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Oritavancin Activity Tested Against *Staphylococcus aureus* and β-haemolytic Streptococci Causing Skin and Soft Tissue Infections in European Union and Other Countries (2010−2012)

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Abstract

Objectives: To assess the oritavancin activity tested against key contemporary pathogens (*S. aureus* and β-haemolytic streptococci [BHS]), including multidrug-resistant (MDR) subsets responsible for skin and soft tissue infections (SSTI) in European and Israeli hospitals.

Methods: 2,259 *S. aureus* and 300 BHS responsible for documented SSTI were collected from 37 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 EUCAST (2012) breakpoint criteria. *S. aureus* and BHS non-susceptible to four and three drug classes or more, respectively, were defined as MDR.

Results: Overall, oritavancin exhibited potent activity against all *S. aureus* (Table). Similar proportions of methicillin-susceptible and -resistant strains (MRSA; 66.7 and 68.4%, respectively) were inhibited at the modal MIC value of 0.03 mg/L (for both groups). Oritavancin had $MIC_{50/90}$ values 8-fold lower than daptomycin and 16- to 32-fold lower than vancomycin and linezolid against MRSA. Other comparators, such as teicoplanin (99.8% susceptible) and trimethoprim/sulfamethoxazole (99.1% susceptible) were also active against MRSA, while tetracycline and clindamycin (86.9% and 71.5% susceptible, respectively) showed suboptimum results. MDR and non-MDR *S. aureus* strains had similar oritavancin MIC results, with 89.2 and 91.8% of strains inhibited at ≤0.06 mg/L, respectively. Penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100% susceptible), oritavancin and daptomycin were the most potent drugs tested against BHS. Clindamycin ($MIC_{50/90}$, ≤0.25/≤0.25 mg/L; 93.3% susceptible), levofloxacin ($MIC_{50/90}$, ≤0.5/1 mg/L; 92.3% susceptible) and trimethoprim/sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L; 97.3% susceptible) were also active against BHS. Oritavancin demonstrated MIC_{50} and MIC_{90} values against Group A and MDR BHS strains slightly (2-fold) lower than those observed for Group B strains, and inhibited all BHS at ≤0.5 mg/L.

Conclusions: Oritavancin showed potent *in vitro* activity when tested against the main pathogens responsible for SSTI, including MDR subsets, among European and other hospitals surveyed recently (2010-2012). These results suggest that oritavancin may have promise as an empiric treatment option for SSTI. Pending regulatory approval, continued monitoring of oritavancin activity against Gram-positive pathogens is warranted.

Organism[a] (No. tested)	Oritavancin MIC (mg/L)		Vancomycin MIC (mg/L)			Daptomycin MIC (mg/L)			Linezolid MIC (mg/L)		
	50%	90%	50%	90%	%S[b]	50%	90%	%S	50%	90%	%S
S. aureus (2,259)	0.03	0.06	1	1	100.0	0.25	0.5	99.9	1	2	100.0
MSSA (1,708)	0.03	0.06	1	1	100.0	0.25	0.5	100.0	1	2	100.0
MRSA (551)	0.03	0.06	1	1	100.0	0.25	0.5	99.6	1	2	99.9
Non-MDR (2,065)	0.03	0.06	1	1	100.0	0.25	0.5	100.0	1	2	100.0
MDR (194)	0.03	0.12	1	1	100.0	0.25	0.5	99.0	1	1	100.0
BHS (300)	0.06	0.25	0.25	0.5	100.0	≤0.06	0.25	100.0	1	1	100.0
Group A BHS (190)	0.03	0.12	0.25	0.5	100.0	≤0.06	≤0.06	100.0	1	1	100.0
Group B BHS (110)	0.06	0.25	0.5	0.5	100.0	0.12	0.25	100.0	1	1	100.0
MDR[c] (17)	0.06	0.25	0.5	0.5	100.0	0.12	0.25	100.0	1	1	100.0

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; BHS = β-haemolytic streptococci.
b. %S = percentage susceptible (EUCAST, 2012).
c. Consists of four and 13 Group A and B BHS isolates, respectively.

Introduction

Oritavancin, a semisynthetic bactericidal lipoglycopeptide, has documented broad *in vitro* activity against Gram-positive pathogens, including multidrug-resistant (MDR) strains of methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci and streptococci. This potent activity results from three distinct mechanisms of action, which consist of (1) disruption of bacterial membrane integrity; (2) inhibition of the transglycosylation step of the bacterial cell wall synthesis; and (3) inhibition of the transpeptidation step of cell wall synthesis. The multiple mechanisms of action confer on oritavancin a potent, concentration-dependent bactericidal activity against a broad-spectrum of Gram-positive pathogens.

The efficacy and safety of a single-dose of intravenous oritavancin therapy compared with twice-daily doses of vancomycin (7 - 10 days) for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) is being assessed through Phase 3 clinical trials (SOLO-1 and SOLO-2). Preliminary data from the SOLO-1 trial showed oritavancin to be non-inferior to vancomycin in the efficacy analyses for the early clinical evaluation endpoints (48 - 72 hour; Food and Drug Administration [FDA] endpoint criteria) and the later endpoints (7-14 days after end of treatment; European Medicines Agency [EMA] endpoint criteria). The efficacy was similar in the overall population and in those patients with microbiologically confirmed MRSA infections. This study reports the *in vitro* activity of oritavancin and other agents tested against key contemporary pathogens responsible for skin and soft tissue infections (SSTI) from European and Israeli hospitals.

Methods

Bacterial strain collection. *S. aureus* isolates (2,259) and β-haemolytic streptococci (BHS; 300) collected from unique hospitalized patients with documented infections in 37 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 test 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: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619. Interpretation of comparator MIC results was in accordance with published CLSI (M100-S23) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2013) criteria.

Subsets of MDR *S. aureus* and BHS strains were identified according to the resistance phenotypes. *S. aureus* strains were considered as MDR when resistant to at least four of the following drugs: oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline. MDR strains of BHS were represented by isolates displaying resistance phenotypes to at least three of the following drugs: erythromycin, clindamycin, levofloxacin and tetracycline.

Results

- Oritavancin displayed low MIC_{50} and MIC_{90} results (0.03 and 0.06 mg/L, respectively) when tested against all *S. aureus* (Table 1). Equivalent modal MIC (0.03 mg/L) and MIC_{50} (0.03 mg/L) results were observed for oritavancin when tested against subsets of resistant *S. aureus* strains, including MDR clinical isolates.
- Oritavancin ($MIC_{50/90}$, 0.03/0.06-0.12 mg/L), vancomycin ($MIC_{50/90}$, 1/1 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and linezolid ($MIC_{50/90}$, 1/1-2 mg/L) showed similar MIC_{50} and MIC_{90} results when tested against MRSA and MDR isolates (Table 2); however, oritavancin MIC_{50} values were at least eight-fold lower than those of these comparators.
- Overall, oritavancin showed MIC_{50} and MIC_{90} results of 0.06 and 0.25 mg/L, respectively, when tested against clinical isolates of BHS (Tables 1 and 2). The oritavancin MIC values obtained against Group B and MDR subsets of BHS ($MIC_{50/90}$, 0.06/0.25 mg/L) were slightly higher than those obtained against Group A BHS ($MIC_{50/90}$, 0.03/0.12 mg/L).
- Among agents tested, oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L), daptomycin ($MIC_{50/90}$, ≤0.06/0.25 mg/L) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L) exhibited lowest MIC_{50} results when tested against all BHS; while oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L), and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L) had lowest MIC_{50} values against MDR strains (Tables 1 and 2).
- Oritavancin and penicillin showed MIC_{50} values at least two- and eight-fold lower than daptomycin ($MIC_{50/90}$, 0.12/0.25 mg/L) and vancomycin ($MIC_{50/90}$, 0.5/0.5 mg/L), and at least 16-fold lower than levofloxacin ($MIC_{50/90}$, 1/2 mg/L) and linezolid ($MIC_{50/90}$, 1/1 mg/L) when tested against MDR BHS (Table 2).

Table 1. MIC distribution of oritavancin tested against *S. aureus* and β-haemolytic streptococci (BHS), including resistant subsets as part of the 2010 – 2012 international oritavancin surveillance programme.

Organism (number tested)[a]	MIC (mg/L)		Number (cumulative %) inhibited at each oritavancin MIC (mg/L)[b]						
	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
S. aureus (2,259)	0.03	0.06	59(2.6)	506(25.0)	**951(67.1)**	553(91.6)	166(98.9)	24(100.0)	
Methicillin-susceptible (1,708)	0.03	0.06	47(2.8)	381(25.1)	**711(66.7)**	429(91.8)	122(99.0)	18(100.0)	
Methicillin-resistant (551)	0.03	0.06	12(2.2)	125(24.9)	**240(68.4)**	124(90.9)	44(98.9)	6(100.0)	
Non-multidrug-resistant (2,065)	0.03	0.06	53(2.6)	462(25.0)	**868(67.0)**	513(91.8)	147(98.9)	22(100.0)	
Multidrug-resistant (194)	0.03	0.12	6(3.1)	44(25.8)	**83(68.6)**	40(89.2)	19(99.0)	2(100.0)	
BHS (300)	0.06	0.25	20(6.7)	41(20.3)	**86(49.0)**	73(73.3)	47(89.0)	30(99.0)	3(100.0)
Group A BHS (190)	0.03	0.12	14(7.4)	28(22.1)	**57(52.1)**	44(75.3)	30(91.1)	16(99.5)	1(100.0)
Group B BHS (110)	0.06	0.25	6(5.5)	13(17.3)	**29(43.6)**	**29(70.0)**	17(85.5)	14(98.2)	2(100.0)
Multidrug-resistant (17)[c]	0.06	0.25	0(0.0)	2(11.8)	3(29.4)	4(52.9)	**6(88.2)**	2(100.0)	

a. Multidrug-resistant (MDR) *S. aureus* strains are represented by isolates displaying resistance phenotypes to at least four of the following drugs: oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline. MDR strains of BHS are represented by isolates displaying resistance phenotypes to at least three of the following drugs: erythromycin, clindamycin, levofloxacin and tetracycline.
b. Modal MIC results are in bold.
c. Consists of four and 13 Group A and B BHS isolates, respectively.

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against *S. aureus* and β-haemolytic streptococci (BHS), including resistant subsets as part of the 2010 – 2012 international oritavancin surveillance programme.

Organism[a] (no. tested) / Agent	Range	MIC (mg/L)		% Susceptible/Resistant[b]	
		50%	90%	CLSI	EUCAST
MSSA (1,708)					
Oritavancin	≤0.008 – 0.25	0.03	0.06	-[c] / -	- / -
Vancomycin	0.5 – 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	2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	≤0.25	>4	85.0 / 13.8	85.0 / 14.8
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	97.8 / 2.2	97.5 / 2.2
Tetracycline	≤0.25 – >8	≤0.25	0.5	94.8 / 4.5	94.4 / 5.5
Levofloxacin	≤0.5 – >4	≤0.5	≤0.5	94.5 / 5.1	94.5 / 5.1
TMP/SMX[d]	≤0.5 – >4	≤0.5	≤0.5	99.3 / 0.7	99.3 / 0.4
MRSA (551)					
Oritavancin	≤0.008 – 0.25	0.03	0.06	- / -	- / -
Vancomycin	0.25 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 4	≤2	≤2	100.0 / 0.0	99.8 / 0.2
Daptomycin	0.12 – 2	0.25	0.5	99.6 / -	99.6 / 0.4
Linezolid	0.25 – 2	1	2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	>4	>4	34.8 / 63.3	35.4 / 64.1
Clindamycin	≤0.25 – >2	≤0.25	>2	72.1 / 27.8	71.5 / 27.9
Tetracycline	≤0.25 – >8	≤0.25	>8	87.3 / 11.6	86.9 / 12.9
Levofloxacin	≤0.5 – >4	>4	>4	16.3 / 81.9	16.3 / 81.9
TMP/SMX[d]	≤0.5 – >4	≤0.5	≤0.5	99.1 / 0.9	99.1 / 0.9
MDR *S. aureus* (194)					
Oritavancin	≤0.008 – 0.25	0.03	0.12	- / -	- / -
Oxacillin	0.5 – >2	>2	>2	0.5 / 99.5	0.5 / 99.5
Vancomycin	0.5 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 4	≤2	≤2	100.0 / 0.0	99.5 / 0.5
Daptomycin	0.12 – 2	0.25	0.5	99.0 / -	99.0 / 1.0
Linezolid	0.25 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	>4	>4	4.1 / 92.8	4.1 / 94.3
Clindamycin	≤0.25 – >2	>2	>2	21.1 / 78.9	20.6 / 78.9
Tetracycline	≤0.25 – >8	≤0.25	>8	75.3 / 24.7	74.7 / 24.7
Levofloxacin	≤0.5 – >4	>4	>4	3.6 / 93.8	3.6 / 93.8
TMP/SMX[d]	≤0.5 – >4	≤0.5	≤0.5	97.4 / 2.6	97.4 / 2.6
BHS (300)					
Oritavancin	≤0.008 – 0.5	0.06	0.25	- / -	- / -
Penicillin	≤0.06 – 0.12	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Vancomycin	0.25 – 0.5	0.25	0.5	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	- / -	100.0 / 0.0
Daptomycin	≤0.06 – 0.5	≤0.06	0.25	100.0 / -	100.0 / 0.0
Linezolid	0.25 – 1	1	1	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25 – >4	≤0.25	2	83.0 / 15.3	83.0 / 15.3
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	93.0 / 6.7	93.3 / 6.7
Tetracycline	≤0.25 – >8	0.5	>8	52.0 / 47.7	52.0 / 48.0
Levofloxacin	≤0.5 – >4	≤0.5	1	99.0 / 0.3	92.3 / 1.0
TMP/SMX[d]	≤0.5 – >4	≤0.5	≤0.5	- / -	97.3 / 2.3
MDR BHS (17)					
Oritavancin	0.015 – 0.25	0.06	0.25	- / -	- / -
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Vancomycin	0.25 – 0.5	0.5	0.5	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	- / -	100.0 / 0.0
Daptomycin	≤0.06 – 0.5	0.12	0.25	100.0 / -	100.0 / 0.0
Linezolid	0.5 – 1	1	1	100.0 / -	100.0 / 0.0
Erythromycin	0.5 – >4	>4	>4	0.0 / 94.1	0.0 / 94.1
Clindamycin	≤0.25 – >2	>2	>2	17.6 / 82.4	17.6 / 82.4
Tetracycline	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	≤0.5 – >4	1	2	94.1 / 5.9	82.4 / 5.9
TMP/SMX[d]	≤0.5 – >4	≤0.5	>4	- / -	82.4 / 11.8

a. Multidrug-resistant (MDR) *S. aureus* strains are represented by isolates displaying resistance phenotypes to at least four of the following drugs: oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline. MDR strains of BHS are represented by isolates displaying resistance phenotypes to at least three of the following drugs: erythromycin, clindamycin, levofloxacin and tetracycline.
b. Breakpoint criteria according to CLSI (M100-S23, 2013) and EUCAST (2013).
c. Breakpoints not available.
d. Trimethoprim/sulfamethoxazole.

Conclusions

- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) demonstrated potent activity against this recent (2010 - 2012) collection of *S. aureus* clinical isolates, including a subset of MDR strains responsible for SSTI in European hospitals and other regions. In addition, oritavancin inhibited 98.9% of *S. aureus* at ≤0.12 mg/L (all strains were inhibited at ≤0.25 mg/L).
- Oritavancin tested against BHS clinical isolates showed potent MIC results ($MIC_{50/90}$, 0.06/0.25 mg/L), and this agent demonstrated similar activity when tested against a subset of MDR BHS strains.
- Oritavancin continues to exhibit potent antimicrobial activity against *S. aureus* and BHS, the main pathogens responsible for SSTI. These *in vitro* surveillance results will provide a benchmark for oritavancin against current pathogens as this agent progresses through clinical development.

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