C-823 Oritavancin Activity against Gram-positive Pathogens Responsible for Documented Infections in US Hospitals (2012-2013)

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Abstract

Background: Oritavancin has been developed for the treatment of serious Gram-positive infections. This study investigated oritavancin *in vitro* activity against staphylococcal and streptococcal pathogens in the United States.

Methods: 9,213 clinically relevant (7,268 *S. aureus*, 492 coagulase-negative staphylococci [CoNS] and 1,453 streptococci) pathogens were included. Identification was performed by standard algorithms and MALDI-TOF. Susceptibility testing was based on CLSI guidelines (M07-A9 and M100-S24). MIC interpretation for comparator agents was guided by EUCAST (2014) and CLSI (2014) breakpoints.

Results: Methicillin-resistant *S. aureus* (MRSA) were inhibited by oritavancin at ≤0.25 µg/ml. Oritavancin showed MIC_{50} values of 0.03-0.06 µg/ml against isolates with elevated MIC results to vancomycin (MIC, 2 µg/ml) or daptomycin (MIC, 1-2 µg/ml). Oritavancin MICs ($MIC_{50/90}$, 0.06/0.12 µg/ml) were at least 4-fold lower than daptomycin ($MIC_{50/90}$, 0.5/1 µg/ml), tetracycline ($MIC_{50/90}$, 0.25/2 µg/ml) or linezolid ($MIC_{50/90}$, 0.5/1 µg/ml) against MRSA with vancomycin MIC = 2 µg/ml. Linezolid, tetracycline and trimethoprim-sulfamethoxazole showed coverage (≥91.4% susceptible) against MRSA with decreased susceptibility to vancomycin or daptomycin. Oritavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml) was the most potent agent against CoNS, followed by daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml), vancomycin ($MIC_{50/90}$, 1/2 µg/ml) and linezolid ($MIC_{50/90}$, 0.5/1 µg/ml). Oritavancin ($MIC_{50/90}$, 0.03/0.12 µg/ml), penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) and daptomycin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) had the lowest MICs against *S. pyogenes*, while oritavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) were the most active against *S. agalactiae.* Penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) and daptomycin ($MIC_{50/90}$, ≤0.06/0.12 µg/ml) had the lowest MICs against *S. dysgalactiae*, whereas oritavancin ($MIC_{50/90}$, ≤0.008/0.015 µg/ml) had lowest MICs against the *S. anginosus* group.

Conclusions: Oritavancin had greater *in vitro* potency than comparators against streptococci and staphylococci, including MRSA with decreased susceptibility to currently prescribed drugs for serious infections. These results confirm the potent activity of oritavancin against Gram-positive pathogens, including those responsible for serious skin and skin structure infections.

Introduction

Oritavancin is a semisynthetic bactericidal lipoglycopeptide recently approved by the Food and Drug Administration (FDA) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI). The oritavancin activity originates from multiple mechanisms of action consisting of disruption of bacterial membrane integrity, and inhibition of the transglycosylation and transpeptidation steps of cell wall synthesis. 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 ABSSSI were assessed in Phase 3 clinical trials (SOLO-I and SOLO-II). Data analysis from these trials showed oritavancin to be non-inferior to vancomycin.

Gram-positive isolates, mainly methicillin-resistant *Staphylococcus aureus* (MRSA), continue to challenge the management of community- and hospital-associated infections. Additional therapeutic options with different pharmacokinetic profiles such as the prolonged terminal half-life of oritavancin allowing for the administration of a single dose could provide specific advantages over traditionally available agents. In this study, the *in vitro* activity of oritavancin was investigated against a contemporary (2012–2013) collection of staphylococcal and streptococcal pathogens responsible for infections in hospitalized patients in the United States.

Methods

Bacterial strain collection. A total of 9,213 clinically relevant (7,268 *S. aureus*, 492 coagulase-negative staphylococci [CoNS] and 1,453 streptococci) pathogens were included in the study. These isolates were recovered from specimens associated with clinical infections, per local guidelines, in hospitalised patients from 27 sites in the USA between 2012 and 2013. Selected isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program. Isolates were primarily identified by the participating laboratory and identification confirmed by the reference monitoring by standard algorithms and supported by MALDI-TOF-MS (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-A9 document. Testing was performed using panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These validated panels provide MIC results equivalent to the CLSI-approved broth microdilution method which includes 0.002% polysorbate-80 in the broth. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Quality of the MIC values was assured by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges (M100-S24). Oritavancin MIC values were interpreted based on FDA-approved breakpoint criteria. MIC interpretations for comparators were based on the CLSI M100-S24 (2014) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2014) breakpoint criteria, as available.

Results

- Oritavancin showed MIC_{50} and MIC_{90} results against *S. aureus* of 0.03 and 0.06 µg/ml, respectively, regardless of methicillin susceptibility phenotype, and inhibited all isolates at ≤0.25 µg/ml (Table 1).
- Slightly higher oritavancin MIC results ($MIC_{50/90}$, 0.06/0.12 µg/ml) were noted for those MRSA with vancomycin MIC values of 2 µg/ml compared with a subset displaying vancomycin MIC values at ≤1 µg/ml ($MIC_{50/90}$, 0.03/0.06 µg/ml; Table 1). Oritavancin MIC_{50} values (0.03 µg/ml) were similar when tested against MRSA with daptomycin MIC results at ≤0.5 or ≥1 µg/ml.
- Comparator agents, such as vancomycin ($MIC_{50/90}$, 1/1 µg/ml), tetracycline ($MIC_{50/90}$, 0.25/1 µg/ml), daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml) and linezolid ($MIC_{50/90}$, 1/1 µg/ml) demonstrated MIC results that were at least 8-fold higher than oritavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml) against MRSA (Table 2).
- Oritavancin MIC values ($MIC_{50/90}$, 0.06/0.12 µg/ml) were at least 4-fold lower than daptomycin ($MIC_{50/90}$, 0.5/1 µg/ml), tetracycline ($MIC_{50/90}$, 0.25/2 µg/ml) or linezolid ($MIC_{50/90}$, 0.5/1 µg/ml) against MRSA exhibiting decreased susceptibility to vancomycin (MIC = 2 µg/ml; Table 2).
- The majority of CoNS (70.5%) were oxacillin-resistant; oritavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml) was the most potent agent tested against these isolates, followed by daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml), vancomycin ($MIC_{50/90}$, 1/2 µg/ml) and linezolid ($MIC_{50/90}$, 0.5/1 µg/ml; Table 2).
- Overall, oritavancin was active when tested against β-hemolytic streptococci (BHS; $MIC_{50/90}$, 0.03/0.012 µg/ml), with $MIC_{50/90}$ results against *S. agalactiae*, *S. pyogenes* and *S. dysgalactiae* of 0.03/0.06, 0.03/0.25 and 0.06/0.25 µg/ml, respectively (Table 1).
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 µg/ml), penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) and daptomycin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) had the lowest MIC values against *S. pyogenes*. Oritavancin ($MIC_{50/90}$, 0.03/0.06 µg/ml) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) were the most active against *S. agalactiae* (Table 2).
- Viridans group streptococci (VGS) exhibited low MIC values for oritavancin ($MIC_{50/90}$, 0.008/0.06 µg/ml), including a subset of isolates from the *S. anginosus* group ($MIC_{50/90}$, 0.008/0.015 µg/ml; Table 1). Oritavancin was at least 4-fold more active than comparators when tested against all VGS or the *S. anginosus* group.

Table 1. Antimicrobial activity and MIC distribution for oritavancin against a contemporary collection (2012 – 2013) of clinical isolates from US medical centers.

Organism[a] (no. tested)	MIC (µg/ml)		Number (cumulative %) inhibited at oritavancin MIC (µg/ml)[b]								
	50%	90%	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5
S. aureus (7,268)	0.03	0.06	24 (0.3)	8 (0.4)	196 (3.1)	1981 (30.4)	**2976 (71.3)**	1642 (93.9)	377 (99.1)[c]	64 (100.0)	
MSSA (3,789)	0.03	0.06	12 (0.3)	7 (0.5)	124 (3.8)	1036 (31.1)	**1529 (71.5)**	872 (94.5)	180 (99.2)	29 (100.0)	
MRSA (3,479)	0.03	0.06	12 (0.3)	1 (0.4)	72 (2.4)	945 (29.6)	**1447 (71.2)**	770 (93.3)	197 (99.0)	35 (100.0)	
Vancomycin MIC, ≤1 µg/ml (3,410)	0.03	0.06	10 (0.3)	1 (0.3)	72 (2.4)	942 (30.1)	**1430 (72.0)**	739 (93.7)	184 (99.1)	32 (100.0)	
Vancomycin MIC, 2 µg/ml (69)	0.06	0.12	2 (2.9)	0 (2.9)	0 (2.9)	3 (7.2)	17 (31.9)	**31 (76.8)**	13 (95.7)	3 (100.0)	
Daptomycin MIC, ≤0.5 µg/ml (3,443)	0.03	0.06	12 (0.3)	1 (0.4)	72 (2.5)	941 (29.8)	**1432 (71.4)**	759 (93.4)	192 (99.0)	34 (100.0)	
Daptomycin MIC, ≥1 µg/ml (35)	0.03	0.12	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.4)	**14 (51.4)**	11 (82.9)	5 (97.1)	1 (100.0)	
CoNS (492)	0.03	0.06	9 (1.8)	18 (5.5)	89 (23.6)	76 (39.0)	**139 (67.3)**	**139 (95.5)**	22 (100.0)		
Vancomycin MIC, ≤1 µg/ml (274)	0.015	0.06	9 (3.3)	18 (9.9)	**87 (41.6)**	68 (66.4)	60 (88.3)	29 (98.9)	3 (100.0)		
Vancomycin MIC, ≥2 µg/ml (218)	0.06	0.06	0 (0.0)	0 (0.0)	2 (0.9)	8 (4.6)	79 (40.8)	**110 (91.3)**	19 (100.0)		
BHS (987)	0.03	0.12	18 (1.8)	6 (2.4)	133 (15.9)	**292 (45.5)**	247 (70.5)	119 (82.6)	81 (90.8)	55 (96.4)	35 (99.9)[d]
S. dysgalactiae (43)	0.06	0.25	0 (0.0)	0 (0.0)	3 (7.0)	5 (18.6)	8 (37.2)	8 (55.8)	**10 (79.1)**	6 (93.0)	3 (100.0)
S. pyogenes (423)	0.03	0.25	12 (2.8)	3 (3.5)	72 (20.6)	**116 (48.0)**	73 (65.2)	55 (78.3)	48 (89.6)	27 (96.0)	16 (99.8)[d]
S. agalactiae (452)	0.03	0.06	0 (0.0)	0 (0.0)	50 (11.1)	**167 (48.0)**	156 (82.5)	42 (91.8)	18 (95.8)	11 (98.2)	8 (100.0)
VGS (466)	0.008	0.06	104 (22.3)	52 (33.5)	**135 (62.4)**	75 (78.5)	46 (88.4)	37 (96.4)	16 (99.8)	1 (100.0)	
S. anginosus group (154)	0.008	0.015	48 (31.2)	21 (44.8)	**64 (86.4)**	19 (98.7)	2 (100.0)				

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
b. Modal MIC values are shown in bold.
c. Underline values represent percentage of susceptible isolates according to FDA-approved criteria.
d. One isolate displayed a MIC of 1 µg/ml.

Table 2. Antimicrobial activity of oritavancin and comparator agents against a contemporary collection of clinical isolates from US medical centers.

Organism[a] (no. tested) / Antimicrobial agent	Range	MIC (µg/ml)		% Susceptible/%Intermediate/%Resistant[b]	
		50%	90%	CLSI	EUCAST
MRSA (3,479)					
Oritavancin	≤0.002 – 0.25	0.03	0.06	99.0[c] / - / -	-[d] / - / -
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	>16	>16	10.8 / 2.0 / 87.2	11.0 / 0.4 / 88.6
Clindamycin	≤0.25 – >2	≤0.25	>2	72.7 / 0.1 / 27.2	72.3 / 0.4 / 27.3
Tetracycline	0.06 – >32	0.25	1	95.1 / 0.3 / 4.6	93.1 / 1.7 / 5.2
Levofloxacin	≤0.12 – >4	4	>4	32.4 / 1.5 / 66.1	32.4 / 1.5 / 66.1
Daptomycin	≤0.06 – 2	0.25	0.5	99.9 / - / -	99.9 / 0.0 / 0.1
Linezolid	≤0.12 – >8	1	1	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
TMP/SMX[e]	≤0.5 – >4	≤0.5	≤0.5	97.8 / 0.0 / 2.2	97.8 / 0.1 / 2.1
MRSA (vancomycin MIC, 2 µg/ml) (69)					
Oritavancin	≤0.002 – 0.25	0.06	0.12	95.7 / - / -	- / - / -
Vancomycin	2	2	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	0.25 – >16	>16	>16	7.2 / 1.5 / 91.3	7.2 / 1.5 / 91.3
Clindamycin	≤0.25 – >2	>2	>2	40.6 / 0.0 / 59.4	39.1 / 1.5 / 59.4
Tetracycline	0.06 – >32	0.25	2	92.8 / 1.4 / 5.8	85.5 / 7.3 / 7.2
Levofloxacin	≤0.12 – >4	>4	>4	13.0 / 0.0 / 87.0	13.0 / 0.0 / 87.0
Daptomycin	0.25 – 2	0.5	1	95.7 / - / -	95.7 / 0.0 / 4.3
Linezolid	≤0.12 – 2	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	94.2 / 0.0 / 5.8	94.2 / 0.0 / 5.8
CoNS (492)					
Oritavancin	≤0.002 – 0.12	0.03	0.06	- / - / -	- / - / -
Oxacillin	≤0.25 – >2	1	>2	29.5 / 0.0 / 70.5	29.5 / 0.0 / 70.5
Vancomycin	0.5 – 4	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	>16	>16	38.6 / 1.8 / 59.6	39.0 / 1.0 / 60.0
Clindamycin	≤0.25 – >2	≤0.25	>2	69.3 / 2.4 / 28.3	68.1 / 1.2 / 30.7
Tetracycline	≤0.03 – >32	0.25	16	86.2 / 1.0 / 12.8	80.9 / 4.9 / 14.2
Levofloxacin	≤0.12 – >4	0.5	>4	57.7 / 1.4 / 40.9	57.7 / 1.4 / 40.9
Daptomycin	≤0.06 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – >8	0.5	1	99.2 / 0.0 / 0.8	99.2 / 0.0 / 0.8
TMP/SMX	≤0.5 – >4	≤0.5	>4	69.1 / 0.0 / 30.9	69.1 / 15.9 / 15.0

Organism[a] (no. tested) / Antimicrobial agent	Range	MIC (µg/ml)		% Susceptible/%Intermediate/%Resistant[b]	
		50%	90%	CLSI	EUCAST
***S. pyogenes* (423)**					
Oritavancin	≤0.002 – 1	0.03	0.25	96.0 / - / -	- / - / -
Penicillin	≤0.06 – 0.12	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	≤0.12 – 0.5	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	≤0.12	4	83.6 / 0.5 / 15.9	83.6 / 0.5 / 15.9
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	94.8 / 0.2 / 5.0	95.0 / 0.0 / 5.0
Tetracycline	0.06 – >32	0.25	16	83.7 / 0.9 / 15.4	83.7 / 0.0 / 16.3
Levofloxacin	0.25 – 2	0.5	1	100.0 / 0.0 / 0.0	94.3 / 5.7 / 0.0
Daptomycin	≤0.06 – 0.25	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	≤0.12 – 2	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	- / - / -	97.6 / 0.5 / 1.9
***S. agalactiae* (452)**					
Oritavancin	0.008 – 0.5	0.03	0.06	98.2 / - / -	- / - / -
Penicillin	≤0.06 – 0.12	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	0.25 – 1	0.5	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	2	>16	45.5 / 1.1 / 53.4	45.5 / 1.1 / 53.4
Clindamycin	≤0.25 – >2	≤0.25	>2	67.0 / 0.6 / 32.4	67.6 / 0.0 / 32.4
Tetracycline	0.12 – >32	32	>32	13.6 / 1.1 / 85.3	13.2 / 0.4 / 86.4
Levofloxacin	≤0.12 – >4	0.5	1	98.5 / 0.6 / 0.9	96.9 / 1.6 / 1.5
Daptomycin	≤0.06 – 0.5	0.25	0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 1	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	- / - / -	99.6 / 0.2 / 0.2
VGS (466)					
Oritavancin	≤0.002 – 0.25	0.008	0.06	100.0 / - / -	- / - / -
Penicillin	≤0.06 – >8	≤0.06	0.5	76.8 / 20.8 / 2.4	84.8 / 12.8 / 2.4
Vancomycin	≤0.12 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	0.25	16	50.4 / 3.5 / 46.1	- / - / -
Clindamycin	≤0.25 – >2	≤0.25	>2	89.0 / 0.4 / 10.6	89.4 / 0.0 / 10.6
Tetracycline	≤0.03 – >32	0.5	>32	64.7 / 3.8 / 31.5	- / - / -
Levofloxacin	≤0.12 – >4	1	2	93.8 / 0.8 / 5.4	- / - / -
Daptomycin	≤0.06 – 1	0.25	1	100.0 / - / -	- / - / -
Linezolid	≤0.12 – 4	0.5	1	99.8 / - / -	- / - / -
TMP/SMX	≤0.5 – >4	≤0.5	4	- / - / -	- / - / -

a. MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci.
b. Breakpoint criteria for comparator agents were those from CLSI (M100-S24, 2014) and/or EUCAST (2014), as available.
c. Oritavancin breakpoint criteria according to the product package insert, as available. Interpretation against VGS used the *S. anginosus* group criterion.
d. Breakpoint not available.
e. Trimethoprim/sulfamethoxazole.

Conclusions

- Oritavancin demonstrated potent *in vitro* activity against *S. aureus*, including MRSA clinical isolates displaying decreased susceptibility to currently prescribed antibiotics for serious infections, such as vancomycin and daptomycin.
- Oritavancin had *in vitro* activity similar to or greater than comparator agents when tested against streptococcal isolates responsible for documented infections.
- These results confirm the potent *in vitro* activity of oritavancin against a contemporary (2012-2013) collection of staphylococcal and streptococcal pathogens responsible for infections in hospitalized patients in the United States.

Disclosures/Acknowledgments

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

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Presented at ICAAC 2014 (54th Interscience Conference on Antimicrobial Agents and Chemotherapy) September 5-9, 2014, Washington, DC