In vitro Activity of Oritavancin Against Streptococcal Clinical Isolates, Including Macrolide- and/or Lincosamide (Constitutive)-resistant and Multidrug-resistant Isolates from European Hospitals (2010-2013)

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Abstract

Objectives: To evaluate the *in vitro* activity of oritavancin against a current collection of streptococci, including resistance subsets from European countries and adjacent geographic regions. Oritavancin was approved (August, 2014) by the United States FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSI).

Methods: 2569 streptococci collected from 12 European countries (37 sites), and Russia (3 sites), Turkey (3 sites) and Israel (one site) were included. Isolates were submitted to a monitoring laboratory as part of the SENTRY Antimicrobial Surveillance Programme. Identification was confirmed and susceptibility testing performed by CLSI methods. MIC interpretation used the USA-FDA (oritavancin), and CLSI (2014) and/or EUCAST (2014) criteria. Isolates were segregated based on erythromycin and clindamycin resistance phenotypes (CLSI). Isolates exhibiting resistance phenotypes (CLSI) to at least 3 classes of drugs were considered as multidrug-resistant (MDR).

Results: 9.8, 8.1 and 6.4% of beta-haemolytic streptococci (BHS) displayed erythromycin resistance, erythromycin and clindamycin resistance and MDR phenotype, respectively. Oritavancin (98.5 – 100.0% susceptible using US FDA breakpoints) demonstrated modal MIC (0.03 mg/L) and MIC_{50} (0.03 mg/L) values that were the same for all BHS or drug-resistant subsets, including MDR. Overall, oritavancin and penicillin showed consistent MIC_{50} values against all BHS and drug-resistant subsets. Vancomycin and daptomycin had MIC_{50} values two- to four-fold higher when tested against erythromycin- and clindamycin-resistant or MDR subsets of BHS compared with susceptible isolates. These vancomycin and daptomycin MIC_{50} results were due to higher MICs observed against *S. agalactiae*. Oritavancin showed an MIC_{50} value of 0.06 mg/L against *S. dysgalactiae*, which was similar to those of daptomycin (MIC_{50}, ≤0.06 mg/L) and penicillin (MIC_{50}, ≤0.06 mg/L). Levofloxacin (93.8 – 99.1% susceptible), linezolid (100.0% susceptible) and trimethoprim-sulfamethoxazole (96.5 – 98.5% susceptible) also showed coverage against all BHS and drug-resistant subsets. Among viridans group streptococci (VGS), 28.3, 12.7 and 11.6% showed erythromycin resistance, erythromycin and clindamycin resistance and MDR phenotype, respectively. Oritavancin (99.9 – 100.0% susceptible using US FDA breakpoints) had low MICs against all VGS and drug-resistant subsets. Oritavancin ($MIC_{50/90}$, ≤0.008/0.06 mg/L), vancomycin ($MIC_{50/90}$, 0.5/0.5-1 mg/L), daptomycin ($MIC_{50/90}$, 0.25-0.5/0.5-1 mg/L), linezolid ($MIC_{50/90}$, 0.5-1/1 mg/L) and levofloxacin ($MIC_{50/90}$, 1/2 mg/L) showed consistent potencies against VGS and drug-resistant subsets, except for levofloxacin ($MIC_{50/90}$, 1/>4 mg/L) that had decreased activity against MDR.

Conclusions: Overall, oritavancin demonstrated potency similar to or greater than comparators against this recent collection of streptococci, including drug-resistant subsets from European and adjacent countries.

Introduction

Streptococcal isolates are important human pathogens that cause a variety of clinical manifestations. *Streptococcus pyogenes* causes an estimated 700 million cases of mild, non-invasive infections each year worldwide, of which approximately 650,000 progress to severe invasive (at a sterile site) infections with an associated mortality of approximately 25%. *S. pyogenes* causing an estimated 11,500 cases of invasive disease and 1,100 deaths in the United States (US) in 2013, mainly among patients older than 65 years. Invasive infections due to *Streptococcus agalactiae* were second with an estimate of 28,500 cases and 1,750 deaths. Moreover, although *Staphylococcus aureus* is responsible for most acute bacterial skin and skin structure infections (ABSSSIs), *S. pyogenes*, *S. agalactiae*, *Streptococcus dysgalatiae* and *Streptococcus anginosus* group are associated with approximately 15% of the cases.

Oritavancin (ORBACTIV™, oritavancin for injection) is a semisynthetic bactericidal lipoglycopeptide approved by the US Food and Drug Administration (FDA) for the treatment of adults with ABSSSIs caused by *S. aureus* (including methicillin-susceptible [MSSA] and -resistant *S. aureus* [MRSA]), *S. pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only). The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion in January 2015, recommending the granting of a marketing authorisation for oritavancin for the treatment of ABSSSI in adults. This study evaluated the *in vitro* activity of oritavancin against a current collection of β-haemolytic (BHS) and viridans group (VGS) streptococci, including resistance subsets from European countries and adjacent geographic regions.

Methods

Bacterial strain collection. A total of 2,569 streptococci (1,759 BHS and 810 VGS) collected from 12 European countries (37 sites), and Russia (3 sites), Turkey (3 sites) and Israel (one site) during 2010-2013 were included. Selected isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Programme. Isolates were primarily identified by the participating laboratory and identification confirmed by the reference monitoring laboratory (JMI Laboratories) using Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods. Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Testing was performed using panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These panels provide oritavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strain (*Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges (M100-S25). MIC interpretations were based on the FDA (oritavancin), and CLSI M100-S25 (2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2015) breakpoint criteria, as available. The *in vitro* activities of oritavancin and comparator agents were evaluated according to resistance phenotypes (CLSI criteria), including multidrug resistance (MDR) defined as resistance to at least three other classes of drugs.

Results

- A total of 9.8, 8.1 and 6.4% of BHS displayed erythromycin resistance alone, erythromycin and clindamycin (constitutive) resistance, and MDR phenotype, respectively (Table 1). These rates were higher among *S. agalactiae* (9.8, 14.5 and 13.4%, respectively) when compared with *S. pyogenes* (7.7, 3.3 and 1.8%, respectively).
- Oritavancin (95.7 – 100.0% susceptible using US FDA breakpoints) demonstrated MIC_{50} (0.03 mg/L) values that were the same for *S. pyogenes, S. agalactiae* and the respective drug-resistant subsets, including MDR (Table 1).
- Vancomycin and daptomycin tested against *S. pyogenes* had MIC_{50} values of 0.25 mg/L and ≤0.06 mg/L, respectively, while higher MIC results were observed for these agents when tested against *S. agalactiae* (MIC_{50}, 0.5 and 0.25 mg/L, respectively; Table 2).
- Oritavancin showed MIC_{50} values against *S. pyogenes* and *S. agalactiae* (MIC_{50}, 0.03 mg/L) that were two-fold lower than that obtained against *S. dysgalactiae* (MIC_{50}, 0.06 mg/L). The latter MIC_{50} value was similar to those of daptomycin (MIC_{50}, ≤0.06 mg/L; 100.0% susceptible) and penicillin (MIC_{50}, ≤0.06 mg/L; 100.0% susceptible; Table 2).

Table 1. Antimicrobial activity and MIC distribution for oritavancin against contemporary (2010 – 2013) streptococcal clinical isolates displaying several antimicrobial susceptibility phenotypes.

Group/Organism[a] Phenotype[b] (no. tested)	MIC (mg/L)		Number (cumulative %) inhibited at oritavancin MIC (mg/L) of:						
	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
BHS (1,759)	**0.03**	**0.25**	**146 (8.3)**	**379 (29.8)**	**424 (54.0)**	**347 (73.7)**	**268 (88.9)**	**170 (98.6)**	**25 (100.0)**
***S. pyogenes* (756)**	**0.03**	**0.12**	**76 (10.1)**	**180 (33.9)**	**194 (59.5)**	**130 (76.7)**	**108 (91.0)**	**59 (98.8)**	**9 (100.0)**
ERY-R, CLI-S (58)	0.03	0.12	8 (13.8)	17 (43.1)	17 (72.4)	4 (79.3)	9 (94.8)	3 (100.0)	
ERY-R, CLI-R (23)	0.03	0.12	3 (13.0)	6 (39.1)	3 (52.2)	4 (69.6)	5 (91.3)	1 (95.7)	1 (100.0)
MDR (14)	0.03	0.12	1 (7.1)	4 (35.7)	3 (57.1)	4 (85.7)	2 (100.0)		
Non-MDR (742)	0.03	0.12	75 (10.1)	176 (33.8)	191 (59.6)	126 (76.5)	106 (90.8)	59 (98.8)	9 (100.0)
***S. agalactiae* (640)**	**0.03**	**0.12**	**44 (6.9)**	**154 (30.9)**	**174 (58.1)**	**129 (78.3)**	**81 (90.9)**	**51 (98.9)**	**7 (100.0)**
ERY-R, CLI-S (63)	0.03	0.12	5 (7.9)	13 (28.6)	17 (55.6)	13 (76.2)	10 (92.1)	5 (100.0)	
ERY-R, CLI-R (93)	0.03	0.25	7 (7.5)	18 (26.9)	29 (58.1)	17 (76.3)	11 (88.2)	11 (100.0)	
MDR (86)	0.03	0.25	6 (7.0)	17 (26.7)	26 (57.0)	17 (76.7)	10 (88.4)	10 (100.0)	
Non-MDR (554)	0.03	0.12	38 (6.9)	137 (31.6)	148 (58.3)	112 (78.5)	71 (91.3)	41 (98.7)	7 (100.0)
***S. dysgalactiae* (107)**	**0.06**	**0.25**	**5 (4.7)**	**14 (17.8)**	**13 (29.9)**	**32 (59.8)**	**20 (78.5)**	**23 (100.0)**	
ERY-R, CLI-S (15)	0.06	0.25	2 (13.3)	3 (33.3)	1 (40.0)	6 (80.0)	0 (80.0)	3 (100.0)	
Non-MDR (106)	0.06	0.25	5 (4.7)	14 (17.9)	13 (30.2)	32 (60.4)	20 (79.2)	22 (100.0)	
VGS (810)	**≤0.008**	**0.06**	**490 (60.5)**	**130 (76.5)**	**89 (87.5)**	**61 (95.1)**	**33 (99.1)**	**6 (99.9)**	**1 (100.0)**
ERY-R, CLI-S (229)	≤0.008	0.06	121 (52.8)	42 (71.2)	36 (86.9)	18 (94.8)	12 (100.0)		
ERY-R, CLI-R (103)	≤0.008	0.06	56 (54.4)	26 (79.6)	8 (87.4)	7 (94.2)	5 (99.0)	1 (100.0)	
MDR (94)	≤0.008	0.06	48 (51.1)	25 (77.7)	9 (87.2)	7 (94.7)	4 (98.9)	1 (100.0)	
Non-MDR (716)	≤0.008	0.06	442 (61.7)	105 (76.4)	80 (87.6)	54 (95.1)	29 (99.2)	5 (99.9)	1 (100.0)
***S. anginosus*[c] (228)**	**≤0.008**	**0.015**	**200 (87.7)**	**20 (96.5)**	**5 (98.7)**	**2 (99.6)**	**1 (100.0)**		

a. BHS = β-haemolytic streptococci (includes: 640 *S. agalactiae*, 107 *S. dysgalactiae*, one *S. equi*, nine *S. equisimilis*, 756 *S. pyogenes*, 68 Group C streptococci, six Group F streptococci, 171 Group G streptococci, and one unspeciated BHS); VGS = viridans group streptococci (includes: 228 *S. anginosus* group, 53 *S. bovis/gallolyticus* group, 334 *S. mitis/oralis*, three *S. mutans*, 43 *S. salivarius*, and 149 unspeciated VGS).
b. ERY = erythromycin; CLI = clindamycin; a multidrug resistance (MDR) phenotype was defined when resistance was observed to three or more drug classes.
c. Includes 160 *S. anginosus*, 61 *S. constellatus* and seven *S. intermedius*.

- Other agents, such as penicillin (MIC_{50}/MIC_{90}, ≤0.06/≤0.06 mg/L; 100.0% susceptible), linezolid (MIC_{50}/MIC_{90}, 0.5-1/1 mg/L; 100.0% susceptible) and levofloxacin (MIC_{50}/MIC_{90}, ≤0.5/1 mg/L; 93.8 – 99.1% susceptible) also showed a high degree of coverage against all BHS and drug-resistant subsets.
- Among viridans group streptococci (VGS), 28.3, 12.7 and 11.6% showed erythromycin resistance, erythromycin and clindamycin (constitutive) resistance, and MDR phenotype, respectively (Table 1).
- Oritavancin (99.9 – 100.0% susceptible using US FDA breakpoints) had low MIC results against VGS, *S. anginosus* group and drug-resistant subsets. Oritavancin ($MIC_{50/90}$, ≤0.008/0.06 mg/L), vancomycin (MIC_{50}, 0.5 mg/L), daptomycin (MIC_{50}, 0.25-0.5 mg/L), linezolid (MIC_{50}, 0.5-1 mg/L) and levofloxacin (MIC_{50}, 1 mg/L) showed consistent potencies against VGS and drug-resistant subsets (Table 2).

Table 2. Antimicrobial activity of oritavancin and comparator agents against contemporary (2010 - 2013) streptococcal clinical isolates displaying several antimicrobial susceptibility phenotypes.

Group/Organism[a] Phenotype[c] (no. tested)	MIC_{50}, MIC_{90} (mg/L) and % susceptible[b] for each agent														
	Oritavancin			Vancomycin			Daptomycin			Linezolid			Clindamycin		
	50%	90%	%S	50%	90%	%S	50%	90%	%S	50%	90%	%S	50%	90%	%S
BHS (1,759)	**0.03**	**0.25**	**98.6**	**0.25**	**0.5**	**100.0**	**≤0.06**	**0.25**	**100.0**	**1**	**1**	**100.0**	**≤0.25**	**≤0.25**	**91.9**
***S. pyogenes* (756)**	**0.03**	**0.12**	**98.8**	**0.25**	**0.5**	**100.0**	**≤0.06**	**≤0.06**	**100.0**	**1**	**1**	**100.0**	**≤0.25**	**≤0.25**	**97.0**
ERY-R, CLI-S (58)	0.03	0.12	100.0	0.25	0.5	100.0	≤0.06	≤0.06	100.0	1	1	100.0	≤0.25	≤0.25	100.0
ERY-R, CLI-R (23)	0.03	0.12	95.7	0.25	0.5	100.0	≤0.06	0.12	100.0	0.5	1	100.0	>2	>2	0.0
MDR (14)	0.03	0.12	100.0	0.25	0.5	100.0	≤0.06	0.12	100.0	0.5	1	100.0	>2	>2	0.0
Non-MDR (742)	0.03	0.12	98.8	0.25	0.5	100.0	≤0.06	≤0.06	100.0	1	1	100.0	≤0.25	≤0.25	98.8
***S. agalactiae* (640)**	**0.03**	**0.12**	**98.9**	**0.5**	**0.5**	**100.0**	**0.25**	**0.25**	**100.0**	**1**	**1**	**100.0**	**≤0.25**	**>2**	**85.3**
ERY-R, CLI-S (63)	0.03	0.12	100.0	0.5	0.5	100.0	0.25	0.25	100.0	1	1	100.0	≤0.25	≤0.25	100.0
ERY-R, CLI-R (93)	0.03	0.25	100.0	0.5	0.5	100.0	0.25	0.25	100.0	1	1	100.0	>2	>2	0.0
MDR (86)	0.03	0.25	100.0	0.5	0.5	100.0	0.25	0.25	100.0	1	1	100.0	>2	>2	0.0
Non-MDR (554)	0.03	0.12	98.7	0.5	0.5	100.0	0.25	0.25	100.0	1	1	100.0	≤0.25	≤0.25	98.6
***S. dysgalactiae* (107)**	**0.06**	**0.25**	**100.0**	**0.25**	**0.25**	**100.0**	**≤0.06**	**0.12**	**100.0**	**1**	**1**	**100.0**	**≤0.25**	**≤0.25**	**94.4**
ERY-R, CLI-S (15)	0.06	0.25	100.0	0.25	0.25	100.0	≤0.06	0.25	100.0	0.5	1	100.0	≤0.25	≤0.25	100.0
Non-MDR (106)	0.06	0.25	100.0	0.25	0.25	100.0	≤0.06	0.12	100.0	1	1	100.0	≤0.25	≤0.25	95.3
VGS (810)	**≤0.008**	**0.06**	**99.9**	**0.5**	**1**	**100.0**	**0.25**	**0.5**	**99.5**	**1**	**1**	**100.0**	**≤0.25**	**>2**	**86.9**
ERY-R, CLI-S (229)	≤0.008	0.06	100.0	0.5	0.5	100.0	0.25	1	98.7	1	1	100.0	≤0.25	≤0.25	86.8
ERY-R, CLI-R (103)	≤0.008	0.06	100.0	0.5	1	100.0	0.5	1	100.0	0.5	1	100.0	>2	>2	0.0
MDR (94)	≤0.008	0.06	100.0	0.5	1	100.0	0.25	1	98.9	0.5	1	100.0	>2	>2	6.4
Non-MDR (716)	≤0.008	0.06	99.9	0.5	1	100.0	0.25	0.5	99.6	1	1	100.0	≤0.25	≤0.25	97.5
***S. anginosus*[d] (228)**	**≤0.008**	**0.015**	**100.0**	**0.5**	**1**	**100.0**	**0.25**	**0.5**	**100.0**	**1**	**1**	**100.0**	**≤0.25**	**>2**	**86.8**

a. BHS = β-haemolytic streptococci (includes: 640 *S. agalactiae*, 107 *S. dysgalactiae*, one *S. equi*, nine *S. equisimilis*, 756 *S. pyogenes*, 68 Group C streptococci, six Group F streptococci, 171 Group G streptococci, and one unspeciated BHS); VGS = viridans group streptococci (includes: 228 *S. anginosus* group, 53 *S. bovis/gallolyticus* group, 334 *S. mitis/oralis*, three *S. mutans*, 43 *S. salivarius*, and 149 unspeciated VGS).
b. Breakpoint criteria for oritavancin according to the labeling supplement for the product ORBACTIV™ (i.e. ≤0.25 mg/L for susceptible). Breakpoint criteria for comparator agents were those from EUCAST (2015).
c. ERY = erythromycin; CLI = clindamycin; a multidrug resistance (MDR) phenotype was defined when resistance was observed to three or more drug classes.
d. Includes 160 *S. anginosus*, 61 *S. constellatus* and seven *S. intermedius*.

Conclusions

- *S. pyogenes* tended to be more susceptible than *S. agalactiae*, which showed higher rates of resistance to erythromycin alone, and erythromycin plus clindamycin (constitutive), as well as higher rates of the MDR phenotype. These resistance rates were even higher among VGS clinical isolates (28.3, 12.7 and 11.6%, respectively).
- However, it is important to mention that these resistance rates were likely underestimated, since isolates included in this study were not screened for the presence of the inducible macrolide, lincosamide and streptogramin B (MLS_B) resistance phenotype.
- Among BHS, oritavancin was slightly less potent (two-fold) against *S. dysgalactiae*, while vancomycin and daptomycin were slightly less potent against *S. agalactiae.*
- Overall, oritavancin demonstrated potency similar to or greater than comparators against this recent collection of streptococci, including drug-resistant subsets from European and adjacent countries.

Disclosures

This study was sponsored by an educational/research grant from The Medicines Company (Parsippany, New Jersey, United States) via the SENTRY Antimicrobial Surveillance Programme platform.

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