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Analysis of Oritavancin Activity Tested Against a Challenge Set of *Staphylococcus aureus* from Europe (2008-2010)

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Abstract

Objectives: To assess the activities of oritavancin and comparators tested against *Staphylococcus aureus* from Europe. In addition, this analysis includes categorization of strains with decreased susceptibility to vancomycin, teicoplanin and daptomycin. Oritavancin has demonstrated potent activity against Gram-positive isolates, including vancomycin-resistant staphylococcal and enterococcal strains. Moreover, it has been demonstrated that oritavancin possesses multiple mechanisms of action.

Methods: A total of 7,053 consecutive, non-duplicate *S. aureus* were collected from 29 hospitals in 13 Europe countries, including Turkey and Israel, as part of the SENTRY Antimicrobial Surveillance Program. Isolates were submitted to a central monitoring laboratory and species identification confirmed by conventional parameters and Vitek 2, as needed. Isolates were tested for susceptibility using CLSI methods (M07-A8, 2009). EUCAST (2011) and CLSI (2011) interpretive criteria were applied, when available. Oritavancin activity was also evaluated against a challenge set of strains displaying higher MIC values for vancomycin (2 mg/L), teicoplanin (2 – 8 mg/L) and daptomycin (1 – 2 mg/L).

Results: Most isolates were from bacteremia (38.5%) and skin and skin structure infections (37.8%). 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) and linezolid ($MIC_{50/90}$, 1/2 mg/L) when tested against all *S. aureus*. Oritavancin exhibited similar potency when tested against methicillin-susceptible *S. aureus* (MSSA) with decreased susceptibility to vancomycin ($MIC_{50/90}$, 0.03/0.06 mg/L), teicoplanin ($MIC_{50/90}$, 0.03/0.06 mg/L) or daptomycin ($MIC_{50/90}$, 0.03/0.12 mg/L) compared to their respective counterparts with lower MIC results (all $MIC_{50/90}$, 0.03/0.06 mg/L). When oritavancin was tested against a challenge set of methicillin-resistant *S. aureus* (MRSA), slightly higher (two- to four-fold) $MIC_{50/90}$ values were noted for those strains with elevated MIC results for vancomycin ($MIC_{50/90}$, 0.03/0.12 mg/L), teicoplanin ($MIC_{50/90}$, 0.03/0.12 mg/L) and daptomycin ($MIC_{50/90}$, 0.06/0.25 mg/L).

Conclusions: Oritavancin exhibited overall greater potency (≥eight-fold) than main comparators against all *S. aureus*. When tested against a challenge set of MSSA clinical isolates, oritavancin sustained high activity. Oritavancin showed higher MIC values against MRSA strains with elevated MIC results for vancomycin, teicoplanin and daptomycin, yet inhibiting all *S. aureus* at ≤0.25 mg/L. The oritavancin multiple mechanisms of actions likely provide advantageous *in vitro* activity even against isolates with decreased susceptibility to same class agents.

Introduction

Oritavancin is a semisynthetic lipoglycopeptide under final stages of clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI). This compound is derived from the addition of a 4'-chlorobiphenylmethyl side chain to a naturally occurring vancomycin-like molecule, chloroeremomycin. This modification imparts to oritavancin enhanced activity, including against vancomycin-resistant enterococci (VRE) and *Staphylococcus aureus* (VRSA), and a unique pharmacokinetic-pharmacodynamic profile.

Recent studies have demonstrated that oritavancin has multiple mechanisms of action. This drug shares with vancomycin the ability to block transglycosylation. However, oritavancin also exerts an intermediate effect on transpeptidation. In addition, oritavancin induces membrane permeabilization along with changes in bacterial membrane integrity by collapsing transmembrane electrochemical potential and may partially inhibit RNA synthesis. This study aimed to assess the activities of oritavancin and comparators tested against *S. aureus* from Europe. Moreover, this analysis includes categorization of strains with decreased susceptibility to vancomycin, teicoplanin and/or daptomycin.

Methods

Bacterial isolates. A total of 7,053 consecutive, non-duplicate *S. aureus* were collected from 29 hospitals in 13 European countries, including Turkey and Israel, as part of the SENTRY Antimicrobial Surveillance Program. Isolates were mostly collected from blood cultures (38.5%) and skin and skin structure infections (37.8%). Clinical strains were submitted to a central microbiology laboratory and local bacterial species identifications were confirmed by Gram's stain, standard biochemical tests and the automated Vitek 2 System (bioMérieux, Hazelwood, Missouri, USA), as needed.

Antimicrobial susceptibility testing. All isolates were tested for susceptibility by reference broth microdilution methods following the Clinical Laboratory Standards Institute (CLSI) recommendations (M07-A8, 2009). Susceptibility testing was performed in validated dry-form panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). The applied dry-form formulation provides equivalent oritavancin minimum inhibitory concentration (MIC) results to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80 (M100-S21, 2011).

Methods-Continued

Quality assurance of the MIC values obtained was performed by concurrent testing of CLSI-recommended (M100-S21, 2011) quality control (QC) strains: *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213. MIC ranges for oritavancin and comparators tested against ATCC QC strains were those recently published in the CLSI M100-S21 (2011) document. All results were within published ranges.

Interpretations of comparator MIC values were performed using the CLSI (M100-S21, 2011) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2011) criteria, when available. Analysis of oritavancin activity was performed against a challenge set of strains displaying elevated MIC values for vancomycin (2 mg/L), teicoplanin (2 – 8 mg/L) and/or daptomycin (1 – 2 mg/L).

Results-1

- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) exhibited potent activity when tested against methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA; **Table 1**).
- When tested against subsets of MSSA strains displaying higher MIC results for vancomycin (MIC, 2 mg/L), teicoplanin (MIC, >1 mg/L) or daptomycin (MIC, 1 mg/L), oritavancin ($MIC_{50/90}$, 0.03/0.06-0.12 mg/L) demonstrated modal MIC values equivalent to their respective counterparts with lower MIC results (all $MIC_{50/90}$, 0.03/0.06 mg/L; **Table 1**).
- MRSA strains with vancomycin and teicoplanin MIC values of 2 mg/L and >1 mg/L, respectively, demonstrated oritavancin MIC_{90} results (0.12 mg/L for both) that were two-fold higher than those isolates with lower MIC results for these marketed glycopeptides (**Table 1**).
- Only 1.2 % (22/1,811) of the MRSA clinical isolates exhibited a daptomycin MIC result of 1 – 2 mg/L. When tested against this subset of strains, oritavancin showed MIC_{50} (0.06 mg/L) and MIC_{90} (0.25 mg/mL) values that were two- and four-fold higher, respectively, than those obtained against strains with lower MIC results for daptomycin ($MIC_{50/90}$, 0.03/0.06 mg/L; **Table 1**).

Results-2

- Overall, oritavancin (MIC_{90}, 0.06 mg/L) exhibited MIC_{90} values, respectively, eight-, 16- and 32-fold lower than daptomycin (MIC_{90}, 0.5 mg/L; 99.9% susceptible), vancomycin (MIC_{90}, 1 mg/L; 100.0% susceptible) and linezolid (MIC_{90}, 2 mg/L; 98.0% susceptible; **Table 2**) when tested against all MRSA strains.
- All comparator agents demonstrated broad coverage (≥93.8% susceptible) against a collection of MSSA clinical isolates, except for erythromycin (84.7% susceptible; **Table 2**).

Table 1. MIC distribution of oritavancin tested against *S. aureus* and subsets of organisms submitted as part of the 2008 – 2010 international oritavancin surveillance program.

Organism Subset [a] (no. tested)	MIC (mg/L)		Number (cumulative %) inhibited at oritavancin MIC (mg/L) of [b]:					
	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25
MSSA								
All (5,242)	0.03	0.06	189(3.6)	1592(34.0)	**2552(82.7)**	789(97.7)	108(99.8)	12(100.0)
Vancomycin MIC, <2 mg/L (5,181)	0.03	0.06	189(3.6)	1578(34.1)	**2528(82.9)**	770(97.8)	106(99.8)	10(100.0)
Vancomycin MIC, 2 mg/L (61)	0.03	0.06	0(0.0)	14(23.0)	**24(62.3)**	19(93.4)	2(96.7)	2(100.0)
Teicoplanin MIC, <2 mg/L (5,224)	0.03	0.06	189(3.6)	1587(34.0)	**2547(82.7)**	784(97.7)	107(99.8)	11(100.0)
Teicoplanin MIC, 2 – 8 mg/L (18)	0.03	0.12	1(5.6)	5(33.3)	5(61.1)	5(88.9)	1(94.4)	1(100.0)
Daptomycin MIC, <1 mg/L (5,218)	0.03	0.06	189(3.6)	1588(34.1)	**2537(82.7)**	784(97.7)	108(99.8)	12(100.0)
Daptomycin MIC, 1 mg/L (24)	0.03	0.06	0(0.0)	4(16.7)	**15(79.2)**	5(100.0)	–	–
MRSA								
All (1,811)	0.03	0.06	53(2.9)	525(31.9)	**911(82.2)**	266(96.9)	46(99.5)	9(>99.9)
Vancomycin MIC, <2 mg/L (1,771)	0.03	0.06	52(2.9)	524(32.5)	**893(82.9)**	252(97.2)	42(99.5)	7(>99.9.0)
Vancomycin MIC, 2 mg/L (40)	0.03	0.12	1(2.5)	1(5.0)	**18(50.0)**	14(85.0)	4(95.0)	2(100.0)
Teicoplanin MIC, <2 mg/L (1,773)	0.03	0.06	53(3.0)	520(32.3)	**894(82.7)**	255(97.1)	43(99.5)	7(>99.9)
Teicoplanin MIC, 2 – 8 mg/L (38)	0.03	0.12	0(0.0)	5(13.2)	**17(57.9)**	11(86.8)	3(94.7)	2(100.0)
Daptomycin MIC, <1 mg/L (1,788)	0.03	0.06	52(2.9)	523(32.2)	**903(82.7)**	259(97.1)	44(99.6)	6(>99.9)
Daptomycin MIC, 1 – 2 mg/L (22)	0.06	0.25	1(4.5)	2(13.6)	**7(45.5)**	**7(77.3)**	2(86.4)	3(100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*.
b. Modal MIC results are in bold, when known.

Table 2. Antimicrobial activity of oritavancin and comparators tested against methicillin-susceptible and -resistant *S. aureus* collected as part of the 2008 – 2010 international oritavancin surveillance program.

Antimicrobial agent (no. tested)	MIC (mg/L)		% susceptible / % resistant [a]		Antimicrobial agent (no. tested)	MIC (mg/L)		% susceptible / % resistant [a]	
	50%	90%	CLSI	EUCAST		50%	90%	CLSI	EUCAST
MRSA (1,181)					MSSA (5,242)				
Oritavancin	0.03	0.06	- [b] / -	- / -	Oritavancin	0.03	0.06	- / -	- / -
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0	Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤1	≤1	100.0 / 0.0	98.6 / 1.4	Teicoplanin	≤1	≤1	100.0 / 0.0	99.8 / 0.2
Daptomycin	0.25	0.5	99.9 / -	99.9 / 0.1	Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0	Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	32.6 / 66.4	33.3 / 66.5	Erythromycin	≤0.25	>2	84.1 / 14.7	84.7 / 14.9
Clindamycin	≤0.25	>2	64.2 / 35.5	63.4 / 35.8	Clindamycin	≤0.25	≤0.25	97.7 / 2.1	97.2 / 2.3
Tetracycline	≤2	>8	84.3 / 14.6	83.7 / 16.0	Tetracycline	≤2	≤2	94.7 / 4.7	94.3 / 5.6
Levofloxacin	>4	>4	12.5 / 86.7	12.5 / 86.7	Levofloxacin	≤0.5	≤0.5	93.8 / 5.7	93.8 / 5.7
Trim/sulfa [c]	≤0.5	≤0.5	98.0 / 2.0	98.0 / 2.0	Trim/sulfa [c]	≤0.5	≤0.5	99.5 / 0.5	99.5 / 0.5

a. Breakpoint susceptibility criteria as published by CLSI M100-S21 (2011) and EUCAST (2011).
b. –, indicates no susceptibility and/or resistant breakpoints are available for the respective drug/organism combination.
c. Trimethoprim/sulfamethoxazole

Conclusions

- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) exhibited sustained *in vitro* potency when tested against MSSA strains, regardless of the stratification analysis performed. The only exception was a one doubling dilution increase in the oritavancin MIC_{90} result ($MIC_{50/90}$, 0.03/0.12 mg/L) when tested against a subset of strains with decreased susceptibility to teicoplanin (MIC, 2 – 8 mg/L).
- MRSA strains with elevated MIC values for marketed glycopeptides or for daptomycin exhibited oritavancin MIC values that were two- to four-fold higher than the comparator subsets of isolates. However, oritavancin inhibited all strains at ≤0.25 mg/L.
- Overall, oritavancin displayed activity against MRSA that was ≥eight-fold more potent than those of other clinically available anti-Gram-positive agents. These *in vitro* data warrant continued longitudinal surveillance to monitor for oritavancin activity against *S. aureus* in Europe as this agent advances into Phase 3 trials.

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