Oritavancin Activity against Enterococcus faecalis In Vitro and in a Murine Thigh Infection Model

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Updated Abstract

Background: Oritavancin (ORI) is a lipoglycopeptide that has intrinsically active against enterococci. We evaluated the pharmacodynamic (PD) activity, in vitro and in vivo, of ORI against Enterococcus faecalis. Oritavancin bactericidal breakpoints (7) were determined in a murine thigh infection model (1-4).

Methods: 5 vancomycin-susceptible E. faecalis were tested against ORI and vancomycin (VAN). MICs were determined by CLSI M7 (3) and E-test (4) methods. Time-kill experiments were performed in triplicate in MHA with 0.016-256 µg/mL ORI and 0.12-16 µg/mL VAN tested. (Figures 1-5).

Results: ORI MICs ranged from 0.016 – 8 µg/mL. Twenty-eight percent (7/25) of strains tested were resistant to ORI and ORI exhibited bactericidal activity against all but 2 strains at both inoculum densities. Results for 24 hour CFU were shown in the Table below.

Conclusion: ORI was bactericidal against E. faecalis. In the TI model, ORI activity was similar to VAN and both drugs produced bacterial killing at equivalent exposures. Further studies are warranted.

Bacterial Strains

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC (µg/mL)</th>
<th>MBC (µg/mL)</th>
<th>Time Kill</th>
<th>Bioassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORI 0.25 µg/mL</td>
<td>0.016</td>
<td>&gt;0.25</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ORI 2 µg/mL</td>
<td>&gt;0.25</td>
<td>&gt;0.25</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>VAN 4 µg/mL</td>
<td>&gt;0.25</td>
<td>&gt;0.25</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Thigh Infection Model: Male Sprague-Dawley rats were infected with 10^5 CFU of E. faecalis ATCC 29212, 23241 or 33816. (Figures 6-7).

Pharmacodynamic Model:

**Figure 1.** Time-kill kinetics of ORI and VAN against E. faecalis ATCC 29212 at 0.016 µg/mL CFU/mL.

**Figure 2.** Time-kill kinetics of ORI and VAN against E. faecalis ATCC 23241 at 0.016 µg/mL CFU/mL.

**Figure 3.** Time-kill kinetics of ORI and VAN against E. faecalis ATCC 23241 at 2 µg/mL CFU/mL.

**Figure 4.** Time-kill kinetics of ORI and VAN against E. faecalis ATCC 29212 at 16 µg/mL CFU/mL.

**Figure 5.** Time-kill kinetics of ORI and VAN against E. faecalis ATCC 23241 at 16 µg/mL CFU/mL.

**Figure 6.** Time-kill kinetics of ORI and VAN against E. faecalis ATCC 33816 at 16 µg/mL CFU/mL.

**Figure 7.** Activity of Oritavancin and Vancomycin against E. faecalis in a Neutropenic Mouse Thigh Infection Model.

**Figure 8.** Relationship between Oritavancin Total Drug AUC and Change in Log CFU in a Neutropenic Mouse Thigh Infection Model Due to E. faecalis.

Summary & Conclusions

- ORI MICs of 0.016 µg/mL were determined in a murine thigh infection model.
- ORI exhibited bactericidal activity against all but 2 strains at both inoculum densities.
- Oritavancin was approved in 2014 for the treatment of complicated skin and skin-structure infections caused by E. faecalis.

References