Background

- The emergence of azole resistance globally among Aspergillus fumigatus has major clinical and agricultural implications.
- At our center, isavuconazole (ISA), posaconazole (POS) and voriconazole (VOR) have been used as antifungal prophylaxis or pre-emptive therapy in solid organ transplant (SOT) patients.
- We previously showed that Azole breakthrough (BT) fungi were more likely to be non-\*fumigatus Aspergillus (non-AF) spp.
- Azole BT isolates exhibited higher azole MICS than non-BT isolates, with 7% pan-azole resistance.
- Rezafungin (RZF) is an investigational echinocandin with long serum half-life, suitable for prolonged dosing intervals.
- It has potent activity against Aspergillus spp., including azole-resistant isolates.

Objectives

- To determine the azole minimum inhibitory concentrations (MICS) against Aspergillus isolates recovered from lung transplant recipients.
- To determine the minimum effective concentrations (MECs) of caspofungin (CAS) and RZF against Aspergillus clinical isolates from our center.

Methods

- Aspergillus clinical isolates: obtained from UPMC lung transplant repository from June 2016 to July 2019.
- Aspergillus speciation was performed using standard phenotypic analysis, and confirmed by ITS and D1/D2 sequencing.
- Determination of antifungal MICS (ISA, POS, VOR, AmB) and MECs (RZF, CAS) was performed using EUCAST methods (Edef 9.3.1).
- Isolates tested at least in duplicates.
- EUCAST proposed clinical breakpoints for susceptibility:
  - ISA/VOR/AmB ≤ 1 μg/mL
  - POS ≤ 0.125 μg/mL

Table 1 – Antifungal MICs against Aspergillus isolates (median MICs)*

<table>
<thead>
<tr>
<th>Aspergillus spp</th>
<th>ISAs</th>
<th>POSA</th>
<th>VORI</th>
<th>AmB</th>
<th>Caspo</th>
<th>RZF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. calidoustus</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>8</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>A. flavus</td>
<td>18</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>4</td>
<td>0.25</td>
</tr>
<tr>
<td>A. fumigatus</td>
<td>61</td>
<td>0.125</td>
<td>0.06</td>
<td>0.125</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>A. glauces</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
<td>0.25</td>
<td>0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>A. niger</td>
<td>10</td>
<td>0.25</td>
<td>0.125</td>
<td>0.25</td>
<td>4</td>
<td>0.125</td>
</tr>
<tr>
<td>A. terreus</td>
<td>7</td>
<td>0.25</td>
<td>0.125</td>
<td>0.25</td>
<td>4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 2 – Antifungal resistance against Aspergillus isolates

Results

Figure 1 – Distribution of Aspergillus spp. tested and overall RZF and CAS MECs

There was no difference in CAS and RZF MECs (p=0.86).

Figure 2 – MECs of RZF and CAS against selected POS-susceptible (POS-S) and –resistant (POS-R) Aspergillus spp.

- Overall, there was no difference in RZF and CAS MECs among Aspergillus isolates with azole-S or azole-R, except for A. flavus, where the RZF and CAS MECs were higher for POS-R than for POS-S isolates (p=0.0008 and 0.001, respectively).

- High RZF and CAS MECs (>1 μg/mL) were predominantly observed among A. flavus and to a lesser extent, A. calidoustus isolates.

Conclusions

- Azole resistance was most prevalent among non-A. fumigatus spp.
  - A. calidoustus, A. flavus and A. niger were the most common Aspergillus spp. associated with azole resistance.
- The rate of 26% of amphotericin B resistance is of concern, and might reflect the common and prolonged use of inhaled amphotericin B at our center for lung transplant recipients.
- The excellent activity of RZF and CAS suggests that these drugs are potential therapeutic options for patients infected with azole-resistant or azole-breakthrough Aspergillus isolates.
- The long-half life and high tolerability of RZF make this agent an attractive consideration for antifungal prophylaxis.