	≤0.12	0.25	97.8	0.5 [b]	1.6
C. glabrata (*n*=89)					
Rezafungin	0.06	0.12	97.8	—	—
Anidulafungin	0.06	0.12	93.3	3.4	3.4
Caspofungin	0.03	0.06	96.6	0.0	3.4
Micafungin	0.015	0.03	95.5	1.1	3.4
Fluconazole	4	64	—	79.8 [b]	20.2
C. parapsilosis (*n*=66)					
Rezafungin	1	2	100.0	—	—
Anidulafungin	2	2	95.5	4.5	0.0
Caspofungin	0.25	0.5	100.0	0.0	0.0
Micafungin	1	1	100.0	0.0	0.0
Fluconazole	0.5	32	84.8	0.0 [b]	15.2
C. tropicalis (*n*=61)					
Rezafungin	0.03	0.06	100.0	—	—
Anidulafungin	0.03	0.06	100.0	0.0	0.0
Caspofungin	0.03	0.06	100.0	0.0	0.0
Micafungin	0.03	0.06	100.0	0.0	0.0
Fluconazole	0.25	1	93.4	0.0 [b]	6.6
C. krusei (*n*=50)					
Rezafungin	0.03	0.06	100.0	—	—
Anidulafungin	0.06	0.06	100.0	0.0	0.0
Caspofungin	0.12	0.25	100.0	0.0	0.0
Micafungin	0.06	0.12	100.0	0.0	0.0
Fluconazole	32	64	—	—	—
C. dubliniensis (*n*=14)					
Rezafungin	0.06	0.12	100.0	—	—
Anidulafungin	0.06	0.12	—	—	—
Caspofungin	0.03	0.06	—	—	—
Micafungin	0.015	0.03	—	—	—
Fluconazole	≤0.12	0.25	—	—	—

[a] Clinical interpretive criteria published in CLSI M27M44S (2022). ECV criteria published in CLSI M57S (2022).
[b] Intermediate is interpreted as susceptible-dose dependent.
"—", Criteria not available.

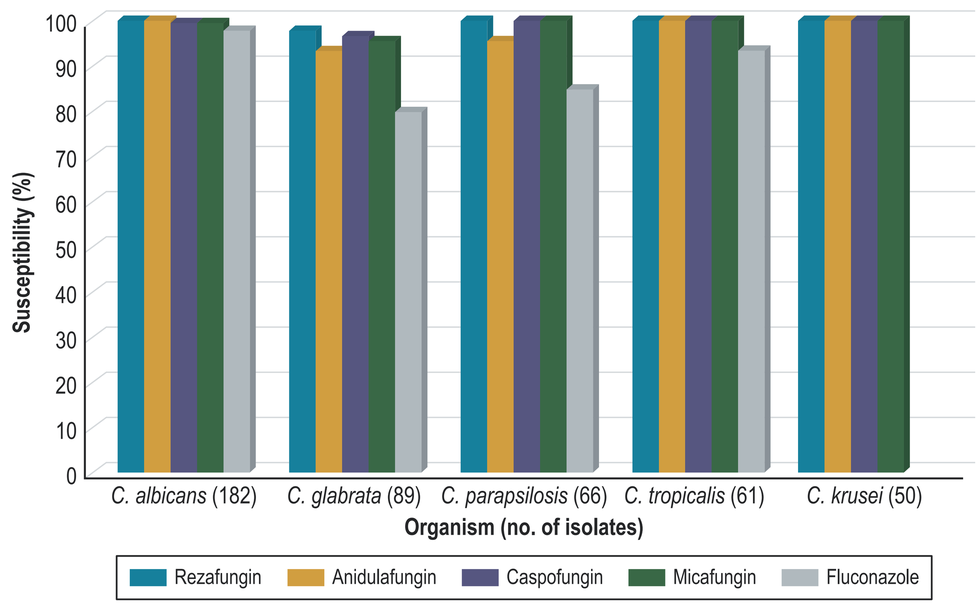
RESULTS

- *C. albicans* (39.4%) was the most common organism, followed by *C. glabrata* (19.3%), *C. parapsilosis* (14.3%), *C. tropicalis* (13.2%), *C. krusei* (10.8%), and *C. dubliniensis* (3.0%; Figure 1).
- Rezafungin ($MIC_{50/90}$, 0.03/0.06 mg/L) inhibited all *C. albicans* at the susceptible breakpoint and displayed similar activity to anidulafungin ($MIC_{50/90}$, 0.015/0.06 mg/L; 100% susceptible), caspofungin ($MIC_{50/90}$, 0.015/0.03 mg/L; 99.5% susceptible), and micafungin ($MIC_{50/90}$, 0.015/0.03 mg/L; 99.5% susceptible; Table 2 and Figure 2).
- Rezafungin inhibited the growth of 97.8% of *C. glabrata* and 100% of *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. dubliniensis* at the susceptible breakpoint (Figure 2).
- Rezafungin *in vitro* activity was similar to the activities of other echinocandins against *C. glabrata* (93.3%–96.6% susceptible), *C. parapsilosis* (95.5%–100.0% susceptible), *C. tropicalis* (100.0% susceptible), and *C. krusei* (100.0% susceptible; Table 2 and Figure 2).
  - Only 2 *C. glabrata* isolates (from the US and Spain) were nonsusceptible to rezafungin (MIC, 2 mg/L), and these isolates displayed resistance to the other echinocandins.
  - Anidulafungin-nonsusceptible phenotype was noted in 9 *Candida* spp. isolates, including 6 *C. glabrata* (3 US, 2 Spain, and 1 Croatia) and 3 *C. parapsilosis* (2 US and 1 Spain).
  - 1 *C. albicans* (Ireland) and 3 *C. glabrata* (2 US and 1 Spain) were resistant to caspofungin and micafungin.
- Fluconazole resistance was observed in 35 (7.6%) *Candida* isolates, including 18 *C. glabrata* (20.2%), 10 *C. parapsilosis* (15.2%), 4 *C. tropicalis* (6.6%), and 3 *C. albicans* (1.6%; Table 2 and Figure 3).
  - Fluconazole-resistant isolates were more frequently observed in the US (15), followed by Italy (8), Croatia (2), France (2), and Turkey (2).
  - All fluconazole-resistant isolates were susceptible to rezafungin.

CONCLUSIONS

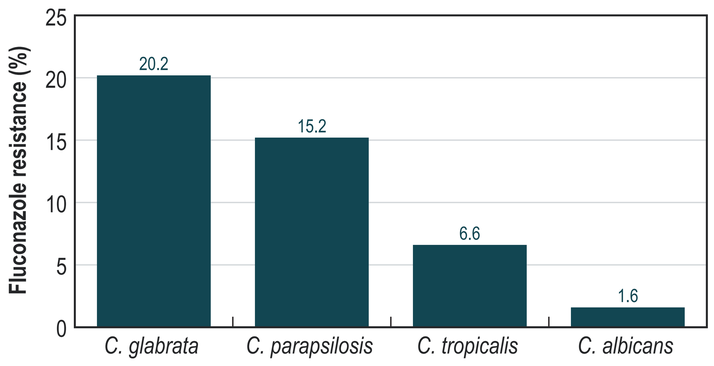
- Rezafungin showed *in vitro* activity against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. dubliniensis* from HTUs worldwide.
- Rezafungin and other echinocandins exhibited similar activity against *Candida* spp.
- Fluconazole resistance was higher in *C. glabrata* (20.2%), *C. parapsilosis* (15.2%), *C. tropicalis* (6.6%), and *C. albicans* (1.6%) HTU isolates vs. 1.8%, 9.0%, 0.4%, and 0.2%, respectively, for non-HTU isolates of these species collected during 2014–2021.
- *C. krusei* (intrinsically fluconazole-R) represented 10.8% of HTU patient isolates vs. 2.6% of the non-HTU isolates collected across the six *Candida* spp. included in surveillance.
- Rezafungin displayed *in vitro* activity against all fluconazole-resistant *Candida* isolates at their respective susceptible breakpoints.

Figure 2. Susceptibility rates of rezafungin and comparator agents tested against *Candida* spp.



Criteria as published by CLSI M27M44S (2022).
Fluconazole non-resistant *C. glabrata* is interpreted as susceptible-dose dependent.

Figure 3. Fluconazole-resistance rates among *Candida* spp. recovered from HTUs



HTUs, onco-hematology and transplant units.

FUNDING

This study was supported by Mundipharma Research. CG Carvalhaes, PR Rhomberg, GJ Strand, and M Castanheira are employees of JMI Laboratories, which was paid consultant to Mundipharma in connection with the development of this poster. T Sandison is an employee of Cidara Therapeutics.

ACKNOWLEDGMENTS

The authors thank the SENTRY Antifungal program participant centers for providing isolates.

REFERENCES

1. Barantsevich N, Barantsevich E. Diagnosis and Treatment of Invasive Candidiasis. Antibiotics (Basel). 2022 May 26;11(6):718.
2. CLSI (2017). M27Ed4. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, fourth edition. Wayne, PA.
3. CLSI (2022). M27M44SEd3. Performance standards for antifungal susceptibility testing of yeasts, third edition. Wayne, PA.
4. CLSI (2022). M57SEd4. Epidemiological cutoff values for antifungal susceptibility testing, fourth edition. Wayne, PA.
5. Garcia-Effron G. Rezafungin-Mechanisms of Action, Susceptibility and Resistance: Similarities and Differences with the Other Echinocandins. J Fungi (Basel). 2020 Nov 1;6(4):262.
6. Ham YY, Lewis JS 2nd, Thompson GR 3rd. Rezafungin: a novel antifungal for the treatment of invasive candidiasis. Future Microbiol. 2021 Jan;16(1):27-36.