Introduction

• Enterococcal infections remain a clinical challenge due to the efficiency of these pathogens at attaining antimicrobial resistance

• Enterococci represent the second and third most common pathogen across all healthcare-associated infections (HAI) in the United States and Europe, respectively. This is also the single most common pathogen among central line-associated bloodstream infection (CLABSI)s in the United States based on the Centers for Disease Control and Prevention 2011-2014 report

• The vast majority of enterococcal infections are caused by Enterococcus faecalis and Enterococcus faecium, and E. faecium-caused HAI

  - This change in epidemiology is of paramount clinical importance, since E. faecium isolates often display a multidrug-resistant (MDR) phenotype

  - The lipopolysaccharide (LPS) of E. faecium possesses long-acting activity against Gram-positive bacteria

  - Oritavancin possesses multiple mechanisms of action and a rapid concentration-dependent bactericidal activity

  - Oritavancin inhibits transpeptidation and transglycosylation by binding to the peptidoglycan-missing portion of the cell wall and to the peptidoglycan precursor, respectively

  - In addition, oritavancin appears to cause membrane depolarization and permeabilization

• The in vitro activities of oritavancin and comparator agents were assessed against E. faecalis and E. faecium from US hospitals and a global challenge set of enterococci, including vancomycin-nonsusceptible, linezolid-nonsusceptible, and daptomycin-nonsusceptible isolates

Materials and Methods

Bacterial isolates

• A total of 391 E. faecalis and 179 E. faecium isolates recovered from US hospitals during 2017 were studied

• Isolates were responsible for bloodstream infection (43.7%), urinary tract (18.1%), and skin structure (18.6%) and intra-abdominal infections (18.4%)

• Isolates originated from 31 sites located in 21 states in US census divisions and were submitted to JMI Laboratories (North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program

• A worldwide challenge set of daptomycin-nonsusceptible E. faecium isolates were tested, as well as 97 molecularly characterized linezolid-nonsusceptible isolates, including 24 opta/Carb-X+ E. faecalis isolates

• Isolates were initially identified by the participating laboratory, and identifications were confirmed at JMI Laboratories using matrix assisted laser desorption ionization time of flight technology mass spectrometry (Bruker Daltonics, Bremen, Germany) and genome sequencing

Table 1 MIC distribution of oritavancin against Enterococcus spp. clinical isolates collected from US medical centers

<table>
<thead>
<tr>
<th>Organism Type</th>
<th>Number of isolates</th>
<th>Number and cumulative % of isolates inhibited at MIC (mg/L)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecalis (391)</td>
<td>74</td>
<td>179</td>
<td>101</td>
<td>97</td>
</tr>
<tr>
<td>Vancomycin-susceptible (379)</td>
<td>7</td>
<td>17</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>VanA (11)</td>
<td>1</td>
<td>6</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>E. faecium (179)</td>
<td>12</td>
<td>42</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>Vancomycin-susceptible (62)</td>
<td>5</td>
<td>15</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>VanA (107)</td>
<td>2</td>
<td>15</td>
<td>19</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 2 MIC distribution of oritavancin against a global subset of multidrug-resistant Enterococcus spp. clinical isolates

<table>
<thead>
<tr>
<th>Organism Type</th>
<th>Number of isolates</th>
<th>Number and cumulative % of isolates inhibited at MIC (mg/L)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecalis</td>
<td>22</td>
<td>94</td>
<td>50</td>
<td>9.5</td>
</tr>
<tr>
<td>Vancomycin-nonsusceptible (33)</td>
<td>22</td>
<td>94</td>
<td>50</td>
<td>9.5</td>
</tr>
<tr>
<td>opta/Carb-X+</td>
<td>22</td>
<td>94</td>
<td>50</td>
<td>9.5</td>
</tr>
<tr>
<td>E. faecium</td>
<td>9</td>
<td>33</td>
<td>60</td>
<td>36</td>
</tr>
<tr>
<td>Linezolid-nonsusceptible (94)</td>
<td>9</td>
<td>33</td>
<td>60</td>
<td>36</td>
</tr>
</tbody>
</table>

Antimicrobial susceptibility testing

• Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07 (2018) document

  - Vancomycin-BRO (0.004 to 0.12 mg/L) was included in the CAMHB when testing oritavancin, while calcium (Ca++) supplementation (50 mg/L) was used for testing daptomycin

  - Quality assurance was performed by concurrently testing the CLSI-recommended quality control strain E. faecalis ATCC 29212

  - Breakpoint criteria for comparator agents were from the CLSI M100 (2018) document

• Screening for gentamicin and streptomycin high-level (HL) resistance used EUCAST methods and criteria

• E. faecalis and E. faecium displaying vancomycin and teicoplanin MIC results of ≤2 mg/L, respectively, were classified as VanA phenotype

• E. faecalis and E. faecium isolates with vancomycin MIC results of ≤2 mg/L and teicoplanin MIC results of ≤8 mg/L were classified as VanB phenotype

Results

• Oritavancin inhibited all 391 E. faecalis and E. faecium isolates from US medical centers, including those displaying a VanA phenotype, at the susceptible breakpoint for vancomycin-susceptible E. faecalis (≤0.12 mg/L) (Table 1)

• Antimicrobial MIC activities of oritavancin and comparator agents against a US collection of vancomycin-susceptible (Table 1) and a global collection of linezolid-nonsusceptible E. faecalis (Table 2), including a subcommittee opta carrying carb-X+ (E. faecalis) were 8-fold higher than that of vancomycin-susceptible, albeit an MIC<sub>50</sub> value of 0.12 mg/L was noted (Table 1)

• Isolates displaying gentamicin HL resistance phenotype were more common among E. faecalis (25.8%) than E. faecium (12.8%), but streptomycin HL resistance was more frequent among E. faecium (33.0% vs. 16.6% E. faecalis) (Table 3)

• Oritavancin (MIC<sub>50</sub> 0.004/0.008 mg/L) showed low MIC<sub>50</sub> and MIC<sub>90</sub> values against vancomycin-susceptible E. faecium, while oritavancin MIC results (MIC<sub>50</sub> 0.03/0.06 mg/L mg/L) were 8-fold higher against VanA-type E. faecalis (Table 1)

• All E. faecium isolates were inhibited by oritavancin at ≤0.12 mg/L

• Similar MIC<sub>50</sub> results were obtained for oritavancin when tested against daptomycin-nonsusceptible (MIC<sub>50</sub> 0.03/0.25 mg/L) or linezolid-nonsusceptible E. faecalis (MIC<sub>50</sub> 0.015/0.12 mg/L) E. faecium (Table 2)

• VanA E. faecium showed a multidrug-resistance phenotype in which linezolid and daptomycin remained active (100.0% susceptible) (Table 3)

Conclusions

• Oritavancin showed potent in vitro activity against E. faecalis and E. faecium isolates causing infections, including against VanA phenotype pathogens, in hospitalized patients in US medical centers

• Oritavancin also displayed potent in vitro activity against a worldwide challenge set of nonsusceptible isolates

  - All isolates but 1 were inhibited by oritavancin at ≤0.25 mg/L (Table 2)

• Overall, E. faecalis isolates remained susceptible to ampicillin, linezolid, daptomycin (100%), and vancomycin (96.6%); however, 25.8% of E. faecalis showed gentamicin HL resistance, which may compromise the standard empiric β-lactam-aminoglycoside combination approach for serious invasive infections (Table 3)

• High vancomycin resistance rates were observed among E. faecalis isolates, and only oritavancin, linezolid, tigecycline, and daptomycin remained active in vitro against those isolates (Table 3)

• The potent in vitro activity of oritavancin reported against vancomycin-resistant E. faecalis isolates and linezolid-nonsusceptible isolates suggests that this agent may be considered as part of the therapeutic options against highly resistant E. faecium

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References


