Manogepix, the Active Moiety of the Investigational Agent Fosmanogepix, Demonstrates In vitro Activity Against Members of the Fusarium oxysporum and Fusarium solani Species Complexes

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 BACKGROUND

- Invasive fusariosis is associated with marked morbidity and mortality in immunocompromised hosts, and treatment options are limited (Nucci et al. Clin Microbiol Infect 2014).
- Common etiologic agents include members of the Fusarium oxysporum and F. solani species complexes (FOSC and FSSC, respectively).
- Manogepix (MGX; Figure 1), the active moiety of fosmanogepix, is a novel GWT1 inhibitor with broad antifungal activity (Myazaki, et al. Antimicrob Agents Chemother 2011; Pfaller, et al. Antimicrob Agents Chemother 2019; Rivero-Menendez et J Antimicrob Chemother 2019).

 OBJECTIVE

Our objective was to evaluate the in vitro activity of manogepix (MGX) against clinical isolates of the F. oxysporum and F. solani species complexes (FOSC and FSSC, respectively).

 MATERIALS AND METHODS

- Clinical isolates of FOSC (n=49) and FSSC (n=19) were identified by phenotypic characteristics and DNA sequence analysis of the translation elongation factor 1-alpha (TEF1α) and RNA polymerase II second largest subunit (RPB2).
- Susceptibility testing was performed by CLSI M38 broth microdilution. Minimum effective concentrations (MEC) and minimum inhibitory concentrations (MIC) were read after 48 hours of incubation at 50% and 100% inhibition of growth for MGX. MEC is now standard endpoint used for manogepix activity vs. filamentous fungi.
- MIC values were read for amphotericin B (AMB), posaconazole (PSC), isavuconazole (ISC), and voriconazole (VRC) at 100% inhibition of growth.

 RESULTS

- MGX demonstrated potent in vitro activity against both FOSC and FSSC isolates (Figure 2).
- Against FOSC isolates, MGX MECs ranged from ≤0.015-0.03 µg/mL, and MICs at the 50% inhibition of growth endpoint ranged from ≤0.015-0.12 µg/mL (Table). MIC values were higher when read at 100% inhibition of growth.
- Similar results were observed against FSSC isolates (MEC and MIC ranges ≤0.015 and ≤0.015-0.25 µg/mL, respectively).
- MGX MEC and MIC 50% inhibition values were in close agreement for both FOSC and FSSC isolates.
- AMB demonstrated in vitro good activity (MIC ranges 1-4 and 0.25-4 µg/mL against FOSC and FSSC, respectively). In contrast, the azoles demonstrated reduced susceptibility (MIC range 1-16 µg/mL).

 CONCLUSIONS

- MGX demonstrated good in vitro activity against FOSC and FSSC clinical isolates.
- Both changes in fungal morphology (MEC) and reductions in growth (MIC 50% inhibition) were observed. The MEC endpoint is now considered the standard endpoint for MGX against filamentous fungi.
- Clinical studies are ongoing to determine the efficacy and safety of fosmanogepix in patients with invasive fungal infections.

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Manogepix (MGX)</th>
<th>AMB</th>
<th>PSC</th>
<th>ISC</th>
<th>VRC</th>
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<tbody>
<tr>
<td>Endpoint</td>
<td>MEC</td>
<td>MIC 50%</td>
<td>MIC 100%</td>
<td>MIC 50%</td>
<td>MIC 100%</td>
</tr>
<tr>
<td>F. oxysporum species complex (n = 49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Range</td>
<td>≤0.015-0.03</td>
<td>≤0.015-0.12</td>
<td>&gt;8</td>
<td>1.4</td>
<td>1-16</td>
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<td>MEC/MICs</td>
<td>≤0.015</td>
<td>≤0.015</td>
<td>&gt;8</td>
<td>2</td>
<td>&gt;16</td>
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<tr>
<td>MEC/MICs</td>
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<td>≤0.015</td>
<td>&gt;8</td>
<td>2</td>
<td>&gt;16</td>
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<tr>
<td>GM MEC/MIC</td>
<td>≤0.015</td>
<td>0.021</td>
<td>&gt;8</td>
<td>1.59</td>
<td>6.11</td>
</tr>
</tbody>
</table>

| F. solani species complex (n = 19) |
| Range    | ≤0.015 | ≤0.015-0.25 | >8 | 1 | >16 | >16 | >16 |
| MEC/MICs | ≤0.015 | ≤0.015 | >8 | 1 | >16 | >16 | >16 |
| MEC/MICs | ≤0.015 | ≤0.015 | >8 | 2 | >16 | >16 | >16 |
| GM MEC/MIC | ≤0.015 | 0.017 | 5.95 | 1.08 | >16 | >16 | 16 |

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Figure 1. Structure of manogepix.

Figure 2. MIC/MEC distributions of MGX, AMB, PSC, ISC, and VRC against FOSC & FSSC. F. oxysporum Species Complex (n = 49)

Table 1. MIC/MEC ranges, 50 and 90% inhibition values, and geometric mean (GM) values for MGX, AMB, PSC, ISC, and VRC against FOSC & FSSC.