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Activity of Oritavancin Tested against Uncommonly Isolated Gram-positive Pathogens Responsible for Documented Infections in Hospitals Worldwide

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Abstract

Background: Oritavancin is a semisynthetic lipoglycopeptide in late stage of clinical development. This study assessed the *in vitro* activity of oritavancin tested against uncommonly isolated coagulase-negative staphylococci (CoNS), streptococci and other Gram-positive isolates.

Methods: A total of 2,027 CoNS, 674 streptococci and 80 Gram-positive isolates collected over a five-year period (SENTRY Program, 2008-2012) were included. Identification was performed by standard algorithms and Vitek® 2, and supported by MALDI-TOF. Susceptibility testing was performed by CLSI methods (M07-A9).

Results: Overall, oritavancin was highly active against all CoNS ($MIC_{50/90}$, 0.015/0.06 μg/mL) with MIC_{50} values among tested species of ≤0.008 - 0.015 μg/mL, while slightly higher MIC results were noted for *S. haemolyticus*, *S. saprophyticus* and *S. xylosus* ($MIC_{50/90}$, 0.03/0.06 μg/mL; Table). Vancomycin and daptomycin showed MIC_{50} results of 1 and 0.12-0.5 μg/mL, respectively, when tested against these CoNS species. Overall, streptococcal isolates exhibited low MIC_{50} (≤0.008 μg/mL) values for oritavancin, with the exception of *S. bovis* (0.03 μg/mL), *S. dysgalactiae* (0.06 μg/mL) and *S. salivarius/vestibularis* groups (0.06 μg/mL) which showed higher MIC_{50} results. Other Gram-positive isolates such as *Micrococcus* spp. ($MIC_{50/90}$, ≤0.008/≤0.008 μg/mL), *Listeria monocytogenes* ($MIC_{50/90}$, ≤0.008/0.015 μg/mL) and *Corynebacterium* spp. ($MIC_{50/90}$, ≤0.008/0.06 μg/mL) were inhibited by oritavancin at ≤0.008, ≤0.03 and ≤0.06 μg/mL, respectively.

Conclusions: Oritavancin exhibited potent *in vitro* activity against these uncommonly isolated Gram-positive pathogens, for which very limited susceptibility information is currently available to guide therapy. While variations in the oritavancin activity were noted within tested species/groups, this drug inhibited all tested Gram-positive isolates but one *S. haemolyticus* at ≤0.25 μg/mL.

Abstract Table

Organism (no. tested)	MIC 50/90%	Organism (no. tested)	MIC 50/90%
CoNS[a] (2,027)		Other species (80)	
S. auricularis (28)	≤0.008/0.03	*Corynebacterium* spp. (17)	≤0.008/0.06
S. capitis (260)	0.015/0.03	*Listeria monocytogenes* (37)	≤0.008/0.015
S. caprae (18)	0.015/0.03	*Micrococcus* spp. (26)	≤0.008/≤0.008
S. cohnii (27)	0.015/0.06		
S. haemolyticus (545)	0.03/0.06	*Streptococcus* spp. (674)	
S. hominis (565)	≤0.008/0.06	*S. anginosus* group (194)	≤0.008/0.015
S. intermedius (14)	≤0.008/0.015	*S. bovis* group (47)	0.03/0.06
S. lugdunensis (244)	≤0.008/0.015	*S. dysgalactiae* group (47)	0.06/0.12
S. pettenkoferi (10)	≤0.008/0.015	*S. mitis* group (303)	≤0.008/0.06
S. saprophyticus (120)	0.03/0.06	*S. mutans* group (20)	≤0.008/0.06
S. scuiri (19)	0.015/0.03	*S. salivarius*[b] (49)	0.06/0.12
S. simulans (38)	0.015/0.03	*S. milleri* group[c] (14)	≤0.008/≤0.008
S. warneri (130)	0.015/0.03		
S. xylosus (39)	0.03/0.06		

a. CoNS, coagulase-negative staphylococci.
b. *S. salivarius/S. vestibularis* group.
c. Taxonomy dictates a close relationship to *S. anginosus* group.

Introduction

Oritavancin is a bactericidal lipoglycopeptide for which two multicenter clinical trials (SOLO I and II) were completed in December 2012 and July 2013, respectively. These trials assessed the efficacy and safety of oritavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) compared with vancomycin. This drug has documented *in vitro* activity against frequently isolated Gram-positive pathogens during longitudinal surveillance studies. Oritavancin MIC_{50} and MIC_{90} results of 0.03 and 0.06 μg/mL, respectively, have been reported against MRSA. In addition, coagulase-negative staphylococci (CoNS; $MIC_{50/90}$, 0.03/0.06 μg/mL), *Streptococcus pyogenes* ($MIC_{50/90}$, 0.12/0.25 μg/mL), and vancomycin-resistant (VanA) *Enterococcus faecalis* ($MIC_{50/90}$, 0.25/0.5 μg/mL) and *E. faecium* ($MIC_{50/90}$, 0.03/0.12 μg/mL), and *S. aureus* and CoNS with elevated vancomycin MIC values ($MIC_{50/90}$, 0.12/0.25 μg/mL, for both) have demonstrated low oritavancin MIC results.

Gram-positive organisms (staphylococci, enterococci and streptococci) are commonly responsible for infections in the nosocomial and community settings. More often than appreciated, these infections may involve a causative agent exhibiting a multidrug resistance (MDR) phenotype, and when associated with critically-ill patients may provide an even greater challenge for antimicrobial therapies. In addition, infections caused by Gram-positive pathogens less often recovered in the clinical settings, and for which *in vitro* data are limited, are scenarios experienced by health practitioners. Therefore, this study assessed the *in vitro* activity of oritavancin tested against rarely isolated CoNS, streptococci and other Gram-positive pathogens recovered from hospitalized patients during a five-year longitudinal, multicenter, SENTRY Antimicrobial Surveillance Program for oritavancin.

Methods

Bacterial strain collection. A total of 2,027 CoNS (14 species), 674 streptococci (seven groups) and 80 Gram-positive species (three genera) collected over a five-year period as part of the SENTRY Antimicrobial Surveillance Program (2008-2012) were included. Isolates were primarily identified by the participating laboratory and identification confirmed by the reference monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) by standard algorithms and Vitek® 2 (bioMérieux, Hazelwood, Missouri, USA), and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods. Isolates were tested for susceptibility by broth microdilution method following the Clinical and Laboratory Standards Institute (CLSI) M07-A9 document. Testing was performed using dry-form panels manufactured by Thermo Fisher Scientific (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, *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619.

Results

- Overall, oritavancin was highly active against CoNS with MIC_{50} and MIC_{90} of 0.015 and 0.06 μg/mL, respectively (Table 1). MIC_{50} values of ≤0.008 or 0.015 μg/mL were observed for most tested CoNS species, while slightly higher MIC_{50} results were noted for *S. haemolyticus*, *S. saprophyticus* and *S. xylosus* ($MIC_{50/90}$, 0.03/0.06 μg/mL).
- Vancomycin and daptomycin showed MIC_{50} results of 1 and 0.12-0.5 μg/mL, respectively, when tested against these CoNS species, except for *S. pettenkoferi* and *S. sciuri*, which showed daptomycin MIC_{50} results of 1 μg/mL (data not shown).
- Only 36.0% of CoNS were susceptible to methicillin (oxacillin) with broad variation of susceptibility rates within species. The highest oxacillin susceptibility rates were noted for *S. lugdenensis* (94.7%) and *S. intermedius* (92.9%). Oxacillin susceptibility was lowest for *S. cohnii* (3.7%), *S. sciuri* (5.3%), *S. saprophyticus* (5.8%), *S. haemolyticus* (15.8%) and *S. xylosus* (18.0%), while other species showed rates between 29.5 and 66.7% (data not shown).
- Streptococcal isolates exhibited oritavancin MIC_{50} and MIC_{90} results of ≤0.008 and 0.06 μg/mL, respectively; most streptococcal groups showed MIC_{50} values of ≤0.008 μg/mL, except for the *S. bovis* (0.03 μg/mL), *S. dysgalactiae* (0.06 μg/mL) and *S. salivarius/vestibularis* (0.06 μg/mL) groups (Table 2). *S. sanguinis* and *S. parasanguinis* had MIC_{50} values (0.015 and 0.03 μg/mL, respectively) that were higher than other streptococcal species within the *S. mitis* groups (MIC_{50}, ≤0.008 μg/mL).
- Oritavancin was very active against *Micrococcus* spp. ($MIC_{50/90}$, ≤0.008/≤0.008 μg/mL), *Listeria monocytogenes* ($MIC_{50/90}$, ≤0.008/0.015 μg/mL) and *Corynebacterium* spp. ($MIC_{50/90}$, ≤0.008/0.06 μg/mL; Table 2).

Table 1. Uncommonly isolated staphylococcal species tested by reference CLSI methods against oritavancin.

Genera/group	Number (cumulative % inhibited) at oritavancin MIC in μg/mL:							MIC (μg/mL)
Organism (no. tested)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	50%/90%
Coagulase-negative staphylococci (2,057)	**810 (39.4)**	**459 (61.7)**	**481 (85.1)**	**233 (96.4)**	**63 (99.5)**	**10 (>99.9)**	**1 (100.0)**	**0.015/0.06**
S. auricularis (28)	18 (64.2)	4 (78.6)	5 (96.4)	0 (96.8)	1 (100.0)			≤0.008/0.03
S. capitis (260)	129 (49.6)	73 (77.7)	40 (93.1)	17 (99.6)	1 (100.0)			0.015/0.03
S. caprae (18)	3 (16.7)	12 (83.3)	3 (100.0)					0.015/0.03
S. cohnii (27)	7 (25.9)	10 (63.0)	7 (88.9)	3 (100.0)				0.015/0.06
S. haemolyticus (545)	44 (8.1)	141 (33.9)	201 (70.8)	111 (91.2)	41 (98.7)	6 (99.8)	1 (100.0)	0.03/0.06
S. hominis (565)	308 (54.5)	96 (71.5)	91 (87.6)	59 (98.1)	8 (99.5)	3 (100.0)		≤0.008/0.06
S. intermedius (14)	7 (50.0)	6 (92.9)	0 (92.9)	0 (92.9)	1 (100.0)			≤0.008/0.015
S. lugdunensis (244)	218 (89.3)	17 (96.3)	2 (97.1)	4 (98.8)	3 (100.0)			≤0.008/0.015
S. pettenkoferi (10)	8 (80.0)	2 (100.0)						≤0.008/0.015
S. saprophyticus (120)	10 (8.8)	25 (29.2)	57 (76.7)	23 (95.8)	5 (100.0)			0.03/0.06
S. sciuri (19)	6 (31.6)	8 (73.7)	3 (89.5)	1 (94.7)	1 (100.0)			0.015/0.03
S. simulans (38)	11 (29.0)	21 (84.2)	4 (94.7)	0 (94.7)	2 (100.0)			0.015/0.03
S. warneri (130)	37 (28.5)	40 (59.4)	41 (90.8)	12 (100.0)				0.015/0.03
S. xylosus (39)	4 (10.3)	4 (20.5)	27 (89.7)	3 (97.4)	0 (97.4)	1 (100.0)		0.03/0.06

Table 2. Uncommonly isolated streptococcal species and other Gram-positive isolates tested by reference CLSI methods against oritavancin.

Genera/group	Number (cumulative % inhibited) at oritavancin MIC in μg/mL:							MIC (μg/mL)
Organism (no. tested)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	50%/90%
***Streptococcus* spp. (674)**	**398 (59.1)**	**84 (71.5)**	**70 (81.9)**	**78 (93.5)**	**39 (99.3)**	**4 (99.9)**	**1 (100.0)**	**≤0.008/0.06**
S. anginosus group (194)	174 (89.7)	6 (92.8)	6 (95.9)	7 (99.5)	1 (100.0)			≤0.008/0.015
S. anginosus (128)	113 (91.9)	4 (95.1)	5 (99.2)	6 (100.0)				≤0.008/≤0.008
S. constellatus (44)	44 (100.0)							≤0.008/≤0.008
S. intermedius (22)	17 (77.3)	2 (86.4)	1 (90.9)	1 (95.5)	1 (100.0)			≤0.008/0.03
S. bovis group (47)	16 (34.0)	6 (46.8)	9 (66.0)	12 (91.5)	4 (100.0)			0.03/0.06
S. dysgalactiae group (47)	11 (23.4)	1 (25.3)	7 (40.4)	11 (63.8)	13 (91.5)	3 (97.9)	1 (100.0)	0.06/0.12
S. dysgalactiae (31)	8 (25.8)	1 (29.0)	6 (48.4)	7 (71.0)	6 (90.3)	3 (100.0)		0.06/0.12
S. equisimilis (16)	3 (18.8)	0 (18.8)	1 (25.0)	4 (50.0)	7 (93.8)	0 (93.8)	1 (100.0)	0.06/0.12
S. mitis group (303)	162 (53.5)	57 (72.3)	44 (86.8)	28 (96.0)	12 (100.0)			≤0.008/0.06
S. mitis (195)	118 (60.5)	33 (77.4)	21 (88.2)	15 (95.9)	8 (100.0)			≤0.008/0.06
S. gordonii (13)	9 (69.2)	3 (92.3)	1 (100.0)					≤0.008/0.015
S. oralis (25)	13 (52.0)	5 (72.0)	4 (88.0)	2 (96.0)	1 (100.0)			≤0.008/0.06
S. parasanguinis (35)	10 (28.6)	7 (48.6)	9 (74.3)	7 (94.3)	2 (100.0)			0.03/0.06
S. sanguinis (35)	12 (34.3)	9 (60.0)	9 (85.7)	4 (97.1)	1 (100.0)			0.015/0.06
S. mutans group (20)	10 (50.0)	5 (75.0)	1 (80.0)	3 (95.0)	0 (95.0)	1 (100.0)		≤0.008/0.06
S. salivarius/S. vestibularis group (49)	12 (24.5)	9 (42.9)	3 (49.0)	16 (81.6)	9 (100.0)			0.06/0.12
S. milleri group (14)[a]	13 (92.9)	0 (92.9)	0 (92.9)	1 (100.0)				≤0.008/≤0.008
Other species (80)								
Corynebacterium spp. (17)	10 (58.8)	1 (64.7)	3 (82.4)	3 (100.0)				≤0.008/0.06
Listeria monocytogenes (37)	33 (89.2)	3 (97.3)	1 (100.0)					≤0.008/0.015
Micrococcus spp. (26)	26 (100.0)							≤0.008/≤0.008

a. Taxonomy dictates a close relationship to *S. anginosus* group.

Conclusions

- This study presents *in vitro* data for oritavancin tested against 2,811 Gram-positive isolates that are rarely recovered from human clinical specimens, and as a consequence, limited susceptibility information is available in the public domain for these organism groups. Moreover, this report not only provides susceptibility data against several groups of streptococci and staphylococci, but also for numerous species within these groups of organisms, noting subtle differences in the susceptibility profiles within investigated species.
- Oritavancin demonstrated potent activity against the selected Gram-positive organisms, inhibiting 99.4% of tested isolates at ≤0.12 μg/mL. In summary, the results presented herein enhance the oritavancin *in vitro* spectrum of activity prior to regulatory review by the Food and Drug Administration and European Medicines Agency, including against *S. lugdunensis*, and *S. anginosus* and *S. dysgalactiae* groups, which are pathogens responsible for the sought ABSSSI indication.

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