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Assessment of Oritavancin Activity Tested Against Contemporary Clinical Isolates Responsible for Documented Bacteraemia in European Union and Other Countries (2010-2012)

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Abstract

Objectives: To evaluate the oritavancin *in vitro* activity against *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Enterococcus faecalis* and *E. faecium* recovered from blood specimens among hospitalized patients in the European Union and other countries.

Methods: A total of 2,904 clinical strains responsible for documented bacteraemia were collected from 38 sites in 11 European Union countries, Israel, Russia, Turkey and Ukraine, as part of the SENTRY Antimicrobial Surveillance Programme (2010-2012). Identification was performed by standard algorithms and Vitek® 2. Susceptibility testing was performed by CLSI methods (M07-A9), while interpretation of MIC results used the CLSI (M100-S23) and EUCAST (2013) breakpoint criteria. *E. faecalis* and *E. faecium* displaying vancomycin and teicoplanin MIC values of >4 and >2 mg/L, respectively, were considered as VanA-phenotype.

Results: Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was active against all *S. aureus*, inhibiting these strains at ≤0.25 mg/L. Oritavancin modal MIC, MIC_{50} and MIC_{90} results (0.06, 0.06 and 0.12 mg/L, respectively) against *S. aureus* with vancomycin MIC = 2 mg/L were two-fold higher than those obtained against strains with vancomycin MIC at ≤1 mg/L (0.03, 0.03 and 0.06 mg/L, respectively). Similarly, when tested against a subset of CoNS strains with teicoplanin MIC values of ≥8 mg/L, oritavancin ($MIC_{50/90}$, 0.06/0.12 mg/L) had MIC results two-fold higher than those strains with teicoplanin at ≤4 mg/L ($MIC_{50/90}$, 0.03/0.06 mg/L). Vancomycin, daptomycin and linezolid exhibited activity (≥99% susceptible) against MRSA and methicillin-resistant CoNS (MRCoNS), except for teicoplanin that showed marginal results (86.8% susceptible) against MRCoNS. Oritavancin ($MIC_{50/90}$, 0.015/0.06 mg/L) was very active against *E. faecalis* strains, as were ampicillin ($MIC_{50/90}$, ≤1/2 mg/L; 99.6% susceptible), vancomycin ($MIC_{50/90}$, 1/2 mg/L; 99.1% susceptible), teicoplanin (99.1% susceptible), daptomycin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; 100% susceptible). *E. faecium* strains (including VanA-phenotype strains) were very sensitive to oritavancin (highest MIC, 0.12 mg/L). Daptomycin ($MIC_{50/90}$, 2/2 mg/L) and linezolid ($MIC_{50/90}$, 1/2 mg/L; 96.2% susceptible) also showed good coverage against *E. faecium*.

Conclusions: Oritavancin exhibited potent activity against staphylococci and enterococci causing serious and potentially difficult-to-treat infections due to multidrug resistance phenotypes. Higher (two-fold) oritavancin MIC values were noted against strains with reduced susceptibility to vancomycin or teicoplanin; however, oritavancin inhibited all tested strains at ≤0.5 mg/L.

Introduction

Gram-positive organisms (staphylococci, enterococci and streptococci) are largely responsible for infections in the community and nosocomial settings. More often than appreciated, these infections may involve a causative agent exhibiting a multidrug-resistant (MDR) phenotype, and when associated with critically ill patients may provide a greater challenge for antimicrobial therapies. These serious infections are also associated with increased morbidity and mortality, and create a significant economic burden. Moreover, the therapeutic options for treating these serious Gram-positive conditions have become limited since few agents have been recently approved for clinical use.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide in Phase 3 clinical development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). This drug has demonstrated broad *in vitro* activity against Gram-positive pathogens, including MDR strains of methicillin-resistant *Staphylococcus aureus* (MRSA), other *Staphylococcus* spp., streptococci, and enterococci, including strains with elevated vancomycin MIC values. In this study, oritavancin and comparator agent activities were evaluated against *S. aureus*, coagulase-negative staphylococci (CoNS), *Enterococcus faecalis* and *E. faecium* recovered from blood specimens among hospitalized patients in the European Union and other surrounding countries during the international surveillance programme for oritavancin (2010-2012).

Methods

Bacterial strain collection. A total of 2,904 clinical strains responsible for documented bacteraemia among unique hospitalized patients in 38 hospitals in 11 European Union countries, Israel, Russia, Turkey and Ukraine were included in this study (2010-2012). Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), following previously established protocols. Bacterial species identification was performed by using an automated system (Vitek®2; bioMérieux, Hazelwood, Missouri, USA) or conventional biochemical algorithms, as required.

Antimicrobial susceptibility testing methods. Isolates were tested for susceptibility by broth microdilution methods following the Clinical and Laboratory Standards Institute (CLSI; M07-A9, 2012) document. Susceptibility testing was performed in cation-adjusted Mueller-Hinton broth (CA-MHB) using dry-form panels manufactured by Thermo Fisher Scientific, formerly TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). These panels 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-S23, 2013) strains: *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213. Interpretation of comparator MIC results was in accordance with published CLSI (M100-S23) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2013) criteria. *E. faecalis* and *E. faecium* displaying vancomycin and teicoplanin MIC values of >4 and >2 mg/L, respectively, were considered as VanA-phenotype.

Results

- Oritavancin exhibited MIC_{50} and MIC_{90} results of 0.03 and 0.06 mg/L, respectively when tested against a collection of staphylococcal clinical isolates, regardless of the methicillin susceptibility pattern, inhibiting all strains at ≤0.25 mg/L (Table 1).
- Oritavancin MIC_{50}, MIC_{90} and modal MIC results against *S. aureus* isolates with decreased susceptibility to vancomycin (MIC = 2 mg/L) were two-fold higher than those obtained against strains with vancomycin MIC ≤1 mg/L (Table 1).
- When tested against MRSA strains, oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was eight-fold more potent than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and 16- to 32-fold more active than vancomycin ($MIC_{50/90}$, 1/1 mg/L) or linezolid ($MIC_{50/90}$, 1/1 mg/L; Table 2).
- A subset of CoNS clinical isolates causing bacteraemia and displaying a decreased susceptibility to teicoplanin (MIC ≥8 mg/L), demonstrated oritavancin MIC results (highest MIC value, 0.25 mg/L) two-fold higher than strains with teicoplanin MIC ≤4 mg/L (Table 1).
- Oritavancin exhibited MIC_{50} and MIC_{90} results (0.03 and 0.06 mg/L, respectively) eight- and 16-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and linezolid ($MIC_{50/90}$, 0.5/1 mg/L) when tested against CoNS isolates, respectively (Table 2). Moreover, the oritavancin MIC values obtained against CoNS were 32- to 64-fold lower than vancomycin ($MIC_{50/90}$, 2/2 mg/L).
- Oritavancin ($MIC_{50/90}$, 0.015/0.06 mg/L) was very active against *E. faecalis* strains, as were ampicillin ($MIC_{50/90}$, ≤1/2 mg/L; 99.6% susceptible), vancomycin ($MIC_{50/90}$, 1/2 mg/L; 99.1% susceptible), teicoplanin (99.1% susceptible), daptomycin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; 100% susceptible).
- Oritavancin ($MIC_{50/90}$, 0.015/0.06 mg/L) was at least two-fold less active when tested against vancomycin-resistant (VanA-type) *E. faecium* strains compared with the wildtype vancomycin-susceptible population ($MIC_{50/90}$, ≤0.008/≤0.008 mg/L; Tables 1 and 2). However, oritavancin inhibited all VanA-phenotype *E. faecium* strains at ≤0.12 mg/L.
- Daptomycin ($MIC_{50/90}$, 2/2 mg/L; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; 96.2% susceptible) showed good coverage against VanA-phenotype *E. faecium*. However, oritavancin demonstrated MIC_{50} and MIC_{90} results 32- to 64-fold lower than these comparators (Table 2).

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against Gram-positive clinical isolates, including resistant subsets, causing bacteraemia as part of the 2010 – 2012 international oritavancin surveillance programme.

Organism (no. tested) / Agent	Range	MIC (mg/L) 50%	MIC (mg/L) 90%	% Susceptible/Resistant[a] CLSI	% Susceptible/Resistant[a] EUCAST
***S. aureus* - Methicillin-resistant (1,708)**					
Oritavancin	≤0.008 – 0.25	0.03	0.06	–[b] / –	– / –
Vancomycin	0.25 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.12 – 1	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	0.25 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	>4	>4	29.6 / 68.0	29.8 / 69.1
Clindamycin	≤0.25 – >2	≤0.25	>2	59.1 / 40.3	58.9 / 40.9
Tetracycline	≤0.25 – >8	≤0.25	>8	84.9 / 14.2	84.4 / 15.1
Levofloxacin	≤0.5 – >4	>4	>4	8.6 / 90.3	8.6 / 90.3
TMP/SMX[c]	≤0.5 – >4	≤0.5	≤0.5	97.8 / 2.2	97.8 / 2.2
Coagulase-negative staphylococci (646)					
Oritavancin	≤0.008 – 0.25	0.03	0.06	– / –	– / –
Oxacillin	≤0.25 – >2	>2	>2	21.2 / 78.8	21.2 / 78.8
Vancomycin	0.25 – 4	2	2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – >8	≤2	8	97.7 / 0.8	88.9 / 11.1
Daptomycin	≤0.06 – 2	0.25	0.5	99.8 / –	99.8 / 0.2
Linezolid	≤0.12 – >8	0.5	1	99.2 / 0.8	99.2 / 0.8
Erythromycin	≤0.25 – >4	>4	>4	34.9 / 65.1	34.9 / 65.1
Clindamycin	≤0.25 – >2	≤0.25	>2	73.0 / 26.0	70.9 / 27.0
Tetracycline	≤0.25 – >8	1	>8	83.1 / 15.2	68.7 / 19.3
Levofloxacin	≤0.5 – >4	4	>4	39.2 / 56.2	39.2 / 56.2
TMP/SMX[c]	≤0.5 – >4	1	>4	56.5 / 43.5	56.5 / 24.1
***E. faecalis*[d] (445)**					
Oritavancin	≤0.008 – 0.5	0.015	0.06	– / –	– / –
Ampicillin	≤1 – 8	≤1	2	100.0 / 0.0	99.6 / 0.0
Vancomycin	0.5 – >16	1	2	99.1 / 0.9	99.1 / 0.9
Teicoplanin	≤2 – >8	≤2	≤2	99.1 / 0.9	99.1 / 0.9
Daptomycin	≤0.06 – 4	1	1	100.0 / –	– / –
Linezolid	0.5 – 2	1	2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	>4	>4	8.1 / 54.8	– / –
Tetracycline	≤0.25 – >8	>8	>8	26.5 / 73.5	– / –
Levofloxacin	≤0.5 – >4	1	>4	64.3 / 35.3	– / –
***E. faecium* - Vancomycin-susceptible (257)**					
Oritavancin	≤0.008 – 0.015	≤0.008	≤0.008	– / –	– / –
Ampicillin	≤1 – >8	>8	>8	5.8 / 94.2	5.4 / 94.2
Vancomycin	0.5 – 4	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 4	≤2	≤2	100.0 / 0.0	99.6 / 0.4
Daptomycin	0.12 – 4	2	2	100.0 / -	– / –
Linezolid	0.25 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	>4	>4	3.5 / 91.4	– / –
Tetracycline	≤0.25 – >8	0.5	>8	56.0 / 43.2	– / –
Levofloxacin	1 – >4	>4	>4	5.8 / 89.1	– / –
Vancomycin-resistant (VanA-phenotype) (53)					
Oritavancin	≤0.008 – 0.12	0.015	0.06	– / –	– / –
Ampicillin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Vancomycin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>8	>8	>8	0.0 / 96.2	0.0 / 100.0
Daptomycin	0.25 – 4	2	2	100.0 / –	– / –
Linezolid	0.5 – 8	1	2	96.2 / 3.8	96.2 / 3.8
Erythromycin	4 – >4	>4	>4	0.0 / 98.1	– / –
Tetracycline	≤0.25 – >8	0.5	>8	58.5 / 41.5	– / –
Levofloxacin	>4	>4	>4	0.0 / 100.0	– / –

a. Breakpoint criteria according to CLSI (M100-S23, 2013) and EUCAST (2013).
b. Breakpoints not available.
c. Trimethoprim/sulfamethoxazole.
d. Includes four VanA-phenotype strains.

Table 1. MIC distribution of oritavancin tested against Gram-positive clinical isolates, including resistant subsets, causing bacteraemia as part of the 2010 – 2012 international oritavancin surveillance programme.

Organism (no. tested) / Subset	MIC (mg/L) 50%	MIC (mg/L) 90%	Number (cumulative %) inhibited at MIC (mg/L)[a] ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
***S. aureus* (1,498)**									
Methicillin-susceptible (1,126)	0.03	0.06	28(2.5)	247(24.4)	**458(65.1)**	297(91.5)	78(98.4)	18(100.0)	
Methicillin-resistant (372)	0.03	0.06	5(1.3)	86(24.5)	**180(72.9)**	68(91.1)	27(98.4)	6(100.0)	
Vancomycin MIC ≤1 mg/L (1,479)	0.03	0.06	33(2.2)	332(24.7)	**635(67.6)**	354(91.5)	102(98.4)	23(100.0)	
Vancomycin MIC = 2 mg/L (19)	0.06	0.12	0(0.0)	1(5.3)	3(21.1)	**11(78.9)**	3(94.7)	1(100.0)	
Coagulase-negative staphylococci (646)									
Methicillin-susceptible (137)	0.03	0.06	37(27.0)	28(47.5)	**50(83.9)**	21(99.3)	1(100.0)		
Methicillin-resistant (509)	0.03	0.06	100(19.7)	77(34.8)	**181(70.3)**	114(92.7)	33(99.2)	4(100.0)	
Teicoplanin MIC ≤4 mg/L (574)	0.03	0.06	136(23.7)	104(41.8)	**216(79.4)**	99(96.7)	19(100.0)		
Teicoplanin MIC ≥8 mg/L (72)	0.06	0.12	1(1.4)	1(2.8)	15(23.6)	**36(73.6)**	15(94.4)	4(100.0)	
***E. faecalis*[b] (445)**	0.015	0.06	104(23.4)	**204(69.2)**	89(89.2)	30(96.0)	13(98.9)	4(99.8)	1(100.0)
***E. faecium*[c] (315)**	≤0.008	0.015	**269(85.4)**	25(93.3)	12(97.1)	6(99.1)	3(100.0)		
Vancomycin-susceptible (257)	≤0.008	≤0.008	**251(97.7)**	6(100.0)					
VanA-phenotype[d] (53)	0.015	0.06	13(24.5)	**19(60.4)**	12(83.0)	6(94.3)	3(100.0)		

a. Modal MIC values are shown in bold.
b. Includes four VanA-phenotype strains displaying oritavancin MIC values of 0.12 - 0.5 mg/L.
c. Includes five VanB-phenotype strains displaying vancomycin and teicoplanin MIC values of >4 and ≤2 mg/L, respectively. All oritavancin MIC values for these VanB strains were at ≤0.008 mg/L.
d. VanA-phenotype = vancomycin and teicoplanin MIC values of >4 and >2 mg/L, respectively (EUCAST criteria for non-susceptibility).

Conclusions

- Oritavancin demonstrated high *in vitro* potency when tested against this contemporary (2010 - 2012) collection of Gram-positive clinical isolates causing bacteraemia among hospitalized patients in the European Union and surrounding countries.
- The *in vitro* activity of oritavancin tested against staphylococci was not affected by the methicillin-resistance phenotype. In addition, oritavancin MIC results were not significantly (>two-fold) affected by the glycopeptide (vancomycin and teicoplanin) susceptibilities and inhibited all staphylococci, *E. faecalis* and *E. faecium*, including resistant subsets, at ≤0.25, ≤0.5 and ≤0.12 mg/L, respectively.
- This study reports a contemporary analysis of oritavancin activity, including its activity against challenge subsets of clinical isolates. Moreover, it demonstrates that oritavancin *in vitro* potency is consistently greater than the clinical antimicrobial agents currently available for treating serious Gram-positive infections.

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