Current Analysis of Oritavancin Potency when Tested against Vancomycin-resistant and -susceptible Enterococcal Clinical Isolates Recovered from European Medical Centres (2009-2013)

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Introduction

Recent data indicate that enterococcal isolates represent the second and third most frequent pathogens responsible for bloodstream infections (BSI) in the USA and European countries, respectively. Moreover, there are limited therapeutic options available for treating infections caused by multidrug-resistant (MDR) enterococci.

Oritavancin is an investigational lipoglycopeptide for the treatment of patients with complicated skin and soft-tissue infections (SSTIs). Oritavancin has demonstrated potent *in vitro* activity when tested against numerous Gram-positive clinical isolates and is currently under regulatory review by the US-Food and Drug Administration and European Medicines Agency. This study was performed to evaluate oritavancin activity against a recent collection of enterococcal isolates responsible for documented infections in European countries and Israel.

Materials and Methods

Bacterial strain collection. A total of 3,321 enterococci, mostly *Enterococcus faecalis* (1,950) and *Enterococcus faecium* (1,272) were collected from 16 European countries (32 sites) and Israel (one site). Selected isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Programme for 2009 through 2013. Isolates were primarily identified by the participating laboratory and identification confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and Vitek® 2 (bioMérieux, Hazelwood, Missouri, USA), and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods. Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A9 document. Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*Staphylococcus aureus* ATCC 29213 and *E. faecalis* ATCC 29212). All QC results were within published acceptable ranges (M100-S24). MIC interpretations were based on the CLSI M100-S24 (2014) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2014) breakpoint criteria, as available. Isolates displaying vancomycin and teicoplanin MIC results of >4 and >8 mg/L, respectively, were classified as VanA-phenotype, whereas those with vancomycin and teicoplanin MIC results of >4 and ≤8 mg/L, respectively, were classified as VanB-phenotype. *Enterococcus gallinarum* (24 isolates) and *Enterococcus casseliflavus* (14 isolates) were also included (intrinsic VanC producers).

Results

- Oritavancin was equally active when tested against vancomycin-susceptible and -resistant (VanB-phenotype) *E. faecalis* (MIC_{50}, 0.015 mg/L, for both; Table). When tested against vancomycin-resistant *E. faecalis* (VanA) oritavancin had higher MIC results (16-fold) compared to the susceptible counterpart isolates.
- When tested against vancomycin-susceptible *E. faecalis*, oritavancin ($MIC_{50/90}$, 0.015/0.03 mg/L) had MIC values at least 64-fold lower than ampicillin vancomycin, daptomycin and linezolid; these comparators had susceptibility rates of ≥99.9% (Table).
- Both vancomycin-susceptible (MIC_{50}, ≤0.008 mg/L) and -resistant (MIC_{50}, ≤0.008 and 0.015 mg/L for VanB and VanA phenotypes, respectively) *E. faecium* isolates displayed very low MIC_{50} results when tested for oritavancin (Table). These oritavancin MIC_{50} results were at least 64-fold lower than linezolid and daptomycin.
- *E. gallinarum* and *E. casseliflavus* isolates showed increased vancomycin MIC results ($MIC_{50/90}$, 4/8 mg/L; 65.8% susceptible), but these isolates showed high susceptibility rates (≥94.7%) to ampicillin, daptomycin and linezolid. Oritavancin ($MIC_{50/90}$, ≤0.008/0.015 mg/L) MIC results were at least 128-fold lower than these comparators when tested against *E. gallinarum* and *E. casseliflavus* (Table).
- Enterococcal isolates other than *E. faecalis*, *E. faecium* and VanC producers showed oritavancin $MIC_{50/90}$ results of ≤0.008/0.015 mg/L (Table). These isolates also demonstrated overall decreased susceptibility to several agents and only vancomycin, daptomycin and linezolid remained active (Table). Oritavancin had a MIC_{50} result of approximately 64-fold lower than vancomycin, daptomycin and linezolid when tested against these isolates (Table).

Table. Antimicrobial activity of oritavancin and comparator agents against enterococcal clinical isolates from Europe and Israel as part of the 2009–2013 SENTRY Antimicrobial Surveillance Programme.

Organism (number tested)/ Subset/Antimicrobial agent	MIC (mg/L): Range	50%	90%	% Susceptible/%Intermediate/ % Resistant[a]: CLSI	EUCAST
E. faecalis (1,950)					
Vancomycin-susceptible (1,919)					
Oritavancin	≤0.008 – 0.25	0.015	0.03	- / - / -	- / - / -
Ampicillin	≤1 – 8	≤1	2	100.0 / 0.0 / 0.0	99.8 / 0.2 / 0.0
Vancomycin	0.25 – 4	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 4	1	2	100.0 / - / -	- / - / -
Linezolid	0.12 – 8	1	2	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
Erythromycin	≤0.25 – >2	>2	>2	7.3 / 40.1 / 52.6	- / - / -
Tetracycline	≤2 – >8	>8	>8	24.0 / 0.2 / 75.8	- / - / -
Levofloxacin	≤0.5 – >4	1	>4	69.3 / 0.6 / 30.1	- / - / -
Vancomycin-resistant (VanA; 20)					
Oritavancin	0.015 – 0.5	0.25	0.5	- / - / -	- / - / -
Ampicillin	≤1 – >16	2	4	95.0 / 0.0 / 5.0	95.0 / 0.0 / 5.0
Daptomycin	0.5 – 2	0.5	1	100.0 / - / -	- / - / -
Linezolid	0.5 – 1	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	1 – >2	>2	>2	0.0 / 5.0 / 95.0	- / - / -
Tetracycline	≤2 – >8	>8	>8	10.0 / 0.0 / 90.0	- / - / -
Levofloxacin	>4	>4	>4	0.0 / 0.0 / 100.0	- / - / -
E. faecium (1,272)					
Vancomycin-susceptible (851)					
Oritavancin	≤0.008 – 0.03	≤0.008	≤0.008	- / - / -	- / - / -
Ampicillin	≤1 – >8	>8	>8	7.9 / 0.0 / 92.1	7.3 / 0.6 / 92.1
Vancomycin	0.5 – 4	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 4	2	4	100.0 / - / -	- / - / -
Linezolid	0.25 – >8	1	2	99.6 / 0.0 / 0.4	99.6 / 0.0 / 0.4
Erythromycin	≤0.25 – >2	>2	>2	3.2 / 7.7 / 89.1	- / - / -
Tetracycline	≤2 – >8	≤2	>8	57.2 / 1.0 / 41.8	- / - / -
Levofloxacin	≤0.5 – >4	>4	>4	8.9 / 5.1 / 86.0	- / - / -
Vancomycin-resistant (VanA; 374)					
Oritavancin	≤0.008 – 0.25	0.015	0.06	- / - / -	- / - / -
Ampicillin	>8	>8	>8	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Daptomycin	0.25 – 4	2	4	100.0 / - / -	- / - / -
Linezolid	0.5 – 8	1	2	98.9 / 0.0 / 1.1	98.9 / 0.0 / 1.1
Erythromycin	≤0.25 – >2	>2	>2	0.8 / 2.4 / 96.8	- / - / -
Tetracycline	≤2 – >8	4	>8	51.2 / 0.8 / 48.0	- / - / -
Levofloxacin	1 – >4	>4	>4	2.9 / 0.6 / 96.5	- / - / -
VanC[b] (38)					
Oritavancin	≤0.008 – 0.5	≤0.008	0.015	- / - / -	- / - / -
Ampicillin	≤1 – >8	≤1	4	94.7 / 0.0 / 5.3	94.7 / 0.0 / 5.3
Vancomycin	0.5 – >16	4	8	65.8 / 31.6 / 2.6	65.8 / 0.0 / 34.2
Daptomycin	≤0.06 – 4	2	4	100.0 / - / -	- / - / -
Linezolid	0.5 – 2	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.25 – >2	2	>2	39.5 / 36.8 / 23.7	- / - / -
Tetracycline	≤2 – >8	≤2	>8	68.4 / 0.0 / 31.6	- / - / -
Levofloxacin	1 – >4	2	>4	81.6 / 7.9 / 10.5	- / - / -
Other spp.[c] (61)					
Oritavancin	≤0.008 – 0.06	≤0.008	0.015	- / - / -	- / - / -
Ampicillin	≤1 – >8	≤1	>8	67.2 / 0.0 / 32.8	65.6 / 1.6 / 32.8
Vancomycin	0.25 – >16	0.5	1	98.4 / 0.0 / 1.6	98.4 / 0.0 / 1.6
Daptomycin	≤0.06 – 4	0.5	2	100.0 / - / -	- / - / -
Linezolid	0.5 – 2	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.25 – >2	1	>2	44.3 / 14.7 / 41.0	- / - / -
Tetracycline	≤2 – >8	>8	>8	39.3 / 0.0 / 60.7	- / - / -
Levofloxacin	≤0.5 – >4	2	>4	78.7 / 4.9 / 16.4	- / - / -

a. Breakpoint criteria for comparator agents were those from CLSI (M100-S24, 2014) and EUCAST (2014), as available.
b. Includes *E. casseliflavus* (14 isolates) and *E. gallinarum* (24).
c. Includes *E. avium* (30 isolates), *E. durans* (11), *E. hirae* (five), *E. raffinosus* (11) and *Enterococcus* spp. (four).

Conclusions

- Oritavancin demonstrated *in vitro* activity greater than comparators when tested against this collection of enterococcal isolates, regardless of vancomycin phenotype. Of note, when tested against VanA-phenotype isolates, oritavancin was less active (four- to 16-fold) than against the vancomycin-susceptible and VanB-phenotype counterparts; however, all isolates were inhibited at ≤0.5 mg/L.
- This study emphasizes the MDR phenotype exhibited by these enterococcal isolates, especially among vancomycin-resistant (VanA) *E. faecium*, against which limited therapeutic options are available. Nevertheless, oritavancin had greater *in vitro* potency than other active agents tested against this subset.
- These results warrant further investigations to assess the potential of oritavancin for the treatment of serious infections caused by MDR enterococci, including VRE.

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