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Spectrum of Activity of Oritavancin and Comparator Agents Tested against Subsets of Vancomycin-resistant Enterococci from the United States and Europe

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Amended Abstract

Objectives: To evaluate the antimicrobial activities of oritavancin and comparators tested against subsets of vancomycin-resistant enterococci (VRE) recovered from hospitalized patients in the United States (USA) and Europe through the International Oritavancin Surveillance Program (2008-2009), which is part of the worldwide SENTRY Antimicrobial Surveillance Program.

Methods: Enterococci (2,841) were consecutively collected from the USA (28 sites) and Europe (28 sites). Isolates were submitted to a monitoring laboratory where identifications were confirmed by standard algorithms and Vitek 2. Isolates were tested for susceptibility by reference CLSI methods (M07-A8, 2009). Interpretive criteria were those from CLSI (M100-S20, 2010) and EUCAST (2009). The VanA phenotype was characterized by non-susceptibility to vancomycin and teicoplanin, while the VanB phenotype was non-susceptibility to vancomycin and susceptibility to teicoplanin. The VanC phenotype was based on species identification (*E. casseliflavus* and *E. gallinarum*).

Results: Isolates were dominantly from bacteremia (61.5%), skin and skin structure (14.2%) and urinary tract infections (12.5%). 24.8% of strains were non-susceptible to vancomycin, comprising 88.5% VanA and 6.7% VanB phenotypes. 76.7% of vancomycin-non-susceptible were from the USA. *E. faecium* represented 92.4% and 58.3% of strains with VanA and VanB phenotypes, respectively. Oritavancin was ≥4-fold more active against vancomycin-susceptible *E. faecium* (MIC_{50}, ≤0.004 mg/L) than vancomycin-susceptible *E. faecalis* (MIC_{90}, 0.015 mg/L; see table in Results-2 section). Oritavancin activity against isolates displaying a VanB phenotype was similar to that against vancomycin-susceptible isolates from the same species. Oritavancin MIC_{90} values against VanA species were 16-fold higher than their respective susceptible strains. Ampicillin (MIC_{90}, 2 mg/L; 97.8% susceptible), daptomycin (MIC_{90}, 1 mg/L; 100.0% susceptible) and linezolid (MIC_{90}, 2 mg/L; 100.0% susceptible) were also active against *E. faecalis* displaying a VanA phenotype, while daptomycin (MIC_{90}, 2 mg/L; 99.7% susceptible), linezolid (MIC_{90}, 2 mg/L; 98.8% susceptible) and quinupristin/dalfopristin (MIC_{90}, 1 mg/L; 95.2% susceptible) were active against *E. faecium* with a VanA phenotype.

Conclusions: Oritavancin exhibited very potent in vitro activity against this contemporary VRE collection from two regions. Oritavancin MIC values were elevated when tested against isolates displaying a VanA phenotype relative to vancomycin-susceptible and VanB strains; however, all enterococci were inhibited by oritavancin at ≤ 1 mg/L. In addition, oritavancin was at least 2- and 8-fold more active than the comparators when tested against *E. faecalis* and *E. faecium* with a VanA phenotype, respectively.

Introduction

During the last two decades, enterococcal isolates have emerged as important cause of hospital-acquired infections (HAI), ranking as the third or fourth most prevalent genus among nosocomial pathogens. These organisms usually lack high virulence factors; however, several reports have described an increasing international trend in the occurrence of invasive HAI caused by enterococci. The vast majority of enterococcal infections are due to *Enterococcus faecalis* (80 – 90%), while *E. faecium* are responsible for approximately 10-20% of the cases.

Antimicrobial resistance is a major cause of concern among this genus, mainly in *E. faecium*. Resistance to antimicrobial agents includes penicillins (ampicillin), aminoglycosides (high-level resistance) and glycopeptides, each limiting the therapeutic options. Oritavancin is a semisynthetic lipoglycopeptide with a potent and rapid bactericidal activity against a wide range of Gram-positive organisms. The objective of this study was to evaluate the activities of oritavancin and comparators tested against subsets of vancomycin-non-susceptible enterococci recovered from hospitalized patients in the United States (USA) and Europe through the International Oritavancin Surveillance Program (2008-2009).

Methods

Bacterial isolates. Enterococcal clinical isolates (2,841) were collected from hospitalised patients in the USA (28 medical centres) and in 13 European countries (28 medical centres), as part of the International Oritavancin Surveillance Program (2008 – 2009). Isolates were collected in a prevalence mode design and mostly from invasive infections (mostly bacteremia; 61.5%). Other sites of infections were skin and skin structure (14.2%) and urinary tract (12.5%). Bacterial species identifications were confirmed using standard methods and the automated Vitek 2 System (bioMérieux, Hazelwood, Missouri, USA).

Antimicrobial susceptibility testing. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute (CLSI) recommendations (M07-A8, 2009). Susceptibility testing was determined by using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Categorical interpretation of comparator MIC values were determined according to CLSI (M100-S20, 2010) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2009) criteria, when available.

Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20, 2010) quality control (QC) strains: *E. faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213. MIC values for oritavancin and comparators tested against ATCC QC strains were within the published CLSI M100-S20 (2010) document ranges.

The VanA phenotype was defined by non-susceptibility to vancomycin (MIC, >4 mg/L; CLSI criteria) and teicoplanin (MIC, >8 mg/L), while isolates displaying non-susceptible and susceptible phenotypes to vancomycin and teicoplanin, respectively, were considered as VanB-type. Isolates known to intrinsically harbour the *vanC* gene (*E. casseliflavus* and *E. gallinarum*) were regarded as VanC strains.

Results-1

- A total of 1,775 *E. faecalis* and 1,032 *E. faecium* isolates were included in this investigation. Only 3.7% (66) of *E. faecalis* displayed a vancomycin non-susceptible phenotype, while 59.2% (611) *E. faecium* were vancomycin-non-susceptible (Table 1).
- The majority (76.7%) of vancomycin-non-susceptible isolates originated from the USA. In addition, 88.5 and 6.7% of those demonstrated a VanA and VanB phenotype, respectively (Table 1).
- Oritavancin was very potent when tested against vancomycin-susceptible ($MIC_{50/90}$, 0.004/0.008 mg/L) and -resistant (VanB; $MIC_{50/90}$, 0.008/0.008 mg/L) *E. faecium* isolates (Tables 1 and 2).
- VanA *E. faecium* exhibited an oritavancin MIC_{90} value (0.12 mg/L) 16-fold higher than the respective susceptible isolates (MIC_{90}, 0.008 mg/L). However, oritavancin inhibited all VanA *E. faecium* at ≤0.5 mg/L (Tables 1 and 2).
- Daptomycin ($MIC_{50/90}$, 2/2 mg/L), linezolid ($MIC_{50/90}$, 1/2 mg/L) and quinupristin/dalfopristin ($MIC_{50/90}$, 1/1 mg/L) were active against VanA *E. faecium* (≥95.2% susceptible). Oritavancin ($MIC_{50/90}$, 0.03/0.12 mg/L) was eight- to 16-fold more potent than these comparators when tested against VanA *E. faecium* (Table 2).
- *E. faecalis* was very susceptible to ampicillin, daptomycin and linezolid (≥97.8% susceptible; Table 2), regardless of the resistance phenotype to glycopeptides.
- Oritavancin demonstrated equivalent potency when tested against vancomycin-susceptible and -resistant (VanB) *E. faecalis* isolates ($MIC_{50/90}$, 0.015/0.03 mg/L; Tables 1 and 2).
- VanA *E. faecalis* exhibited oritavancin $MIC_{50/90}$ values (0.25/0.5 mg/L) 16-fold higher than their susceptible counterpart strains ($MIC_{50/90}$, 0.015/0.03 mg/L; Tables 1 and 2). All *E. faecalis* were inhibited by oritavancin at ≤0.5 mg/L, except for two isolates (MIC values, 1 mg/L).
- Ampicillin ($MIC_{50/90}$, ≤1/2 mg/L), teicoplanin ($MIC_{50/90}$, ≤2/≤2 mg/L), daptomycin ($MIC_{50/90}$, 2/4 mg/L) and linezolid ($MIC_{50/90}$, 2/2 mg/L) were very active (≥97.1% susceptible) against *E. casseliflavus* and *E. gallinarum* (Table 2). Oritavancin showed MIC_{50} and MIC_{90} of 0.008 and 0.015 mg/L, respectively, against these organisms.
- Overall, elevated rates of high-level gentamicin resistance were observed among *E. faecalis* (28.9 – 83.8%) and *E. faecium* (17.4 – 30.8%; Table 2). High-level gentamicin resistance was not observed among *E. casseliflavus* and *E. gallinarum*.

Results-2

Table 1. MIC distribution of oritavancin tested against enterococcal isolates submitted as part of the 2008 – 2009 international oritavancin surveillance program.

Organism	MIC (mg/L)		Number (cumulative %) of isolates inhibited by oritavancin MIC (mg/L) of:								
Phenotype (no. tested)	50%	90%	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
E. faecium											
Vancomycin-susceptible (421)	≤0.004	0.008	**222(52.7)**[a]	190(97.9)	8(99.8)	1(100.0)					
VanA (583)	0.03	0.12	11(1.9)	42(9.1)	56(18.7)	200(53.0)	**208(88.7)**	58(98.6)	6(99.7)	2(100.0)	
VanB (28)	0.008	0.008	13(46.4)	**14(96.4)**	0(96.4)	1(100.0)					
E. faecalis											
Vancomycin-susceptible (1,709)	0.015	0.03	35(2.0)	443(28.0)	**767(72.8)**	379(95.0)	75(99.4)	7(99.8)	2(99.9)	1(100.0)	
VanA (46)	0.25	0.5	1(2.2)	0(2.2)	1(4.3)	1(6.5)	2(10.9)	5(21.7)	**17(58.7)**	**17(95.7)**	2(100.0)
VanB (20)	0.015	0.03	0(0.0)	7(35.0)	**9(80.0)**	4(100.0)					
***E. casseliflavus* (11) and *E. gallinarum* (23)**											
VanC[b] (34)	0.008	0.015	4(11.8)	**25(85.3)**	4(97.1)	1(100.0)					

a. Modal MIC values are in bold.
b. Isolates known to intrinsically harbour the *vanC* gene were regarded as VanC strains.

Table 2. Antimicrobial activity of oritavancin and comparators tested against enterococcal clinical isolates collected as part of the 2008 – 2009 international oritavancin surveillance program.

Organism/phenotype (no. tested)	MIC (mg/L)		% susceptible / % resistant[a]	
Antimicrobial agent	50%	90%	CLSI	EUCAST
E. faecium				
Vancomycin-susceptible (421)				
Oritavancin	≤0.004	0.008	-[b] / -	- / -
Ampicillin	>16	>16	13.8 / 86.2	13.3 / 86.2
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	2	4	99.3 / -	- / -
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	1	>2	68.4 / 24.5	68.4 / 24.54
Gentamicin (HL[c])	≤500	>1000	72.8 / 27.2	- / -
Levofloxacin	>4	>4	13.8 / 79.8	- / -
Tetracycline	≤2	>8	63.4 / 35.9	- / -
VanA (583)				
Oritavancin	0.03	0.12	- / -	- / -
Ampicillin	>16	>16	0.0 / 100.0	0.0 / 100.0
Vancomycin	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>16	>16	0.0 / 100.0	0.0 / 100.0
Daptomycin	2	2	99.7 / -	- / -
Linezolid	1	2	98.8 / 0.5	98.8 / 0.5
Quinupristin/dalfopristin	1	1	95.2 / 1.2	95.2 / 1.2
Gentamicin (HL)	≤500	>1000	82.6 / 17.4	- / -
Levofloxacin	>4	>4	3.1 / 96.6	- / -
Tetracycline	≤2	>8	57.3 / 41.7	- / -
VanB (28)				
Oritavancin	0.008	0.008	- / -	- / -
Ampicillin	>16	>16	0.0 / 100.0	0.0 / 100.0
Vancomycin	>16	>16	0.0 / 78.6	0.0 / 100.0
Teicoplanin	≤2	8	100.0 / 0.0	64.3 / 35.7
Daptomycin	2	2	100.0 / -	- / -
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	1	>2	75.0 / 25.0	75.0 / 25.0
Gentamicin (HL)	≤500	>1000	69.2 / 30.8	- / -
Levofloxacin	>4	>4	17.9 / 78.6	- / -
Tetracycline	≤2	>8	75.0 / 25.0	- / -

a. Breakpoint susceptibility criteria as published by CLSI M100-S20 (2010) and EUCAST (2009).
b. – indicates no breakpoint is available for the respective drug/organism combination.
c. HL = high-level.
d. Isolates known to intrinsically harbour the *vanC* gene were regarded as VanC strains.

Organism/phenotype (no. tested)	MIC (mg/L)		% susceptible / % resistant[a]	
Antimicrobial agent	50%	90%	CLSI	EUCAST
E. faecalis				
Vancomycin-susceptible (1,709)				
Oritavancin	0.015	0.03	- / -	- / -
Ampicillin	≤1	2	100.0 / 0.0	99.8 / 0.0
Vancomycin	1	2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	1	2	99.9 / -	- / -
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	1.0 / 95.9	1.0 / 95.9
Gentamicin (HL)	≤500	>1000	71.1 / 28.9	- / -
Levofloxacin	1	>4	68.5 / 31.1	- / -
Tetracycline	>8	>8	25.0 / 74.9	- / -
VanA (46)				
Oritavancin	0.25	0.5	- / -	- / -
Ampicillin	≤1	2	97.8 / 2.2	97.8 / 2.2
Vancomycin	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>16	>16	0.0 / 100.0	0.0 / 100.0
Daptomycin	1	1	100.0 / -	- / -
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	2.2 / 95.7	2.2 / 95.7
Gentamicin (HL)	>1000	>1000	16.2 / 83.8	- / -
Levofloxacin	>4	>4	4.3 / 95.7	- / -
Tetracycline	>8	>8	6.5 / 93.5	- / -
VanB (20)				
Oritavancin	0.015	0.03	- / -	- / -
Ampicillin	≤1	2	100.0 / 0.0	100.0 / 0.0
Vancomycin	>16	>16	0.0 / 85.0	0.0 / 100.0
Teicoplanin	≤2	≤2	100.0 / 0.0	95.0 / 5.0
Daptomycin	1	2	100.0 / -	- / -
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	0.0 / 100.0	0.0 / 100.0
Gentamicin (HL)	1000	>1000	21.4 / 78.6	- / -
Levofloxacin	>4	>4	5.0 / 95.0	- / -
Tetracycline	>8	>8	30.0 / 70.0	- / -
***E. casseliflavus* (11) and *E. gallinarum* (23)**				
VanC[d] (34)				
Oritavancin	0.008	0.015	- / -	- / -
Ampicillin	≤1	2	97.1 / 2.9	97.1 / 2.9
Vancomycin	4	8	76.5 / 0.0	76.5 / 23.5
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	2	4	97.1 / -	- / -
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	2.9 / 55.9	2.9 / 55.9
Gentamicin (HL)	≤500	≤500	100.0 / 0.0	- / -
Levofloxacin	2	4	85.3 / 5.9	- / -
Tetracycline	≤2	>8	61.8 / 38.2	- / -

Conclusions

- Oritavancin demonstrated equivalent potencies when tested against vancomycin-resistant (VanB) and -susceptible *E. faecium*. A similar finding was observed among *E. faecalis* isolates.
- *E. faecalis* and *E. faecium* strains of VanA-type displayed an elevated (16-fold) oritavancin MIC_{90} value when compared to their corresponding susceptible strains. However, all tested isolates were inhibited by achievable oritavancin concentrations of 1 mg/L.
- Oritavancin was very potent when tested against these enterococcal isolates (2008 – 2009). These in vitro results combined with the favourable oritavancin pharmacodynamic profiles are encouraging; especially for treating invasive infections where a potent bactericidal activity is crucial and therapeutic options are limited due to emerging resistances.

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