INTRODUCTION

- The US FDA recently approved rezafungin for the treatment of candidemia and invasive candidiasis in adults.
- In addition, rezafungin is in development to prevent invasive fungal disease caused by Candida, Aspergillus, and Pneumocystis spp.
- We evaluated the in vitro activity of rezafungin, caspofungin, micafungin, and anidulafungin against European fungal isolates causing invasive infection.

MATERIALS AND METHODS

- A total of 981 isolates were collected (31 patients) in 2019-2021 from 19 medical centres located in Western Europe (W-EU; n=755; 15 countries) and Eastern Europe (E-EU; n=226; 4 centres; 4 countries; Figure 1).
- Isolates were identified by MALDI-TOF and/or sequencing and tested by CLSI broth microdilution.
- CLSI breakpoints (2022) were applied, including susceptible-only provisional breakpoints for rezafungin.
- A total of 981 isolates were collected (1/patient) in 2019–2021 from 19 medical centres located in Western Europe (W-EU) and Eastern Europe (E-EU).

RESULTS

- Isolates included Candida albicans (403 isolates), Candida parapsilosis (173), Candida glabrata (155), Candida tropicalis (80), Candida krusei (27), Candida dublinensis (12), Aspergillus fumigatus (115), and Aspergillus section Flavi (16).
- Rezafungin inhibited all C. parapsilosis, C. tropicalis, and C. krusei regardless of the region, 99.7%/100% of C. albicans from W-EU and 88.9%/100% of C. dublinensis at their susceptibility breakpoints.
- Rezafungin had similar activity to the other echinocandins against Candida albicans (99.7%/99.1%), C. glabrata (99.1%), C. parapsilosis (100.0%), C. krusei (100.0%), and C. dublinensis (MIC90 range, 0.015-0.03 mg/L) from W-EU.
- Except for caspofungin against C. glabrata (97.8%) and anidulafungin against C. parapsilosis (95.2%), echinocandins inhibited all Candida isolates from E-EU at their respective susceptible breakpoints.
- Out of all Candida isolates tested, only 1 C. albicans (Germany), 1 C. dublinensis (Germany), and 1 C. glabrata (Spain), were nonsusceptible to rezafungin (Table 2).
- The C. albicans and C. glabrata nonsusceptible strains were resistant to all echinocandins and displayed an S634P alteration in Fks1 or an S635P alteration in Fks2, respectively.
- No CLSI breakpoints are published for caspofungin, anidulafungin, or micafungin against Candida dublinensis (Germany), 1 Candida glabrata (Spain), were nonsusceptible to rezafungin (Table 2).
- All A. fumigatus isolates were inhibited by rezafungin at ≤0.06 mg/L.
- Anidulafungin, micafungin, and caspofungin inhibited at A. fumigatus at ≤0.12 mg/L.
- A total of 10 (8.7%) voriconazole-nonsusceptible A. fumigatus isolates (9 W-EU, 1 E-EU) were observed (Table 1). Rezafungin (MEC range, 0.015-0.03 mg/L) and all other echinocandins (MEC range, 0.004-0.06 mg/L) displayed activity against the voriconazole-nonsusceptible A. fumigatus isolates.
- Rezafungin and all other echinocandins inhibited all A. fumigatus isolates at ≤0.06 mg/L.

CONCLUSIONS

- Rezafungin was very active against contemporary Candida spp. isolates causing invasive infections in Europe medical centres.
- Only 3 Candida isolates were nonsusceptible to rezafungin and other echinocandins (C. albicans carrying an S456P alteration in Fks1, C. glabrata carrying an S635P alteration in Fks2, and C. dublinensis that was Fks-WET-like).
- Rezafungin was also very active against A. fumigatus and A. section Flavi isolates causing invasive infections, including voriconazole-nonsusceptible A. fumigatus isolates.

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References


Table 1. Activity of rezafungin and other echinocandins against Candida spp. and Aspergillus spp. isolates causing invasive infections in Western and Eastern Europe

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC50 (mg/L)</th>
<th>MIC90 (mg/L)</th>
<th>CLSI %S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W-EU</td>
<td>E-EU</td>
<td></td>
</tr>
<tr>
<td>C. albicans (329/74)</td>
<td>0.03/0.06</td>
<td>0.015/0.03</td>
<td>100</td>
</tr>
<tr>
<td>C. glabrata (109/46)</td>
<td>0.06/0.06</td>
<td>0.015/0.03</td>
<td>100</td>
</tr>
<tr>
<td>C. parapsilosis (131/42)</td>
<td>0.12/0.12</td>
<td>0.03/0.03</td>
<td>100</td>
</tr>
<tr>
<td>A. fumigatus (45/21)</td>
<td>0.03/0.06</td>
<td>0.015/0.03</td>
<td>100</td>
</tr>
<tr>
<td>A. section Flavi (79)</td>
<td>&gt;0.06/-</td>
<td>&gt;0.06/-</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Characterization of 3 Candida spp. isolates nonsusceptible to rezafungin per CLSI provisional breakpoints

<table>
<thead>
<tr>
<th>Organism</th>
<th>Study Year</th>
<th>Country</th>
<th>Infection Type</th>
<th>MIC (mg/L)</th>
<th>Fks sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>2021</td>
<td>Germany</td>
<td>Bloodstream infection</td>
<td>0.5</td>
<td>5845P</td>
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<tr>
<td>C. albicans</td>
<td>2021</td>
<td>Germany</td>
<td>Bloodstream infection</td>
<td>0.25</td>
<td>12</td>
</tr>
<tr>
<td>C. albicans</td>
<td>2019</td>
<td>Spain</td>
<td>Bloodstream infection</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of 981 fungal isolates included in this study split by Western Europe (W-EU) and Eastern Europe (E-EU).