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Evaluation of the Post-Antifungal Effect of Rezafungin and Micafungin against *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*

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Abstract

Rezafungin, a new echinocandin with an extended half-life, exhibits potent activity against *Candida* spp. Aside from the MIC, specific interactions between antifungal and isolate, including the duration of anti-infective activity, may impact dose interval choices and infection outcome. We evaluated rezafungin and micafungin post-antifungal effect (PAFE) against *C. albicans*, *C. parapsilosis* and *C. glabrata*. Six *Candida* spp. isolates were tested, including two of each species, *C. albicans*, *C. parapsilosis* and *C. glabrata*. Antifungal susceptibility testing was performed using the CLSI reference broth microdilution method. Antifungal concentrations of 1x, 4x and 16x the baseline MIC were used for PAFE determinations. Colony counts were performed at T0 (pre-exposure), after the 1-h drug exposure, after the cell wash (T1), and at T2, T4, T8, T12, T24 and T48 h. Rezafungin PAFE results were equivalent to micafungin PAFE values for one *C. albicans* (>14.9 h) and both *C. glabrata* (>40 h) isolates for all concentrations tested. The rezafungin and micafungin PAFEs could not be determined against one *C. albicans* isolate. Prolonged PAFE results were also noted for rezafungin (range, 18.4 to >40 h) against both *C. parapsilosis* isolates at all concentrations, while no micafungin PAFE or a short PAFE (range, 1.8 to 7.4 h) was observed against these organisms, except at 16x bMIC. Rezafungin showed sustained growth inhibition following drug removal and displayed equivalent or longer PAFE values than micafungin against all tested *Candida* spp.

KEYWORDS
antifungal, antifungal activity, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *Candida spp.*, echinocandin, PAFE

1 | INTRODUCTION

Rezafungin is a novel echinocandin with pharmacokinetic (PK) characteristics that distinguish this agent from current US FDA-approved echinocandins.[1] Rezafungin has a modification in the choline moiety at the cyclic echinocandin core that allows increased solubility and metabolic stability, which reduces toxicity while retaining antifungal activity.[2] Its stability in plasma and lack of degradation products contribute to its much longer half-life (~150 h after the second dose) than the currently available echinocandins (micafungin, 10–17 h; caspofungin, 9–11 h; and anidulafungin, 40–50 h).[1–3]

Consistent with other members of the echinocandin class, rezafungin demonstrates potent in vitro activity against *Candida* species.[4,5] During a 5-year span of global surveillance (2016–2020),

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rezafungin inhibited 97.8%–99.8% of *Candida albicans* ($MIC_{50/90}$, 0.03/0.06 mg/L), 95.7%–98.3% of *Candida glabrata* ($MIC_{50/90}$, 0.06/0.06–0.12 mg/L), 97.4%–100.0% of *Candida tropicalis* ($MIC_{50/90}$, 0.03/0.06 mg/L), 99.6%–100.0% of *Candida parapsilosis* ($MIC_{50/90}$, 1/2 mg/L), 100.0% of *Candida krusei* ($MIC_{50/90}$, 0.03/0.06 mg/L) and 100.0% of *Candida dubliniensis* ($MIC_{50/90}$, 0.06/0.12 mg/L) when applying recently approved provisional CLSI breakpoints to the 5-year dataset.[4,5]

Aside from the MIC, interactions between the drug and the fungal cell may affect therapeutic responses. Among these interactions, the duration of antifungal activity after in vitro clearance may impact dose interval choices and infection outcome.[6] Previous reports showed that although the echinocandins may exhibit prolonged post-antifungal effect (PAFE), this effect can differ by *Candida* species.[7,8]

The in vitro properties of rezafungin have been characterised in a number of studies to-date, such as target-based inhibition, antifungal spectrum and activity, intrinsic resistance potential, mutant prevention concentration and time-kill kinetics.[4,5,9–11] In this study, we characterised the PAFE of rezafungin against *C. albicans*, *C. glabrata* and *C. parapsilosis* isolates using micafungin as a comparator.

2 | MATERIALS AND METHODS

2.1 | Organisms and susceptibility testing

Six isolates were selected for the PAFE experiments based on our extensive experience with these isolates in our laboratory, including two well-known strains, *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019, and four clinical isolates (1 *C. albicans*, 1 *C. parapsilosis* and 2 *C. glabrata*) from the SENTRY Antifungal Surveillance Program. Isolates were identified by MALDI-TOF MS or DNA sequencing, as previously described. Modal baseline MIC (bMIC) values for rezafungin and micafungin were established by susceptibility testing each isolate in triplicate using the CLSI broth microdilution method (CLSI M27). Quality control was performed as recommended in CLSI document M27 using *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019.

2.2 | PAFE experiments

PAFE experiments were conducted as described by Ernst et al.[8] and applied by other researchers.[7,12] Briefly, a starting inocula of $1–5\times10^5$ CFU/ml was tested in RPMI 1640 broth (pH 7.0) supplemented with MOPS buffer and 0.2% glucose, either alone or with an antifungal agent, at concentrations 1x, 4x and 16x the bMIC into a final volume of 10 ml. Following a 1-h incubation, the drug was removed, and the fungal cell pellet was washed three times with pre-warmed RPMI broth then resuspended in 9 ml of pre-warmed RPMI broth. The resuspended samples were incubated at 35°C under agitation. Colony counts were obtained after the final wash at T_0 (pre-antifungal exposure), T_1 (before and after cell washing), T_2, T_4, T_8, T_{12}, T_{24} and T_{48} h post-exposure. The PAFE results were determined using the following equation: PAFE = *T*–*C*, where *T* = time required for the yeast count (CFU/ml) in the test agent culture to increase $1–\log_{10}$ above the count observed immediately after drug removal, and *C* = time required for the yeast count (CFU/ml) in the untreated control culture to increase $1–\log_{10}$ above the count observed immediately after completing the same procedure used on the test agent culture for drug removal. The logarithmic reduction of the colony counts at each time point was compared with the initial inoculum (T_1 post-cell washing).

TABLE 1 Post-Antifungal Effect (PAFE) for rezafungin and micafungin against *C. albicans*, *C. parapsilosis* and *C. glabrata*

Antifungal/Strain	Baseline MIC (mg/L)	PAFE (hours) at the following multiple of baseline MIC		
		1x	4x	16x
Rezafungin				
C. albicans ATCC 90028	0.03	ND	ND	ND
C. albicans #2019–01	0.06	>14.9	>14.9	>14.9
C. parapsilosis ATCC 22019	1	>40.8	>40.8	>40.8
C. parapsilosis #2019–02	1	18.4	35.6	>36.6
C. glabrata #2010–03	0.12	>46.7	>46.7	>46.7
C. glabrata #2019–04	0.12	>42.0	>42.0	>42.0
Micafungin				
C. albicans ATCC 90028	0.03	ND	ND	ND
C. albicans #2019–01	0.015	>14.9	>14.9	>14.9
C. parapsilosis ATCC 22019	1	≤0.0	≤0.0	1.8
C. parapsilosis #2019–02	1	1.6	7.4	31.3
C. glabrata #2010–03	0.06	20.4	>46.7	>46.7
C. glabrata #2019–04	0.03	>42.0	>42.0	>42.0

Note: ND, not determined.

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3 | RESULTS AND DISCUSSION

All *Candida* isolates were susceptible to rezafungin and micafungin, and bMIC results are summarised in Table 1. The PAFE values in hours for rezafungin and micafungin at concentrations 1x, 4x and 16x the bMIC for the six strains tested in this study are also displayed in Table 1. In general, rezafungin displayed an equivalent or more prolonged PAFE than micafungin. The rezafungin and micafungin PAFE values against the *C. albicans* clinical isolate (#2019–01) were equivalent (>14.9 h), but exposure to 1x (0.06 mg/L), 4x (0.25 mg/L)

TABLE 2 Reduction in the starting inocula (PAFE, in log-kill) after 1-h exposure to rezafungin and micafungin at 1x, 4x and 16x the baseline MIC values over the 48-h study period

Organism	Antifungal compound	Antifungal concentration (mg/L)	Reduction in the starting inocula (log-kill) after time					
			2 h	4 h	8 h	12 h	24 h	48 h
C. albicans ATCC 90028	Rezafungin	0.03 (1x MIC)	0.28	0.36	0.77	**0.78**	0.78	0.68
		0.12 (4x MIC)	0.02	0.36	**0.61**	0.41	0.42	0.61
		0.5 (16x MIC)	0.16	0.26	0.54	**0.65**	0.43	0.61
	Micafungin	0.03 (1x MIC)	−0.05	−0.09	**0.32**	0.17	0.25	0.32
		0.12 (4x MIC)	0.28	0.23	0.56	**0.80**	0.77	0.52
		0.5 (16x MIC)	0.29	0.32	0.54	**0.71**	0.51	0.49
C. albicans #2019–01	Rezafungin	0.06 (1x MIC)	0.33	0.55	0.39	**0.69**	0.40	0.21
		0.25 (4x MIC)	0.33	0.59	0.61	0.86	0.62	**0.97**
		1 (16x MIC)	0.30	0.55	0.70	0.76	0.96	**1.49**
	Micafungin	0.015 (1x MIC)	−0.07	0.28	0.17	**0.37**	0.25	0.29
		0.06 (4x MIC)	0.13	0.16	0.31	**0.50**	0.24	0.30
		0.25 (16x MIC)	0.08	0.18	0.26	**0.54**	0.09	0.10
C. parapsilosis ATCC 22019	Rezafungin	1 (1x MIC)	**0.31**	0.30	0.10	−0.10	−0.59	−0.97
		4 (4x MIC)	0.96	**1.00**	0.98	0.85	0.35	0.07
		16 (16x MIC)	**0.97**	0.83	0.79	0.93	0.87	0.43
	Micafungin	1 (1x MIC)	0.02	−0.45	−1.49	−1.65	−2.21	−2.21
		4 (4x MIC)	−0.13	−0.43	−1.33	−1.74	−2.27	−1.96
		16 (16x MIC)	0.14	0.30	−0.94	−1.19	−2.02	−1.56
C. parapsilosis #2019–02	Rezafungin	1 (1x MIC)	−0.11	−0.10	−0.12	−0.10	−0.80	−1.63
		4 (4x MIC)	0.27	0.35	0.44	**0.51**	0.15	−1.05
		16 (16x MIC)	0.62	0.52	0.65	**0.99**	0.87	−0.14
	Micafungin	1 (1x MIC)	−0.03	−0.05	−0.99	−0.95	−1.63	−1.93
		4 (4x MIC)	−0.11	−0.06	−0.63	−0.30	−1.54	−1.90
		16 (16x MIC)	0.07	0.22	0.30	**0.35**	−0.56	−1.12
C. glabrata #2010–03	Rezafungin	0.12 (1x MIC)	0.51	**0.79**	0.69	0.53	−0.34	−0.05
		0.5 (4x MIC)	0.68	1.06	0.82	**1.46**	1.09	0.97
		2 (16x MIC)	0.81	1.28	1.58	1.96	2.19	**NA**
	Micafungin	0.06 (1x MIC)	−0.33	−0.44	−0.48	−0.36	−1.15	−2.85
		0.25 (4x MIC)	0.56	0.79	0.86	1.64	1.51	**1.81**
		1 (16x MIC)	0.28	0.61	1.08	1.38	1.21	**NA**
C. glabrata #2019–04	Rezafungin	0.12 (1x MIC)	0.96	1.52	2.36	2.58	2.06	**2.82**
		0.5 (4x MIC)	1.17	1.57	2.04	2.31	2.27	**2.91**
		2 (16x MIC)	1.19	1.80	2.23	2.29	2.56	**NA**
	Micafungin	0.03 (1x MIC)	0.80	1.61	2.23	**2.81**	2.39	2.55
		0.12 (4x MIC)	1.05	1.64	2.30	2.78	2.78	**3.18**
		0.5 (16x MIC)	1.33	1.57	2.18	2.37	2.70	**NA**

Note: NA, not applicable, or below the limit of detection (10^2 CFU/ml). Negative values indicate that there was no reduction in colony counts compared with the starting inoculum. The largest log reduction in colony counts at each concentration compared with the starting inoculum over the 48-h study period is marked in bold.

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and 16x (1 mg/L) the rezafungin bMIC resulted in a larger log reduction colony count value (0.69, 0.97 and 1.49, respectively) when compared to micafungin (0.37, 0.50 and 0.54, respectively; Table 2). The PAFE for *C. albicans* ATCC 90028 could not be determined because the control and test regrowth fell below the 1–$\log_{10}$ threshold (Figure 1), but a similar reduction in colony count was noted in the micafungin and rezafungin experiments. This study confirms previous reports in which the echinocandins exhibited prolonged and persistent growth inhibition of *C. albicans*.[8,13,14]

The rezafungin PAFE was prolonged, regardless of the concentration tested for the two *C. parapsilosis* isolates, >40.8 h for the ATCC 22019 strain and 18.4 to >36.6 h for the 2019–02 isolate (Table 1). In contrast, micafungin failed to produce PAFE for *C. parapsilosis* ATCC 22019 at 1x and 4x the bMIC concentrations, and the micafungin PAFE was shorter than the rezafungin PAFE against the clinical isolate 2019–02 (Figure 1). In addition, no $\log_{10}$ reduction in the *C. parapsilosis* ATCC 22019 colony counts were observed at 48 h for all three micafungin concentrations, while rezafungin exposure displayed a log reduction of 0.31 to 1.00 $\log_{10}$ against this strain (Table 2). The largest reduction in the log-kill values after a 1-h exposure to 16x the micafungin bMIC was 0.35, while the reduction in the log-kill values after a 1-h exposure to 4x and 16x the rezafungin bMIC was 0.51 and 0.99, respectively. Notably, longer echinocandin PAFEs were obtained against *C. albicans* than *C. parapsilosis*. These findings are consistent with previous reports, suggesting that each *Candida* species could respond differently to treatment with each echinocandin.[7,15]

The rezafungin PAFE was prolonged (>42.0 h) and equivalent to the micafungin PAFE against two *C. glabrata* isolates, regardless of the antifungal concentration, except at 1x the micafungin bMIC against *C. glabrata* #2010–03 (Table 1 and Figure 1). The later isolate displayed a micafungin PAFE of 20.4 h, while the rezafungin PAFE was >46.7 h. Moreover, concentration-dependent killing results were observed when comparing 1x, 4x and 16x the rezafungin bMIC exposures (Table 2). The largest log-kill values at 1x and 4x the rezafungin bMIC were 0.79 and 1.46 against *C. glabrata* 2010–03 and 2.82 and 2.91 against *C. glabrata* #2019–04, respectively (Table 2). Although no reduction in colony count values were observed after a 1-h exposure to 1x the micafungin bMIC against *C. glabrata* 2010–03, a 1.81 $\log_{10}$ reduction was noted in the 4x micafungin MIC experiment. In addition, reductions of 2.81 and 3.18 $\log_{10}$ were observed after 1-h exposure to 1x and 4x the micafungin bMIC against *C. glabrata* #2019–04, respectively. *C. glabrata* isolates failed to grow at 48 h after the exposure to 16x the bMIC for both echinocandins. This result suggests that even a brief exposure to rezafungin or micafungin is likely to severely impair the ability of *C. glabrata* to regrow. As our study extended the PAFE experiments to 48 h, we observed a delay in regrowth at this time point, demonstrating that the PAFE for the echinocandins against some *Candida* species can be markedly prolonged beyond the 12 to 24 h previously demonstrated.[8,13] Interestingly, PAFE did not seem to be predicted by the MICs of the individual strains tested, which was also observed by Smith and colleagues.[7]

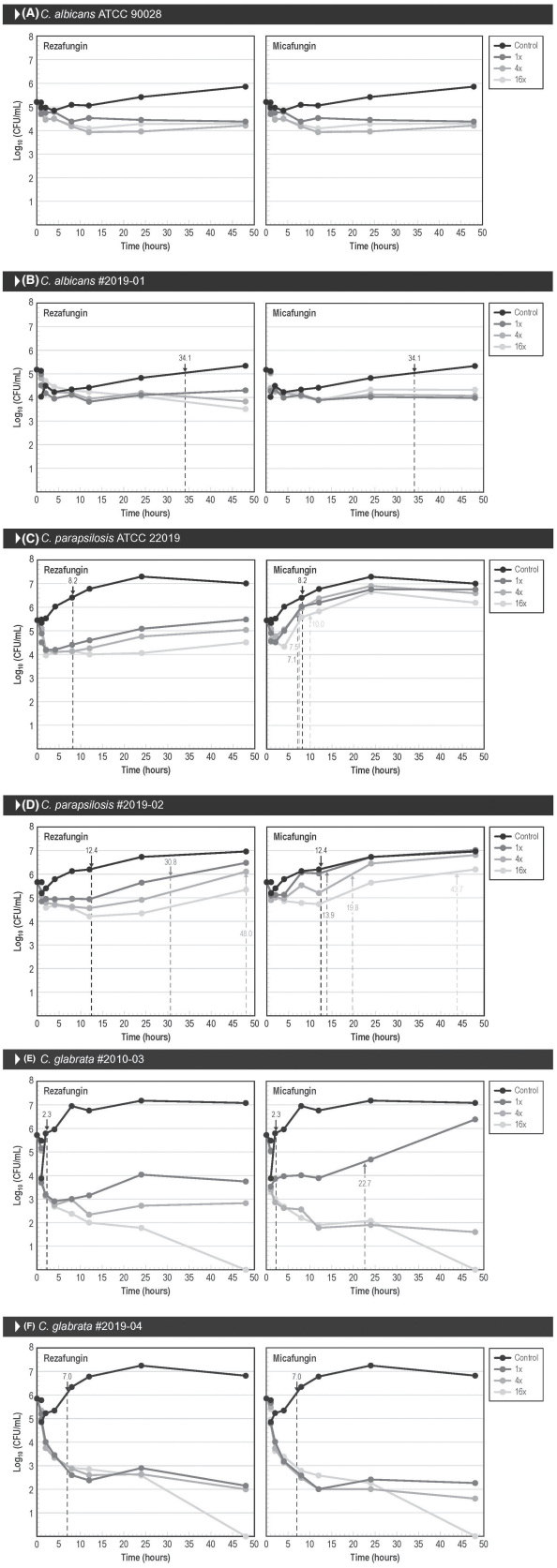

FIGURE 1 Rezafungin and micafungin PAFE against *C. albicans*, *C. parapsilosis* and *C. glabrata*. Dashed lines indicate the time required for the isolate to increase 1–$\log_{10}$ (in CFU) after drug removal

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4 | CONCLUSIONS

Our in vitro findings showed that rezafungin exerts prolonged growth inhibition on *Candida* isolates and helps support large intermittent and less frequent dosing regimens consistent with its mycological and clinical efficacy as demonstrated in the completed Phase 2 study.[16]

Overall, regrowth of all six strains was inhibited for >14.9 h after rezafungin washout regardless the concentration tested. In summary, rezafungin PAFE results against *C. albicans*, *C. parapsilosis* and *C. glabrata* were equivalent to or longer than the micafungin PAFE results, especially in the case of the *C. parapsilosis* isolates. Furthermore, species-specific PAFE differences were observed for both echinocandins. *C. glabrata* and *C. albicans* exhibited longer PAFE than *C. parapsilosis*. These PAFE findings of rezafungin further characterise in vitro attributes contributing to the efficacy of this novel, next-generation echinocandin.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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