1843 Contemporary Analysis of Oritavancin *In Vitro* Activity Against *Staphylococcus aureus* Responsible for Invasive Community- and Hospital-associated Infections Among Patients in the USA (2013-2014)

Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beaver Kreek Centre
rodrigo-mendes@jmilabs.com

RE Mendes, DJ Farrell, HS Sader, RK Flamm, RN Jones JMI Laboratories, North Liberty, IA, USA

Amended Abstract

Background: Oritavancin was approved in the USA (2014) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive pathogens. Oritavancin *in vitro* activity was assessed against *S. aureus* causing invasive community- (CA) and hospital-associated (HA) infections in USA hospitals.

Methods: 1,110 *S. aureus* were recovered from blood during the oritavancin surveillance program for USA (2013 – 2014). Of these, 790 and 218 were defined as CA and HA, respectively, according to CDC definitions; 102 isolates were of unknown origin. Isolates were collected from 29 sites in the nine USA Census regions and were identified by standard algorithms and MALDI-TOF. Susceptibility testing was performed by CLSI methods (M07-A10); interpretation of MIC results used FDA (oritavancin) and CLSI (2015) criteria. MRSA resistant to three or more drug classes were defined as multidrug-resistant (MDR).

Results: Oritavancin (100.0% susceptible) had MIC_{50}, MIC_{90} and MIC_{100} values of 0.03/0.06/0.12 μg/mL against *S. aureus*, regardless of susceptible phenotype or origin. Other agents, including vancomycin, daptomycin and linezolid were active against all subsets. Oritavancin MIC results were eight-fold lower than daptomycin and 16- to 32-fold lower than vancomycin or linezolid. All agents showed antimicrobial coverage (≥92.0% susceptible) against MSSA, except for erythromycin (70.1% susceptible) against the CA-MSSA subset, and erythromycin (60.4% susceptible) and levofloxacin (84.2% susceptible) against HA-MSSA isolates. Erythromycin, levofloxacin and clindamycin resistance rates in HA-MRSA were slightly higher than those found in CA-MRSA (82.1 vs 80.9%, 77.8 vs 69.4% and 38.5 vs 29.9%, respectively). Oritavancin, vancomycin, daptomycin, linezolid, tetracycline and trimethoprim-sulfamethoxazole were active *in vitro* against CA- and HA-MRSA (94.0 – 100.0% susceptible). Oritavancin, vancomycin, daptomycin and linezolid showed consistent coverage against MDR MRSA, regardless of origin.

Conclusions: Oritavancin had potent *in vitro* activity against this contemporary collection of CA and HA *S. aureus* causing invasive infections in USA hospitals. Oritavancin *in vitro* potency was consistently greater than comparator agents.

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become the most prevalent organism responsible for nosocomial infections and has emerged as an important pathogen outside of healthcare settings. Although a downward trend has been observed for invasive MRSA infections in United States (USA) hospitals, community-onset infections have remained stable since 2005. In several USA cities community-associated (CA)-MRSA strains of the USA300 lineage cause the majority of community-onset skin and skin structure infections (SSSI) diagnosed in emergency room visits.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide approved by the USA Food and Drug Administration (FDA, August 2014) and European Medicines Agency (EMA, March 2015) as the first once only treatment of adults with acute bacterial (AB) SSSI. Oritavancin has demonstrated potent *in vitro* antimicrobial activity against Gram-positive organisms such as staphylococci, enterococci and streptococci, including organisms with decreased susceptibility, or resistant, to other commonly-used antibacterial agents. In this study, the oritavancin *in vitro* activity was assessed against *S. aureus* causing invasive CA and hospital-associated (HA) infections.

Methods

Bacterial strain collection. A total of 1,110 *S. aureus* isolates were recovered from blood during the oritavancin surveillance program for USA (2013 – 2014). For data analysis purpose, the following Center for Disease Control and Prevention (CDC) definitions were applied for determining the origin of an isolate: any *S. aureus* isolate recovered from an outpatient or from an inpatient within 48 hours after hospitalization was considered CA, whereas isolates recovered later than 48 hours after hospitalization were considered HA. Among included blood isolates, 790 and 218 were defined as CA and HA, respectively; 102 isolates were of unknown origin and were not included in the data analysis. Isolates were collected in 29 medical centers located in the nine USA Census regions. Isolates were identified by standard algorithms and Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods. Susceptibility of isolates to oritavancin and comparator agents was determined by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Susceptibility testing was performed centrally 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 strains (*S. aureus* ATCC 29213). All QC results were within published acceptable ranges (M100-S25). MIC interpretations for oritavancin were based on the USA FDA breakpoint for *S. aureus* (i.e. ≤0.12 μg/mL). Interpretive criteria from CLSI were applied for comparator agents, as available. MRSA resistant to three or more drug classes in addition to β-lactam agents were defined as multidrug-resistant (MDR).

Results

- Oritavancin (100.0% susceptible) demonstrated MIC_{50}, MIC_{90} and MIC_{100} values of 0.03/0.06/0.12 μg/mL against *S. aureus*, regardless of origin or susceptibility phenotype, including MDR (Tables 1 - 3).
- Other agents, such as vancomycin ($MIC_{50/90}$, 1/1 μg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and linezolid ($MIC_{50/90}$, 1/1 μg/mL) were also active *in vitro* against all subsets analyzed (Tables 2 and 3).
- Oritavancin MIC_{50} and MIC_{90} results (0.03 and 0.06 μg/mL, respectively) were eight-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and 16- to 32-fold lower than vancomycin or linezolid ($MIC_{50/90}$, 1/1 μg/mL, for both), regardless of susceptibility phenotype or origin (Tables 2 and 3).
- Tetracycline and trimethoprim-sulfamethozaxole (TMP-SMX) demonstrated acceptable (i.e. >90% susceptible) antimicrobial coverage (93.3 - 99.0% susceptible) against all subsets. Exceptions were noted for TMP-SMX against MDR isolates (87.2 - 88.9% susceptible; Tables 2 and 3).
- Erythromycin (60.4 - 70.1% susceptible) showed sub-optimal antimicrobial activity against MSSA, and very limited coverage was observed against other MRSA subsets (0.0 - 19.1% susceptible; Tables 2 and 3).
- A high proportion of CA- and HA-MSSA isolates were susceptible to clindamycin (91.1 - 95.6%; inducible resistance not considered), as were MRSA isolates with a non-MDR phenotype (96.9 - 97.2% susceptible; Tables 2 and 3). However, the overall MRSA CA and HA populations (61.5 - 69.8% susceptible) and those isolates with a MDR phenotype (4.4 - 13.8% susceptible) demonstrated low susceptibility rates to clindamycin.
- Levofloxacin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 92.0% susceptible) was active *in vitro* against CA-MSSA (Table 2). Other subsets of *S. aureus* demonstrated decreased susceptibility to levofloxacin (0.0 - 84.2% susceptible), regardless of phenotype or origin.

Table 1. Antimicrobial activity and MIC distribution of oritavancin against *S. aureus* responsible for invasive community- and hospital-associated infections among patients in the USA (2013-2014).

S. aureus[a]	Origin (no. tested)	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Number (cumulative %) inhibited at oritavancin MIC (μg/mL) ≤0.004	0.008	0.015	0.03	0.06	0.12
All	CA (790)	0.03	0.06	1 (0.1)	26 (3.4)	234 (33.0)	315 (72.9)	181 (95.8)	33 (100.0)
	HA (218)	0.03	0.06	1 (0.5)	6 (3.2)	63 (32.1)	89 (72.9)	53 (97.2)	6 (100.0)
MSSA	CA (502)	0.03	0.06	0 (0.0)	18 (3.6)	138 (31.1)	208 (72.5)	119 (96.2)	19 (100.0)
	HA (101)	0.03	0.06	0 (0.0)	1 (1.0)	28 (28.7)	43 (71.3)	26 (97.0)	3 (100.0)
MRSA	CA (288)	0.03	0.06	1 (0.3)	8 (3.1)	96 (36.5)	107 (73.6)	62 (95.1)	14 (100.0)
	HA (117)	0.03	0.06	1 (0.9)	5 (5.1)	35 (35.0)	46 (74.4)	27 (97.4)	3 (100.0)
MDR	CA (94)	0.03	0.06	1 (1.1)	6 (7.4)	28 (37.2)	41 (80.9)	13 (94.7)	5 (100.0)
	HA (45)	0.03	0.06	0 (0.0)	1 (2.2)	10 (24.4)	21 (71.1)	13 (100.0)	
Non-MDR	CA (194)	0.03	0.06	0 (0.0)	2 (1.0)	68 (36.1)	66 (70.1)	49 (95.4)	9 (100.0)
	HA (72)	0.03	0.06	1 (1.4)	4 (6.9)	25 (41.7)	25 (76.4)	14 (95.8)	3 (100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant, defined as MRSA resistant to three or more drug classes in addition to β-lactam agents (methicillin [oxacillin]-resistant); HA = hospital-associated; CA = community-associated.

Table 2. Antimicrobial activity of oritavancin and comparator agents against MSSA and MRSA isolates responsible for invasive community- and hospital-associated infections among patients in the USA (2013-2014).

	Community-associated (n=790)						Hospital-associated (n=218)					
	MSSA (n=502)			MRSA (n=288)			MSSA (n=101)			MRSA (n=117)		
	MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)		
Antimicrobial agent	**50%**	**90%**	**%S[b]**	**50%**	**90%**	**%S[b]**	**50%**	**90%**	**%S[b]**	**50%**	**90%**	**%S[b]**
Oritavancin	0.03	0.06	100.0	0.03	0.06	100.0	0.03	0.06	100.0	0.03	0.06	100.0
Vancomycin	1	1	100.0	1	1	100.0	1	1	100.0	1	1	100.0
Daptomycin	0.25	0.5	99.8	0.25	0.5	98.6	0.25	0.5	100.0	0.25	0.5	100.0
Linezolid	1	1	100.0	1	1	100.0	1	1	100.0	1	1	100.0
Erythromycin	0.25	>16	70.1	>16	>16	13.9	0.25	>16	60.4	>16	>16	11.1
Clindamycin	≤0.25	≤0.25	95.6	≤0.25	>2	69.8	≤0.25	≤0.25	91.1	≤0.25	>2	61.5
Levofloxacin	0.25	0.5	92.0	4	>4	29.2	0.25	4	84.2	>4	>4	20.5
Tetracycline	≤0.5	≤0.5	97.8	≤0.5	1	95.8	≤0.5	≤0.5	96.0	≤0.5	2	95.7
TMP-SMX	≤0.5	≤0.5	99.6	≤0.5	≤0.5	95.1	≤0.5	≤0.5	99.0	≤0.5	≤0.5	94.0

MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; HA = hospital-associated; CA = community-associated. TMP-SMX = trimethoprim-sulfamethoxazole. Breakpoint criteria for oritavancin according to the FDA package insert (≤0.12 μg/mL for susceptible). Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015).

Table 3. Antimicrobial activity of oritavancin and comparator agents against MRSA isolates showing MDR and non-MDR phenotypes responsible for invasive community- and hospital-associated infections among patients in the USA (2013-2014).

	Community (288)						Hospital (117)					
	MDR (94)			Non-MDR (194)			MDR (45)			Non-MDR (72)		
	MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)		
Antimicrobial agent	**50%**	**90%**	**%S[b]**	**50%**	**90%**	**%S[b]**	**50%**	**90%**	**%S[b]**	**50%**	**90%**	**%S[b]**
Oritavancin	0.03	0.06	100.0	0.03	0.06	100.0	0.03	0.06	100.0	0.03	0.06	100.0
Vancomycin	1	1	100.0	1	1	100.0	1	1	100.0	1	1	100.0
Daptomycin	0.25	0.5	96.8	0.25	0.5	99.5	0.25	0.5	100.0	0.25	0.5	100.0
Linezolid	1	1	100.0	1	1	100.0	1	1	100.0	1	1	100.0
Erythromycin	>16	>16	3.2	>16	>16	19.1	>16	>16	0.0	>16	>16	18.1
Clindamycin	>2	>2	13.8	≤0.25	≤0.25	96.9	>2	>2	4.4	≤0.25	≤0.25	97.2
Levofloxacin	>4	>4	0.0	4	>4	43.3	>4	>4	2.2	4	>4	31.9
Tetracycline	≤0.5	2	94.7	≤0.5	≤0.5	96.4	≤0.5	2	93.3	≤0.5	≤0.5	97.2
TMP-SMX	≤0.5	>4	87.2	≤0.5	≤0.5	99.0	≤0.5	>4	88.9	≤0.5	≤0.5	97.2

MDR = multidrug-resistant, defined as MRSA (methicillin [oxacillin]-resistant) resistant to three or more drug classes in addition to β-lactam agents. HA = hospital-associated; CA = community-associated. TMP-SMX = trimethoprim-sulfamethoxazole. Breakpoint criteria for oritavancin according to the FDA package insert (≤0.12 μg/mL for susceptible). Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015).

Conclusions

- Oritavancin had potent *in vitro* activity against this contemporary collection of CA- and HA-*S. aureus* causing invasive infections in USA hospitals. Oritavancin *in vitro* activity was consistently greater than that of comparator agents.
- Oritavancin, vancomycin, daptomycin, linezolid and tetracycline demonstrated consistent *in vitro* coverage against subsets analyzed, while the antimicrobial activities of clindamycin, levofloxacin and TMP-SMX varied according to the subset.

Disclosures

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