The Echinocandin Rezafungin (CD101) Demonstrates Potent In vitro Activity against *Aspergillus fumigatus*, including Azole-Resistant Isolates

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Disclosures

Funding
• Astellas
• Cidara
• bioMerieux
• F2G
• Merck
• Pfizer
• Viamet

Speakers Bureaus
• Gilead
Aspergillosis

• Acute invasive aspergillosis
  • Estimated ~200,000 cases/year
  • Leading cause of invasive mould infections
    ▪ SOT recipients (TRANSNET)
    ▪ Lung transplant recipients (TRANSNET)
    ▪ HSCT recipients (TRANSNET & PATH Alliance)
      • Leading cause IFI in HSCT recipients

• Chronic pulmonary aspergillosis
  • Estimated >3 million people infected worldwide
  • Common with underlying lung disease
    ▪ Tuberculosis, sarcoidosis

• Azole Resistance
  • Point mutations in CYP51A (gene encoding for 14α-demethylase – azole target) observed in A. fumigatus clinical and laboratory isolates with azole
  • Position of point mutation determines azole resistance
    ▪ Some cause pan-resistance, others specific for voriconazole/isavuconazole or posaconazole/itraconazole

• Historically observed with chronic azole exposure

Environmental Exposure to Azoles

- Azole-resistant IA identified in patients without priorazole exposure in parts of Europe
  - Indoor environment in hospitals & direct proximity to medical centers
  - Fields where azole fungicides used
    - Used in agriculture to combat crop failure & other products to prevent rotting
- Mechanisms of azole resistance in environmental isolates & azole-naïve patients
  - $\text{TR}_{34}/\text{L98H}$
  - $\text{TR}_{46}/\text{Y121F/T289A}$

Rezafungin (CD101)

Structural modification yields chemical stability & enhanced biological properties

Permanent charge and highly stable ring structure…

- Prolongs PK (t1/2 130 hrs)
- Allows high exposures: treats less susceptible pathogens
- Enables multiple formulations: intravenous and subcutaneous
Methods

• Wild-type and azole-resistant clinical *A. fumigatus* isolates from U.S. institutions
  • Isolates confirmed to the species level by DNA sequence analysis
    ▪ β-tubulin & calmodulin genes and
    ▪ morphologic/phenotypic characteristics (growth at 50°C)

• Susceptibility testing performed by CLSI M38-A2 broth microdilution methods
  • Rezafungin, caspofungin, & micafungin MECs read at 24 hours
  • Posaconazole & voriconazole MICs read at 48 hours
    ▪ 100% inhibition of growth
Results:
All Isolates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rezafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>All A. fumigatus isolates (n = 46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEC/MIC Range</td>
<td>≤0.015-2</td>
<td>≤0.015-&gt;8</td>
<td>≤0.015-4</td>
<td>0.06-&gt;16</td>
<td>0.125-&gt;16</td>
</tr>
<tr>
<td>MEC/MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0.03</td>
<td>0.03</td>
<td>≤0.015</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MEC/MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>0.12</td>
<td>0.06</td>
<td>0.03</td>
<td>4</td>
<td>&gt;16</td>
</tr>
<tr>
<td>GM MEC/MIC</td>
<td>0.036</td>
<td>0.046</td>
<td>0.020</td>
<td>0.703</td>
<td>1.502</td>
</tr>
</tbody>
</table>
Results:
Wild-Type

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rezafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-Type <em>A. fumigatus</em> isolates (n = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEC/MIC Range</td>
<td>≤0.015-0.12</td>
<td>≤0.015-0.06</td>
<td>≤ 0.015</td>
<td>0.06-0.12</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>MEC/MIC$_{50}$</td>
<td>≤0.015</td>
<td>0.03</td>
<td>≤0.015</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>MEC/MIC$_{90}$</td>
<td>0.06</td>
<td>0.03</td>
<td>≤0.015</td>
<td>0.12</td>
<td>0.5</td>
</tr>
<tr>
<td>GM MEC/MIC</td>
<td>0.024</td>
<td>0.029</td>
<td>≤0.015</td>
<td>0.089</td>
<td>0.301</td>
</tr>
</tbody>
</table>
Results: Azole-Resistant

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rezafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEC/MIC Range</td>
<td>≤0.015-2</td>
<td>≤0.015-&gt;8</td>
<td>≤0.015-4</td>
<td>0.5-&gt;16</td>
<td>0.12-&gt;16</td>
</tr>
<tr>
<td>MEC/MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0.06</td>
<td>0.06</td>
<td>≤0.015</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>MEC/MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>0.12</td>
<td>0.06</td>
<td>0.06</td>
<td>4</td>
<td>&gt;16</td>
</tr>
<tr>
<td>GM MEC/MIC</td>
<td>0.043</td>
<td>0.058</td>
<td>0.023</td>
<td>1.91</td>
<td>3.27</td>
</tr>
</tbody>
</table>

Azole-Resistant A. fumigatus isolates (n = 31)
## Azole-Resistant Isolates

<table>
<thead>
<tr>
<th>Azole Resistance Genotype (CYP51A)</th>
<th>No.</th>
<th>Rezafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP51A only</td>
<td>13</td>
<td>≤ 0.015-0.125</td>
<td>≤ 0.015-0.25</td>
<td>≤ 0.015-0.03</td>
</tr>
<tr>
<td>TR&lt;sub&gt;34&lt;/sub&gt;/L98H</td>
<td>2</td>
<td>0.06-0.125</td>
<td>0.06</td>
<td>≤ 0.015</td>
</tr>
<tr>
<td>TR&lt;sub&gt;46&lt;/sub&gt;/Y121F/T289A</td>
<td>2</td>
<td>≤ 0.015-0.06</td>
<td>0.06</td>
<td>≤ 0.015</td>
</tr>
<tr>
<td>Resistant – no CYP51A mutations</td>
<td>6</td>
<td>≤ 0.015-2</td>
<td>0.03-&gt;8</td>
<td>≤ 0.015-4</td>
</tr>
<tr>
<td>Resistant - CYP51A status unknown</td>
<td>8</td>
<td>≤ 0.015-0.125</td>
<td>≤ 0.015-0.06</td>
<td>≤ 0.015-0.06</td>
</tr>
</tbody>
</table>
Limitations & Next Steps

• Echinocandin MEC endpoint based on changes in morphology
• Relationship to clinical outcome unknown
• In vivo efficacy data needed
  • *CYP51A* mutations only
  • TR\textsubscript{34}L98H
  • TR\textsubscript{46}/Y121F/T289A
  • Unknown mechanisms of resistance
Summary

• Rezafungin demonstrated potent in vitro activity against *Aspergillus fumigatus*
  • Activity similar to that of caspofungin and micafungin

• Activity maintained againstazole-resistant isolates
  • *CYP51A* mutations
  • TR$_{34}$/L98H & TR$_{46}$/Y121F/T289A isolates
  • Unknown mechanisms of resistance

• Further work needed to determine in vivo efficacy and potential clinical utility
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