Comparison of killing activity of rezafungin, anidulafungin, caspofungin and micafungin against *Candida auris* in the presence and absence of serum

Poster P055

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INTRODUCTION

Candida auris is an emerging, difficult-to-treat, multiresistant pathogen against which echinocandins are the recommended standard-of-care treatment (1). Rezafungin is a next-generation echinocandin with similar *in vitro* activity to existing echinocandins, yet it attains much higher *in vivo* concentrations and exposures due to its extended half-life and front-loaded dosing paradigm (2). Because *in vitro* killing data against *C. auris* are limited for existing echinocandins and are lacking for rezafungin, we compared rezafungin to anidulafungin, caspofungin, and micafungin in time-kill assays against *C. auris* isolates in standard RPMI-1640 medium. We also investigated the impact of serum on *in vitro* killing trends.

METHODS

Two *C. auris* clinical isolates from each clade (Japanese/Korean, South Asian/Indian and South African, obtained from the National Mycology Reference Laboratory, UK) were tested. Both South African isolates were autoaggregative. MICs in RPMI-1640 +/-50% human serum were determined using the standard broth macrodilution method (CLSI M27 Ed4). Time-kill studies with the four echinocandins were performed from 0.25 to 32 mg/L in both media, and killing rates were compared (3). Positive *k* values indicate killing; negative values indicate growth.

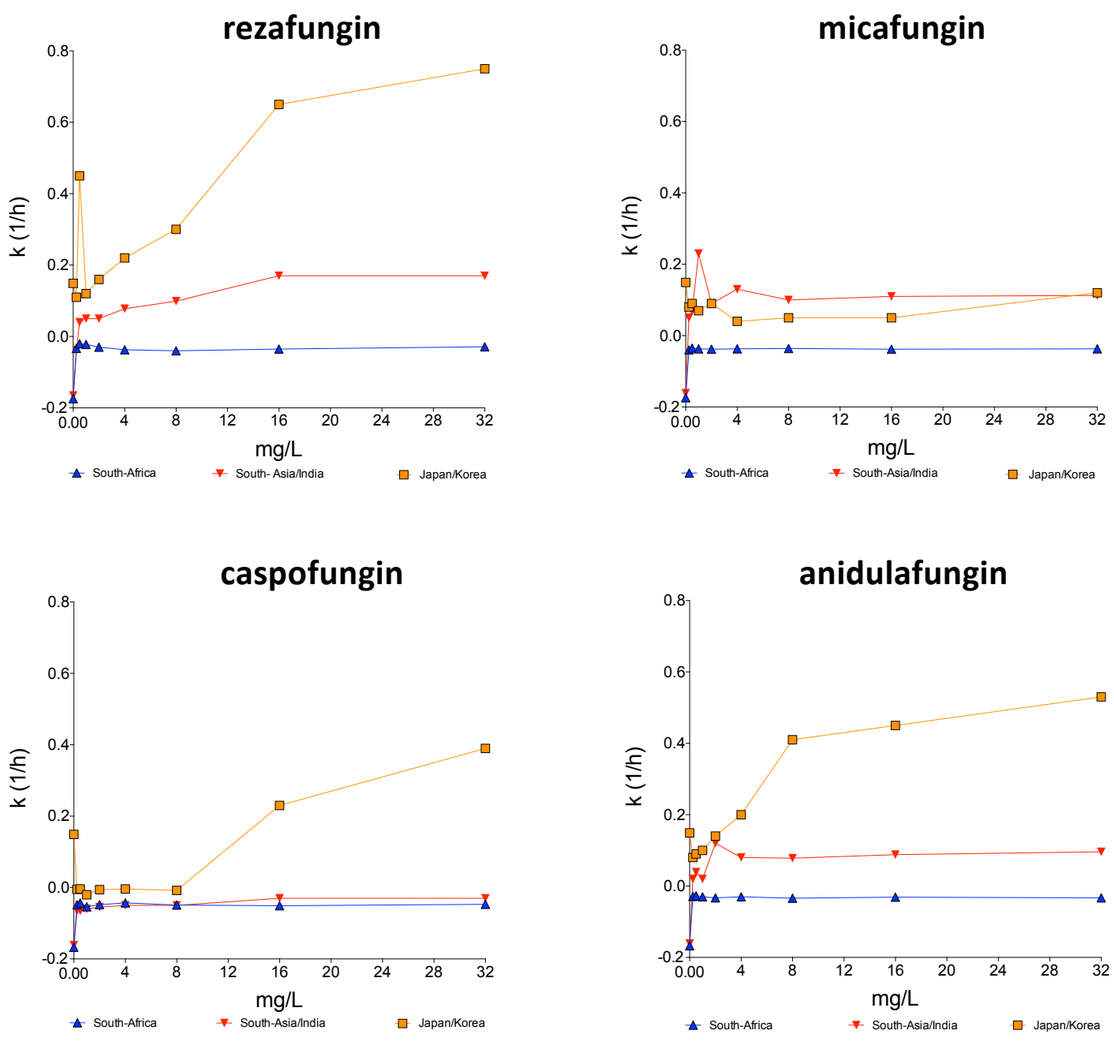
RESULTS

Table 1. MIC values for rezafungin and echinocandin comparators against *C. auris* strains in the presence and absence of 50% serum.

Clade	Isolate	MIC values in RPMI/RPMI + 50% serum (mg/L)			
		rezafungin	anidulafungin	caspofungin	micafungin
South Asia/ India	12	0.03-0.06/0.5	0.12/0.5-1	1/0.5-1	0.12-0.25/1
	27	0.12/1	0.12/2	0.5/2	0.25/2
Japan/Korea	209	0.06/0.5	0.03/0.5-1	0.25/0.5	0.12/2-4
	15	0.03/0.25-0.5	0.03-0.06/1	0.5-1/1	0.12/2
South Africa	204	0.06/0.25-0.5	0.03/1	0.25/0.5-1	0.12/2
	2	0.12/1-2	0.03/1-2	0.5/1	0.25/2-4

In RPMI-1640, at 1xMIC or higher concentrations, all four echinocandins showed only fungistatic effect (Figure 1). None of the echinocandins produced any CFU decrease against aggregating isolates (*k* values in cases of isolates 2 and 204 were always negative). Similar results were found in cases of caspofungin and micafungin against isolates 12, 15 and 27, and isolate 15, respectively. Re-growth was frequently observed for all four echinocandins.

Figure 1. Mean killing rate (*k*) values of the four echinocandins against three *C. auris* clades in RPMI-1640 medium.

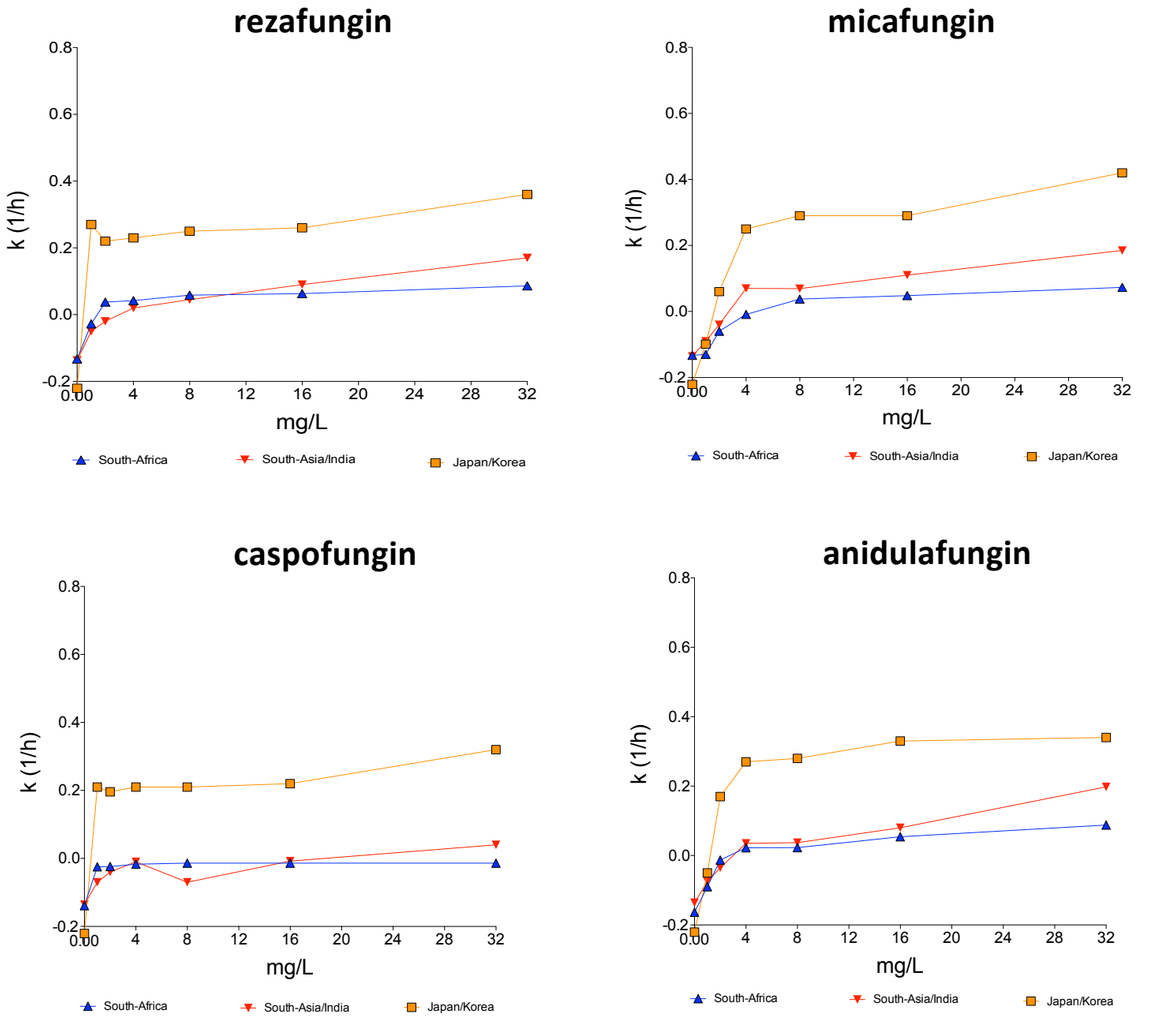


RESULTS (cont'd)

In 50% serum, growth rates were significantly lower. At 1xMIC or higher concentrations, echinocandins showed concentration-dependent killing activity, however, this CFU reduction never reached the fungicidal threshold. The highest *k* values were 0.34, 0.33, 0.34 and 0.29 1/h for rezafungin, anidulafungin, caspofungin and micafungin, respectively (Figure 2).

However, *k* values were always negative at 1-32 mg/L, in the case of isolate 2 (an autoaggregative isolate) for all echinocandins and in cases of isolates 27 and 204 for caspofungin.

Figure 2. Mean killing rate (*k*) values of the four echinocandins against three *C. auris* clades in RPMI-1640 plus 50% serum medium.



CONCLUSIONS

- Killing activity in RPMI-1640 alone was less consistently positive than in 50% serum, and only fungistatic activity was detected in both media. An optimal medium for testing killing activity remains to be found.
- Aggregative isolates were less susceptible to echinocandins than non-aggregative isolates.
- Differences were detected in the killing activity of echinocandins against different *C. auris* clades.
- Rezafungin showed similar or better activity than anidulafungin and micafungin at clinically attainable concentrations.
- The trend towards stronger killing activity in the presence of serum may account for the disconnect between the modest activity of echinocandins *in vitro* time-kill tests and their strong *in vivo* efficacy against *C. auris.* This was previously demonstrated in case of rezafungin in animal models (4,5).

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ACKNOWLEDGEMENTS

This study was funded by European Union and cofinanced by the European Social Fund. Zoltán Tóth and Fruzsina Nagy were supported by the ÚNKP-18-3 New National Excellence Program of the Ministry of Human Capacities. Study material (RZF powder) and editorial support (T. Chung, Scribant Medical) was provided by Cidara Therapeutics.