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

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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* strain in the presence and absence of 50% serum.

<table>
<thead>
<tr>
<th>Clade</th>
<th>Isolate</th>
<th>MIC values in RPMI/RPMI + 50% serum (mg/L)</th>
<th>rezafungin</th>
<th>anidulafungin</th>
<th>caspofungin</th>
<th>micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asia/India</td>
<td>12</td>
<td>0.05/0.06/0.5, 0.12/0.5/1, 1/0.5/1, 0.12/0.25/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan/Korea</td>
<td>27</td>
<td>0.12/1, 0.12/2, 0.5/2, 0.25/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>209</td>
<td>0.06/0.5, 0.03/0.5, 0.25/0.5, 0.12/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.05/0.25/0.5, 0.03/0.06/1, 0.5/1, 0.12/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>204</td>
<td>0.06/0.25/0.5, 0.03/1, 0.25/0.5/1, 0.12/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.12/1-2, 0.03/1-2, 0.5/1, 0.25/2-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 204, 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.

**REFERENCES**


**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).

**ACKNOWLEDGEMENTS**

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