Evaluation of Antifungal Activity of SCY-078 in Combination with Other Antifungals Against Aspergillus Strains

Lisa Long, BA; Emily L. Larkin, BA; Katyna Borroto-Esoda, PhD; Steve Wring, PhD; David Angulo, MD; and Mahmoud A. Ghannoum, PhD
1. Center for Medical Mycology, Case Western Reserve University and University Hospitals Cleveland Medical Center, Cleveland, OH; 2. Scynexis Inc., NJ, USA

INTRODUCTION & PURPOSE

Invasive aspergillosis (IA) is a fungal infection associated with high mortality, affecting vulnerable populations such as patients with hematologic malignancies and hematopoietic cell transplant recipients. The mortality remains high (>20%) in spite of available therapies including Voriconazole, Isavuconazole, Amphotericin B and the Echinocandins. Exploring new treatment paradigms for IA including combination therapy is needed to improve outcomes.1

SCY-078 is an oral and intravenous semi-synthetic triterpenoid antifungal glucan synthase inhibitor, currently in development for the treatment of invasive and mucocutaneous fungal diseases. It has a broad-spectrum of activity against both Aspergillus and Candida species.

The objective of this study was to determine whether the combination of SCY-078 with Amphotericin B, Isavuconazole or Voriconazole would increase their antifungal activity in vitro against Aspergillus fumigatus.

MATERIALS & METHODS

• Six strains of A. fumigatus were tested: 4 wild-type (WT) and 2 with elevated azole MICs (Azole-R) – one of which has a CYP51 mutation at F46Y (strain 28500)
• MIC determinations (at 48h) of the individual antifungals alone and when in combination were determined following a checkerboard design2
• The effect of combination testing was reported according to an Fractional Inhibitory Concentration Index (FICI), which assigns a numerical value (formula below) to the interaction of the two compounds
• FICI interpretation:
  - Synergistic FICI ≤ 0.5
  - Additive FICI > 0.5 but ≤ 4.0
  - Antagonistic FICI > 4.0

RESULTS

Table 1. MIC values (µg/mL) alone & in combination for SCY-078 with other antifungal agents against A. fumigatus (test performed in duplicate, representative value displayed), SY= synergistic, AD = additive, AN = antagonistic

<table>
<thead>
<tr>
<th>Strain</th>
<th>SCY-078 with Isavuconazole (ISA)</th>
<th>SCY-078 with Voriconazole (VRC)</th>
<th>SCY-078 with Amphotericin B (AmB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC Alone</td>
<td>MIC Combo</td>
<td>FICI</td>
</tr>
<tr>
<td></td>
<td>SCY-078</td>
<td>ISA</td>
<td>SCY-078</td>
</tr>
<tr>
<td>WT 20438</td>
<td>4.0 1</td>
<td>0.016 0.5</td>
<td>0.50 SY</td>
</tr>
<tr>
<td>WT 28378</td>
<td>4.0 1</td>
<td>0.125 0.25</td>
<td>0.28 SY</td>
</tr>
<tr>
<td>WT 28382</td>
<td>4.0 1</td>
<td>0.063 0.25</td>
<td>0.27 SY</td>
</tr>
<tr>
<td>WT 28401</td>
<td>4.0 1</td>
<td>0.25 0.25</td>
<td>0.31 SY</td>
</tr>
<tr>
<td>Azole-R</td>
<td>28383</td>
<td>&gt;8 0.063 &gt;8</td>
<td>1.02 AD</td>
</tr>
<tr>
<td>Azole-R</td>
<td>28500</td>
<td>&gt;8 0.125 &gt;8</td>
<td>1.03 AD</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• SCY-078 in combination with Voriconazole, Isavuconazole and Amphotericin B demonstrates synergistic activity against the majority of A. fumigatus isolates tested
• For azole-resistant strains, additive effect was observed
• SCY-078 showed no in vitro antagonism with any of the drugs tested
• Results warrant subsequent evaluations of SCY-078 in combination with mold-active antifungal agents for the treatment of IA


For additional information contact Mahmoud A. Ghannoum, PhD at mag3@case.edu or Scynexis at info@scynexis.com.