C2-1258

Oritavancin Activity against Vancomycin-susceptible and Genetically Characterized Vancomycin-resistant Enterococci from Bacteremic Patients (2009 – 2010)

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Abstract

Background: Oritavancin is a lipoglycopeptide with activity against both vancomycin-susceptible (VSE) and -resistant enterococci (VRE). Potency of oritavancin and comparators was evaluated against contemporary enterococci causing bloodstream infections (BSI).

Methods: 2,260 enterococci (mostly *E. faecalis* [1,312] and *E. faecium* [869]) were collected from 29 sites in the USA and 27 sites in 13 European countries, including Turkey and Israel. Identification was performed by Vitek 2. Susceptibility was tested by CLSI methods. Isolates with vancomycin MIC results at ≥8 μg/mL were screened for *vanA/B1-3* in a multiplex PCR assay. *E. casseliflavus* and *E. gallinarum* identification was PCR-confirmed by the presence of *vanC1-3*.

Results: 37 (2.8%) *E. faecalis* isolates were VRE, among which 27 carried *vanA* and 10 *vanB*. 486 (55.9%) *E. faecium* strains were VRE of which 470 (96.7%) harbored *vanA*. Two USA *vanA E. faecium* exhibited teicoplanin MICs of ≤1 and 4 μg/mL. Oritavancin (MIC_{50}, 0.015 μg/mL) was equally active against VSE and *vanB E. faecalis* strains. *vanA E. faecalis* ($MIC_{50/90}$, 0.25/0.5 μg/mL) had oritavancin MICs 16-fold higher than VSE strains ($MIC_{50/90}$, 0.015/0.03 μg/mL). Ampicillin ($MIC_{50/90}$, ≤1/2 μg/mL; 96% susceptible), daptomycin ($MIC_{50/90}$, 1/2 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/1 μg/mL; 100% susceptible) showed coverage against *vanA E. faecalis*. Similar oritavancin $MIC_{50/90}$ values ($MIC_{50/90}$, ≤0.008/≤0.008 μg/mL) were noted against VSE and *vanB E. faecium*, while oritavancin was less active (≥4-fold) against *vanA E. faecium*. Daptomycin ($MIC_{50/90}$, 2/2 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; 98% susceptible) were active against *E. faecium* carrying *vanA* genes. *vanC*-harboring strains were very susceptible to oritavancin, ampicillin (97% susceptible), daptomycin (100% susceptible) and linezolid (100% susceptible).

Conclusions: This appears to be the first report of VanB phenotype-*vanA* genotype strains in the USA. Oritavancin demonstrated activity greater than comparators against VRE causing BSI. Oritavancin was less active against *vanA* strains, but inhibited all VRE at ≤0.5 μg/mL.

Introduction

Enterococcal isolates currently represent the third most frequent pathogens responsible for healthcare-associated infections in the USA. *Enterococcus faecium* strains, which are often resistant to commonly prescribed antimicrobial agents such as ampicillin, aminoglycosides and glycopeptides, are of great concern. In addition, growing evidences have demonstrated that enterococcal species possess specific traits that enable them to cause a broad range of infections.

Introduction-continued

Enterococcus faecalis and *E. faecium* may acquire glycopeptide resistance determinants via *van*-associated genes. The ability to acquire, retain and express genetic elements further enhances the propensity of enterococci to sustain selective pressure, promoting bacterial colonization, and eventually progressing to an infectious episode. This study describes the activity of oritavancin and comparators tested against enterococcal clinical isolates, including molecularly characterized vancomycin-resistant strains (VRE), causing bloodstream infections (BSI) in USA and European hospitals (2009-2010).

Methods

Bacterial strain collection. A total of 2,260 enterococci (1,312 *E. faecalis*; 869 *E. faecium*, 24 *E. gallinarum* and 15 *E. casseliflavus*) were collected from 29 medical institutions in the USA and 27 centers in 13 European countries, including Turkey and Israel. Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) following established protocols as part of the SENTRY Antimicrobial Surveillance Program. Bacterial species identification was performed by using an automated system (Vitek®2; bioMérieux, Hazelwood, Missouri, USA) or conventional biochemical algorithms, as required.

Antimicrobial susceptibility test methods. Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) recommendations. Susceptibility testing was performed using dry-form panels (TREK Diagnostic Systems, Cleveland, Ohio, USA), which provide results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80. Quality assurance was performed by concurrent testing of CLSI-recommended (M100-S21, 2011) strains: *E. faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213. Interpretation of comparator MIC results was in accordance with published CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.

Screening for *van*-associated elements. All enterococcal isolates exhibiting vancomycin MIC results at ≥8 μg/mL were selected for further molecular screening. These strains were screened for *vanA* and *vanB1-3* in a multiplex PCR format. In addition, the identification of *E. gallinarum* and *E. casseliflavus* was PCR-confirmed by the presence of *vanC1* or *vanC2-3*, respectively.

Results-1

- The majority of enterococcal strains recovered from blood were *E. faecalis* (1,312/2,260; 58.1%), followed by *E. faecium* (869/2,260; 38.5%). *E. faecium* represented the vast majority (486/523; 93.0%) of VRE strains (**Table 1**).
- *vanA* accounted for 73.0% (27/37) and 96.7% (470/486) of the *van* genes among *E. faecalis* and *E. faecium*, respectively. All *vanA*-strains showed a VanA phenotype (i.e. vancomycin and teicoplanin MIC, >16 and >8 μg/mL, respectively), except for two USA *E. faecium* that exhibited teicoplanin MIC values of ≤1 and 4 μg/mL (**Table 2**).
- Oritavancin inhibited all tested enterococci at ≤0.5 μg/mL with potent MIC_{50} and MIC_{90} results against vancomycin-susceptible *E. faecalis* ($MIC_{50/90}$, 0.015/0.03 μg/mL) and *E. faecium* ($MIC_{50/90}$, ≤0.008/≤0.008 μg/mL; **Table 1**).
- Equivalent activity (MIC_{50} results) was observed for oritavancin when tested against *vanB*-type enterococcal strains and their respective vancomycin-susceptible counterparts (**Table 1**).
- *vanA*-type *E. faecalis* exhibited oritavancin MIC values ($MIC_{50/90}$, 0.25/0.5 μg/mL) 16-fold higher than vancomycin-susceptible isolates ($MIC_{50/90}$, 0.015/0.03 μg/mL). *vanA*-type *E. faecium* ($MIC_{50/90}$, 0.03/0.06 μg/mL) showed higher (≥four-fold) oritavancin MIC results compared to vancomycin-susceptible and *vanB*-type strains ($MIC_{50/90}$, ≤0.008/≤0.008 μg/mL; **Table 1**).
- Ampicillin (MIC_{90}, 2 μg/mL; ≥96.3% susceptible), daptomycin (MIC_{90}, 1 – 2 μg/mL; 100% susceptible) and linezolid (MIC_{90}, 1 μg/mL; 100% susceptible) were active against vancomycin-resistant *E. faecalis* (**Table 2**). Oritavancin demonstrated MIC_{90} results 2- to 4- and 64- to 128-fold lower than these comparators tested against *vanA*- and *vanB*-type *E. faecalis*, respectively.
- When tested against vancomycin-resistant *E. faecium*, daptomycin ($MIC_{50/90}$, 2/2 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; ≥98.1% susceptible) demonstrated antimicrobial activity (**Table 2**).
- Quinupristin/dalfopristin ($MIC_{50/90}$, ≤0.5/1 μg/m; 96.6% susceptible) demonstrated activity against *vanA-E. faecium* (**Table 2**), while marginal coverage was noted against vancomycin-susceptible and -resistant (*vanB*) strains ($MIC_{50/90}$, ≤0.5/>2 μg/m; 72.1 – 87.5% susceptible).
- *E. casseliflavus* and *E. gallinarum* showed variable vancomycin MIC results (0.25 – 8 μg/mL; $MIC_{50/90}$, 4/8 μg/mL) and 17.9% of strains were vancomycin intermediate or resistant based on CLSI or EUCAST criteria, respectively. Nevertheless, these strains were very susceptible to oritavancin ($MIC_{50/90}$, ≤0.008/0.015 μg/mL; **Tables 1 and 2**).
- *vanC*-carrying enterococci (*E. casseliflavus* or *E. gallinarum*) were very susceptible (≥97.4%) to ampicillin ($MIC_{50/90}$, ≤1/2 μg/mL), teicoplanin ($MIC_{50/90}$, ≤2/≤2 μg/mL), daptomycin ($MIC_{50/90}$, 1/2 μg/mL) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; **Table 2**).

Results-2

Table 1. Antimicrobial activity of oritavancin tested against vancomycin-susceptible and genetically characterized vancomycin-resistant enterococcal clinical isolates causing bloodstream infections in USA and European hospitals.

Organism	MIC (μg/mL)		Number[a] (cumulative %) inhibited at MIC (μg/mL) of:						
Resistance pattern (no. tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
E. faecalis (1,312)									
Vancomycin-susceptible (1,275)	0.015	0.03	435(34.1)	**575(79.2)**	211(95.8)	43(99.1)	7(99.7)	3(99.9)	1(100.0)
vanA-genotype (27)	0.25	0.5	0(0.0)	1(3.7)	3(14.8)	3(25.9)	0(25.9)	**15(81.5)**	5(100.0)
vanB-genotype (10)	0.015	0.015	1(10.0)	**8(90.0)**	0(90.0)	1(100.0)	–	–	–
E. faecium (869)									
Vancomycin-susceptible (383)	≤0.008	≤0.008	**374(97.7)**	7(99.5)	2(100.0)	–	–	–	–
vanA- genotype (470)	0.03	0.06	76(16.2)	74(31.9)	**146(63.0)**	133(91.3)	37(99.1)	4(100.0)	–
vanB-genotype (16)	≤0.008	≤0.008	**16(100.0)**	–	–	–	–	–	–
E. casseliflavus (15) and *E. gallinarum* (24)									
vanC-genotype (39)	≤0.008	0.015	**34(87.2)**	5(100.0)	–	–	–	–	–

a. Modal MIC values are in bold.

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against vancomycin-susceptible and genetically characterized vancomycin-resistant enterococcal clinical isolates causing bloodstream infections in USA and European hospitals.

Organism (no. tested)		MIC (μg/mL)		% Susceptible/Resistant[a]	
Antimicrobial agent	Range	50%	90%	CLSI	EUCAST
Vancomycin-susceptible *E. faecalis* (1,275)					
Oritavancin	≤0.008 – 0.5	0.015	0.03	–[b] / -	– / -
Ampicillin	≤1 – 8	≤1	2	100.0 / 0.0	99.8 / 0.0
Vancomycin	0.25 – 4	1	2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 4	≤2	≤2	100.0 / 0.0	99.9 / 0.1
Daptomycin	0.12 – 4	1	2	100.0 / -	– / -
Linezolid	0.25 – >8	1	2	99.9 / 0.1	99.9 / 0.1
Quinupristin/dalfopristin	≤0.5 – >2	>2	>2	0.5 / 95.0	0.5 / 89.0
Levofloxacin	≤0.5 – >4	1	>4	69.0 / 30.4	– / -
Tetracycline	≤2 – >8	>8	>8	23.2 / 76.5	– / -
vanA-E. faecalis (27)					
Oritavancin	0.015 – 0.5	0.25	0.5	– / -	– / -
Ampicillin	≤1 – >16	≤1	2	96.3 / 3.7	96.3 / 3.7
Vancomycin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>8	>8	>8	3.7 / 96.3	0.0 / 100.0
Daptomycin	0.5 – 2	1	2	100.0 / -	– / -
Linezolid	1 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	2 – >2	>2	>2	0.0 / 96.3	0.0 / 96.3
Levofloxacin	2 – >4	>4	>4	3.7 / 96.3	– / -
Tetracycline	≤2 – >8	>8	>8	3.7 / 96.3	– / -
vanB-E. faecalis (10)					
Oritavancin	≤0.008 – 0.06	0.015	0.015	– / -	– / -
Ampicillin	≤1 – 2	≤1	2	100.0 / 0.0	100.0 / 0.0
Vancomycin	8 – >16	>16	>16	0.0 / 80.0	0.0 / 100.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	≤0.06 – 2	0.5	1	100.0 / -	– / -
Linezolid	0.5 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	>2	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>4	>4	>4	0.0 / 100.0	– / -
Tetracycline	≤2 – >8	≤2	>8	50.0 / 50.0	– / -
Vancomycin-susceptible *E. faecium* (383)					
Oritavancin	≤0.008 – 0.03	≤0.008	≤0.008	– / -	– / -
Ampicillin	≤1 – >8	>8	>8	14.4 / 85.6	14.1 / 85.6
Vancomycin	0.25 – 4	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 4	≤2	≤2	100.0 / 0.0	99.7 / 0.3
Daptomycin	0.12 – >8	2	4	99.7 / -	– / -
Linezolid	0.5 – >8	1	2	99.2 / 0.8	99.2 / 0.8
Quinupristin/dalfopristin	≤0.5 – >2	≤0.5	>2	72.1 / 15.7	72.1 / 11.7
Levofloxacin	≤0.5 – >4	>4	>4	15.4 / 77.5	– / -
Tetracycline	≤2 – >8	≤2	>8	56.7 / 42.8	– / -

Organism (no.tested)		MIC (μg/mL)		% Susceptible/Resistant[a]	
Antimicrobial agent	Range	50%	90%	CLSI	EUCAST
vanA-E. faecium (470)					
Oritavancin	≤0.008 – 0.25	0.03	0.06	– / -	– / -
Ampicillin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Vancomycin	>16	>16	>16	0.0 / 99.6	0.0 / 100.0
Teicoplanin	≤1 – >8	>8	>8	0.6 / 96.2	0.2 / 99.8
Daptomycin	0.12 – 4	2	2	100.0 / -	– / -
Linezolid	0.5 – >8	1	2	98.1 / 1.3	98.7 / 1.3
Quinupristin/dalfopristin	≤0.5 – >2	≤0.5	1	96.6 / 1.3	96.6 / 1.3
Levofloxacin	2 – >4	>4	>4	0.2 / 99.8	– / -
Tetracycline	≤2 – >8	>8	>8	36.8 / 62.3	– / -
vanB-E. faecium (16)					
Oritavancin	≤0.008	≤0.008	≤0.008	– / -	– / -
Ampicillin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Vancomycin	8 – >16	>16	>16	0.0 / 75.0	0.0 / 100.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.5 – 4	2	2	100.0 / -	– / -
Linezolid	0.5 – 4	1	2	93.8 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	≤0.5 – >2	≤0.5	>2	87.5 / 12.5	87.5 / 12.5
Levofloxacin	>4	>4	>4	0.0 / 100.0	– / -
Tetracycline	≤2 – >8	>8	>8	37.5 / 62.5	– / -
vanC (39)[c]					
Oritavancin	≤0.008 – 0.015	≤0.008	0.015	– / -	– / -
Ampicillin	≤1 – >16	≤1	2	97.4 / 2.6	97.4 / 2.6
Vancomycin	0.25 – 8	4	8	82.1 / 0.0	82.1 / 17.9
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	≤0.06 – 4	1	2	100.0 / -	- / -
Linezolid	0.5 – 2	1	2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	≤0.5 – >2	2	>2	7.7 / 48.7	7.7 / 30.8
Levofloxacin	≤0.5 – >4	2	4	84.6 / 5.1	– / -
Tetracycline	≤2 – >8	≤2	>8	74.4 / 25.6	– / -

a. Criteria for susceptibility as published by the CLSI (M100-S21, 2011) and EUCAST (2011) recommendations.
b. –, no breakpoint available.
c. Includes *E. casseliflavus* (15 isolates) and *E. gallinarum* (24 isolates).

Conclusions

- The present study highlights the emergence of *E. faecium* (38.5% of all enterococci) as an important pathogen responsible for BSI. This is a great concern given the higher antimicrobial resistance and mortality rate associated with this species.
- Two *E. faecium* strains from USA hospitals demonstrated a VanB phenotype-*vanA* genotype. Strains displaying these characteristics have been reported in the East Asia region (Japan, China, Korea and Taiwan). This appears to be the first report of such strains in the USA.
- The *in vitro* activity of oritavancin and comparator agents documented the pronounced oritavancin activity when tested against this collection of clinical isolates. Moreover, oritavancin demonstrated 4- to 128-fold greater potency than the active comparators, particularly when tested against VRE.
- This *in vitro* activity data suggests oritavancin as a promising agent for treating serious infections caused by vancomycin-susceptible and -resistant enterococci, pending further studies.

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51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, September 17-20, 2011