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Assessment of Oritavancin Activity Tested Against β-haemolytic Streptococci Responsible for Skin and Skin Structure Infections in Europe (2008-2010)

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Abstract

Objectives: To evaluate the antimicrobial activity of oritavancin and comparator agents tested against β-haemolytic streptococci (BHS) responsible for documented skin infections in hospitalized patients from Europe. Oritavancin is under final clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in the United States and Europe.

Methods: BHS isolates (457) were consecutively collected from 29 hospitals in 13 European nations, including Turkey and Israel, as part of the SENTRY Antimicrobial Surveillance Program. Isolates were submitted to a central laboratory where bacterial identifications were confirmed using standard algorithms and Vitek 2. Isolates were tested for susceptibility by CLSI methods (M07-A8, 2009). EUCAST (2011) and CLSI (2011) interpretative criteria were applied. Isolates displaying resistance to erythromycin and clindamycin and tetracycline were considered multidrug-resistant (MDR).

Results: Overall, oritavancin (MIC_{90}, 0.12 mg/L) and penicillin (MIC_{90}, 0.06 mg/L; 100% susceptible) showed similar potency against all BHS. Oritavancin (MIC_{90}, 0.12 mg/L) was two-fold more active than daptomycin (MIC_{90}, 0.25 mg/L, 100% susceptible) and four- to eight-fold more active than vancomycin (MIC_{90}, 0.5 mg/L, 100% susceptible), linezolid (MIC_{90}, 1 mg/L, 100% susceptible) and levofloxacin (MIC_{90}, 1 mg/L, 95.0% susceptible [EUCAST]). Clindamycin (91.4% susceptible) was active against BHS, while erythromycin (81.2% susceptible) and tetracycline (51.6% susceptible) showed more limited coverage when EUCAST criteria were applied. Oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L) exhibited slightly higher (two-fold) MIC results against year 2010 isolates compared to previous years ($MIC_{50/90}$, 0.03/0.12 mg/L). Vancomycin, daptomycin, linezolid, levofloxacin and penicillin remained active (≥92.9% susceptible) when tested against MDR strains. Oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L) exhibited equivalent MIC_{90} values compared to daptomycin ($MIC_{50/90}$, 0.25/0.25 mg/L) against MDR BHS; however, oritavancin was two- to 16-fold more active than vancomycin ($MIC_{50/90}$, 0.5/0.5 mg/L) and linezolid ($MIC_{50/90}$, 1/1 mg/L) against MDR strains. Oritavancin ($MIC_{50/90}$, 0.03/0.12 mg/L) was slightly (two-fold) more active against Groups A and C BHS when compared with Groups B and G ($MIC_{50/90}$, 0.06/0.25 mg/L).

Conclusions: Based on MIC_{90} values, oritavancin showed *in vitro* activity equivalent to or greater than those of comparator agents with similar clinical indications, tested against a contemporary collection of BHS. In addition, oritavancin inhibited >99% of all BHS at ≤0.25 mg/L.

Introduction

Oritavancin is a semisynthetic lipoglycopeptide currently under clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients. Potent *in vitro* activity against Gram-positive organisms, including vancomycin-resistant enterococci (VRE) and *Staphylococcus aureus* (VRSA), has been demonstrated for this compound in recent investigational and surveillance reports.

This *in vitro* activity is attributed to multiple mechanisms of action which include inhibition of cell wall synthesis at the level of both transglycosylation and transpeptidation, increase of membrane permeability and effect on the transmembrane electrochemical potential and possibly partial inhibition of RNA synthesis. The combination of these mechanisms provides oritavancin with a rapidly bactericidal and concentration-dependent killing. The objective of this study was to evaluate the activities of oritavancin and comparators tested against β-haemolytic streptococci (BHS) clinical isolates from Europe.

Methods

Bacterial isolates. A total of 457 consecutive, non-duplicate BHS responsible for documented ABSSSIs were collected from 29 hospitals in 13 European countries, including Turkey and Israel, as part of the SENTRY Antimicrobial Surveillance Program. Clinical strains were submitted to a central monitoring 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 oritavancin minimum inhibitory concentration (MIC) results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80 (M100-S21, 2011).

Quality assurance of the MIC values obtained was performed by concurrent testing of the CLSI-recommended (M100-S21, 2011) quality control (QC) *Streptococcus pneumoniae* ATCC 49619 strain. MIC ranges for oritavancin and comparators tested against the ATCC QC strain were those recently published in the CLSI M100-S21 (2011) document. All results were within published ranges.

Methods-Continued

Interpretations of comparator MIC results were performed using the CLSI (M100-S21, 2011) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2011) criteria, where available. Evaluation of oritavancin activity included analysis against isolates displaying a resistance phenotype (CLSI criteria) to erythromycin (MIC, ≥1 mg/L) and clindamycin (MIC, ≥1 mg/L) and tetracycline (≥8 mg/L), which were considered multidrug-resistant (MDR). Isolates displaying susceptibility (CLSI criteria) to erythromycin (≤0.25 mg/L) and clindamycin (≤0.25 mg/L) and tetracycline (≤2 mg/L) were used as a wildtype control group for comparison purposes.

Results-1

- Overall, oritavancin ($MIC_{50/90}$, 0.06/0.12 mg/L) exhibited potent activity when tested against this contemporary (2008 – 2010) European collection of BHS clinical isolates, inhibiting all strains at ≤1 mg/L (**Table 1**).
- When the BHS isolates were stratified by year, oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L) demonstrated slightly higher (two-fold) MIC values against year 2010 strains compared to those results obtained during the 2008 – 2009 sampling year ($MIC_{50/90}$, 0.03/0.12 mg/L; **Table 1**).
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 mg/L) was marginally (two-fold) more active when tested against serogroup A and C BHS compared with strains from serogroup B and G ($MIC_{50/90}$, 0.06/0.25 mg/L; **Table 1**).
- A total of 6.1 % (28/457) of the BHS clinical isolates exhibited a MDR phenotype. When tested against this MDR subset, oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L) showed MIC values two-fold higher than those observed for the control group of wildtype strains ($MIC_{50/90}$, 0.03/0.12 mg/L; **Table 1**).
- Overall, oritavancin ($MIC_{50/90}$, 0.06/0.12 mg/L) and penicillin ($MIC_{50/90}$, ≤0.03/0.06 mg/L; 100.0% susceptible) were the most active compounds tested against all BHS (**Table 2**).
- Oritavancin (MIC_{90}, 0.12 mg/L) was two-fold more active than daptomycin (MIC_{90}, 0.25 mg/L, 100% susceptible) and four- to eight-fold more potent than vancomycin (MIC_{90}, 0.5 mg/L, 100% susceptible), linezolid (MIC_{90}, 1 mg/L, 100% susceptible) and levofloxacin (MIC_{90}, 1 mg/L, 95.0% susceptible [EUCAST]; **Table 2**).

Results-2

- When tested against serogroup B BHS, oritavancin (MIC_{90}, 0.25 mg/L) and penicillin (MIC_{90}, 0.06 mg/L) MIC_{90} values were two-fold higher than those obtained when testing serogroup A strains (MIC_{90}, 0.12 and 0.03 mg/L, respectively; **Table 2**). Similarly, the daptomycin MIC_{90} result (MIC_{90}, 0.25 mg/L) tested against serogroup B strains was at least four-fold higher than that obtained against serogroup A BHS (MIC_{90}, ≤0.06 mg/L).
- Based on MIC_{90} values, oritavancin (MIC_{90}, 0.25 mg/L) was four-fold less active than penicillin (MIC_{90}, 0.06 mg/L) when tested against MDR BHS isolates (**Table 2**). In addition, when tested against these MDR strains, oritavancin ($MIC_{50/90}$, 0.06/0.25 mg/L) and daptomycin ($MIC_{50/90}$, 0.25/0.25 mg/L) exhibited similar potencies (MIC_{90} values), which were two- to four-fold more active than vancomycin ($MIC_{50/90}$, 0.5/0.5 mg/L) and linezolid ($MIC_{50/90}$, 1/1 mg/L).

Table 1. MIC distribution of oritavancin tested against β-haemolytic streptococci and subsets of organisms collected from Europe and submitted as part of the 2008 – 2010 international oritavancin surveillance program.

Organism Subset (no. tested)	MIC (mg/L)		Number (cumulative %) inhibited at oritavancin MIC (mg/L) of [a]:						
	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All [b] (457)	0.06	0.12	36(7.9)	49(18.6)	124(45.7)	**129(74.0)**	78(91.0)	38(99.3)	2(99.8)
2008 (79)	0.03	0.12	2(2.5)	8(12.7)	**32(53.2)**	27(87.3)	8(97.5)	1(98.7)	0(98.7)
2009 (147)	0.03	0.12	21(14.3)	25(31.3)	**47(63.3)**	29(83.0)	18(95.2)	5(98.6)	2(100.0)
2010 (231)	0.06	0.25	13(5.6)	16(12.6)	45(32.0)	**73(63.6)**	52(86.2)	32(100.0)	–
Group A (162)	0.03	0.12	20(12.4)	25(27.8)	**43(54.3)**	41(79.6)	22(93.2)	10(99.4)	0(99.4)
Group B (161)	0.06	0.25	4(2.5)	13(10.6)	46(39.1)	**53(72.0)**	28(89.4)	15(98.8)	2(100.0)
Group C (27)	0.03	0.12	4(14.8)	2(22.2)	**8(51.9)**	7(77.8)	5(96.3)	1(100.0)	–
Group G (86)	0.06	0.25	3(3.5)	8(12.8)	**23(39.5)**	24(67.4)	18(88.4)	10(100.0)	–
Wildtype [c] (201)	0.03	0.12	24(11.9)	29(26.2)	48(50.0)	**54(76.7)**	31(92.1)	14(99.0)	1(100.0)
Erythromycin-resistant (77)	0.03	0.12	4(5.2)	8(15.6)	**28(52.0)**	14(70.1)	15(90.0)	7(98.7)	1(100.0)
Clindamycin-resistant (39)	0.06	0.25	1(2.6)	5(15.4)	**10(41.0)**	9(64.1)	8(84.6)	5(97.4)	1(100.0)
Tetracycline-resistant (200)	0.06	0.25	8(4.0)	17(12.5)	56(40.5)	**61(71.0)**	35(88.5)	22(99.5)	1(100.0)
MDR [d] (28)	0.06	0.25	0(0.0)	4(14.3)	6(35.7)	**9(67.9)**	5(85.7)	3(96.4)	1(100.0)

a. Modal MIC results are in bold.
b. Includes: *Streptococcus dysgalactiae* (14 strains), *Streptococcus equi* (2 strains), *Streptococcus equisimilis* (1 strain), Group A streptococci (162 strains), Group B streptococci (161 strains), Group C streptococci (27 strains), Group F streptococci (4 strains), and Group G streptococci (86 strains).
c. Isolates displaying susceptibility to erythromycin (≤0.25 mg/L) and clindamycin (≤0.25 mg/L) and tetracycline (≤2 mg/L).
d. Isolates displaying resistance to erythromycin (≥1 mg/L) and clindamycin (≥1 mg/L) and tetracycline (≥8 mg/L).

Table 2. Antimicrobial activity of oritavancin and comparators tested against β-haemolytic streptococci collected in Europe 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
All [b] (457)					Group B (161)				
Oritavancin	0.06	0.12	- [c] / -	- / -	Oritavancin	0.06	0.25	- / -	- / -
Penicillin	≤0.03	0.06	100.0 / -	100.0 / 0.0	Penicillin	0.06	0.06	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	100.0 / -	100.0 / 0.0	Vancomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	- / -	100.0 / 0.0	Teicoplanin	≤2	≤2	- / -	100.0 / 0.0
Daptomycin	≤0.06	0.25	100.0 / -	100.0 / 0.0	Daptomycin	0.25	0.25	100.0 / -	100.0 / 0.0
Linezolid	1	1	100.0 / -	100.0 / 0.0	Linezolid	1	1	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	81.2 / 16.8	81.2 / 16.8	Erythromycin	≤0.25	>2	75.8 / 20.5	75.8 / 20.5
Clindamycin	≤0.25	≤0.25	90.8 / 8.6	91.4 / 8.6	Clindamycin	≤0.25	>2	83.1 / 15.0	85.0 / 15.0
Tetracycline	≤2	>8	51.6 / 43.8	51.6 / 48.4	Tetracycline	>8	>8	18.6 / 81.4	18.6 / 81.4
Levofloxacin	≤0.5	1	98.9 / 0.4	95.0 / 1.1	Levofloxacin	≤0.5	1	99.4 / 0.6	96.9 / 0.6
Trim/sulfa [d]	≤0.5	≤0.5	- / -	98.5 / 1.1	Trim/sulfa	≤0.5	≤0.5	- / -	99.4 / 0.0
Group A (162)					MDR [e] (28)				
Oritavancin	0.03	0.12	- / -	- / -	Oritavancin	0.06	0.25	- / -	- / -
Penicillin	≤0.03	0.03	100.0 / -	100.0 / 0.0	Penicillin	0.06	0.06	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	100.0 / -	100.0 / 0.0	Vancomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	- / -	100.0 / 0.0	Teicoplanin	≤2	≤2	- / -	100.0 / 0.0
Daptomycin	≤0.06	≤0.06	100.0 / -	100.0 / 0.0	Daptomycin	0.25	0.25	100.0 / -	100.0 / 0.0
Linezolid	1	1	100.0 / -	100.0 / 0.0	Linezolid	1	1	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	90.7 / 8.0	90.7 / 8.0	Levofloxacin	≤0.5	1	100.0 / 0.0	92.9 / 0.0
Clindamycin	≤0.25	≤0.25	96.3 / 3.7	96.3 / 3.7	Trim/sulfa	≤0.5	≤0.5	- / -	100.0 / 0.0
Tetracycline	≤2	>8	84.0 / 14.2	84.0 / 16.0					
Levofloxacin	≤0.5	1	98.8 / 0.0	92.0 / 1.2					
Trim/sulfa	≤0.5	≤0.5	- / -	96.9 / 2.5					

a. Breakpoint susceptibility criteria as published by CLSI M100-S21 (2011) and EUCAST (2011).
b. Includes: *Streptococcus dysgalactiae* (14 strains), *Streptococcus equi* (2 strains), *Streptococcus equisimilis* (1 strain), Group A streptococci (162 strains), Group B streptococci (161 strains), Group C streptococci (27 strains), Group F streptococci (4 strains), and Group G streptococci (86 strains).
c. –, indicates that no susceptibility and/or resistant breakpoints are available for the respective drug/organism combination.
d. Trimethoprim/sulfamethoxazole.
e. Isolates displaying resistance to erythromycin (≥1 mg/L) and clindamycin (≥1 mg/L) and tetracycline (≥8 mg/L).

Conclusions

- Based on MIC_{90} values, oritavancin showed *in vitro* activity equivalent to or greater than those of comparator agents with similar clinical indications tested against this contemporary collection of BHS (457 strains from Europe).
- Oritavancin was slightly (two-fold) less active when tested against MDR (resistant to three drug classes) strains compared with the activity results observed against wildtype strains. However, all MDR isolates were inhibited by oritavancin MIC results of ≤0.5 mg/L.
- These *in vitro* data on the activity of oritavancin tested against recent European BHS supports continued longitudinal surveillance for monitoring and establishing baseline MIC data prior to clinical introduction of oritavancin.

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