C2-132

Oritavancin Activity Tested Against *Staphylococcus aureus* and β-hemolytic Streptococci Causing Skin and Skin Structure Infections in the USA (2010−2012)

Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beaver Kreek Ctr, Ste A
North Liberty, Iowa, 52317, USA
Phone: 319-665-3370
Fax: 319-665-3371
rodrigo-mendes@jmilabs.com

RE MENDES, HS SADER, RK FLAMM, RN JONES

JMI Laboratories, North Liberty, Iowa

Amended Abstract

Background: Oritavancin is in late development for treatment of acute bacterial skin and skin structure infections (ABSSSI). Oritavancin activity was assessed against key pathogens (*S. aureus* and β-hemolytic streptococci) responsible for skin and skin structure infections (SSSI) in the USA.

Methods: 3,061 *S. aureus* and 301 β-hemolytic streptococci responsible for documented SSSI were collected from 27 sites in nine USA Census regions. Identification was performed by standard algorithms and Vitek 2. Susceptibility testing was performed by CLSI methods (M07-A9) and interpretations by CLSI (M100-S22) and EUCAST (2012) criteria. *S. aureus* non-susceptible (CLSI criteria) to ≥3 drug classes in addition to β-lactams (oxacillin) were defined as multidrug-resistant (MDR).

Results: 52.3% of *S. aureus* were methicillin-resistant (MRSA) and among those 20.0% were MDR. Overall, oritavancin exhibited potent activity against *S. aureus* (Table), inhibiting all strains at ≤0.25 μg/mL. Vancomycin, daptomycin and linezolid showed coverage against MRSA (≥99% susceptible). Oritavancin had $MIC_{50/90}$ values eight-fold lower than daptomycin and 16- to 32-fold lower than vancomycin and linezolid against MRSA. Among other comparators, tetracycline (95.9% susceptible) and trimethoprim/sulfamethoxazole (98.4% susceptible) were also active against MRSA. Oritavancin tested against MDR MRSA displayed equivalent MIC_{50} values compared to methicillin-susceptible *S. aureus*, as did vancomycin, daptomycin and linezolid. Penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL), oritavancin and daptomycin had similar activity against β-hemolytic streptococci. Other tested agents were active (>90.0% susceptible) against β-hemolytic streptococci, except for erythromycin, clindamycin and tetracycline (63.5-86.4% susceptible).

Conclusions: Oritavancin had potent *in vitro* activity against the key pathogens responsible for SSSI, with equal or greater potency than comparators. MDR phenotype did not affect oritavancin activity.

Organism[a] (No. tested)	Oritavancin MIC μg/mL 50%	Oritavancin MIC μg/mL 90%	Vancomycin MIC μg/mL 50%	Vancomycin MIC μg/mL 90%	Vancomycin %S[b]	Daptomycin MIC μg/mL 50%	Daptomycin MIC μg/mL 90%	Daptomycin %S	Linezolid MIC μg/mL 50%	Linezolid MIC μg/mL 90%	Linezolid %S
S. aureus (3,061)	0.03	0.12	1	1	100.0	0.25	0.5	>99.9	1	1	>99.9
MSSA (1,460)	0.03	0.12	1	1	100.0	0.25	0.5	99.9	1	2	100.0
MRSA (1,601)	0.03	0.12	1	1	100.0	0.25	0.5	100.0	1	1	99.9
MDR (320)	0.03	0.12	1	1	100.0	0.25	0.5	100.0	1	1	99.7
Non-MDR (1,281)	0.03	0.12	1	1	100.0	0.25	0.5	100.0	1	1	100.0
BHS (301)	0.03	0.12	0.5	0.5	100.0	≤0.06	0.12	100.0	1	1	100.0
Group A BHS (197)	0.03	0.12	0.25	0.5	100.0	≤0.06	≤0.06	100.0	1	1	100.0
Group B BHS (104)	0.03	0.12	0.5	0.5	100.0	0.25	0.25	100.0	1	1	100.0

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant (resistance to ≥3 classes of drugs in addition to β-lactams [oxacillin]); BHS = β-hemolytic streptococci.
b. %S = percentage susceptible (CLSI, M100-S22).

Introduction

During the last decades, the treatment of nosocomial infections caused by Gram-positive organisms has experienced additional challenges due to the increased prevalence of multidrug-resistant (MDR) isolates of *Staphylococcus aureus* and *Enterococcus faecium*, mainly among critically ill patients. Infections caused by these pathogens pose a clinical threat for antimicrobial therapy, create a significant economic burden, and are associated with increased morbidity and mortality. Although several anti-Gram-positive agents have been clinically developed in the last decades, only linezolid and daptomycin, and more recently ceftaroline and telavancin, have been approved for clinical use, emphasizing the need to constantly identify and develop novel and effective antimicrobial molecules.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide in late-stage clinical development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). This drug has demonstrated broad *in vitro* activity against Gram-positive pathogens, including MDR strains of methicillin-resistant *S. aureus* (MRSA), other staphylococci, streptococci, and enterococci, including strains resistant to vancomycin. The efficacy and safety of a single-dose of intravenous oritavancin therapy compared with multiple doses of vancomycin for the treatment of patients with ABSSSI are currently being assessed in Phase 3 clinical trials (SOLO-1 and SOLO-2). In this study, oritavancin activity was assessed against key pathogens (*S. aureus* and β-hemolytic streptococci [BHS]) responsible for SSSI among patients in USA hospitals during the international surveillance program for oritavancin (2010-2012).

Methods

Bacterial strain collection. *S. aureus* isolates (3,061) and BHS (301) collected (2010-2012) from unique patients with documented SSSIs hospitalized in 27 sites in nine USA Census regions, were included in this study. Isolates included in this evaluation were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa) following previously established protocols. Bacterial species identification was performed by using an automated system (Vitek®2; bioMérieux, Hazelwood, Missouri) and/or conventional biochemical algorithms, as required.

Antimicrobial susceptibility testing. Isolates were tested for susceptibility by broth microdilution methods following the Clinical and Laboratory Standards Institute (CLSI; M07-A9, 2012) document. Susceptibility testing was performed in cation-adjusted Mueller-Hinton broth (CA-MHB) using dry-form panels manufactured by Thermo Fisher Scientific (formerly TREK Diagnostics Systems/Sensititre) (Cleveland, Ohio). These panels provide results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80 (see poster E-1463). Quality assurance was performed by concurrent testing of CLSI-recommended (M100-S22, 2012) strains: *Enterococcus faecalis* American Type Culture Collection (ATCC) 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619. Interpretation of comparator MIC results tested against quality control and clinical strains were in accordance with published CLSI (M100-S22) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2012) criteria.

Results-1

- Oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) was highly active against all *S. aureus* included in this study. When tested against MRSA and MDR isolates, this agent demonstrated modal MIC and MIC_{50} results (0.03 μg/mL for both; 59.7 - 60.6% of MIC values at 0.03 μg/mL) equivalent to that observed for methicillin-susceptible strains (0.03 μg/mL for both; 64.6% of MIC values at 0.03 μg/mL; Table 1).
- Vancomycin ($MIC_{50/90}$, 1/1 μg/mL; 100% susceptible), teicoplanin ($MIC_{50/90}$, ≤2/≤2 μg/mL; ≥99.4% susceptible), daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/1 μg/mL; ≥99.7% susceptible) demonstrated high susceptibility rates when tested against subsets of MRSA and MDR clinical strains (Table 2).
- When tested against the MRSA and MDR groups, oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) was eight-fold more potent than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL), and 16- to 32-fold more potent than vancomycin ($MIC_{50/90}$, 1/1 μg/mL; Table 2).
- Tetracycline ($MIC_{50/90}$, ≤0.25/0.5 μg/mL; 94.0-95.9% susceptible) and trimethoprim/sulfamethoxazole (TMP/SMX; $MIC_{50/90}$, ≤0.5/≤0.5 μg/mL; 98.4% susceptible) also demonstrated *in vitro* coverage when tested against the MRSA subset (Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) exhibited potent activity when tested against a collection of BHS clinical isolates. Equivalent MIC results ($MIC_{50/90}$, 0.03/0.12 μg/mL) were observed for oritavancin when tested against different groups of BHS or a MDR subset (Table 1).
- Overall, oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL; 100.0% susceptible) were the most active compounds tested against Groups A and B of BHS (Table 2). Vancomycin, teicoplanin, daptomycin, linezolid and levofloxacin also demonstrated coverage (≥91.9% susceptible) against both BHS Groups (Table 2). Other comparators, such as clindamycin and tetracycline were active against *S. pyogenes* (90.9-95.4% susceptible).

Results-2

Table 1. MIC distribution of oritavancin tested against key pathogens responsible for SSSI in the USA as part of the 2010 – 2012 international oritavancin surveillance program.

Organism (number tested)[a]	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Number (cumulative %) inhibited at each oritavancin MIC (μg/mL)[b] ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
S. aureus (3,061)	0.03	0.12	76(2.5)	674(24.5)	**1163(62.5)**	819(89.3)	268(98.0)	61(100.0)	–
Methicillin-susceptible (1,460)	0.03	0.06	41(2.8)	338(26.0)	**564(64.6)**	369(90.0)	122(98.2)	26(100.0)	–
Methicillin-resistant (1,601)	0.03	0.12	35(2.2)	336(23.2)	**599(60.6)**	450(88.7)	146(97.8)	35(100.0)	–
MDR (320)	0.03	0.12	6(1.9)	49(17.2)	**136(59.7)**	95(89.4)	31(99.1)	3(100.0)	–
β-hemolytic streptococci (301)	0.03	0.12	38(12.6)	**89(42.2)**	85(70.4)	42(84.4)	31(94.7)	13(99.0)	3(100.0)
Group A (197)	0.03	0.12	37(18.8)	**53(45.7)**	50(71.1)	29(85.8)	18(94.2)	9(99.5)	1(100.0)
Group B (104)	0.03	0.12	1(1.0)	**36(35.6)**	35(69.2)	13(81.7)	13(94.2)	4(98.1)	2(100.0)
MDR (35)	0.03	0.12	2(5.7)	**12(40.0)**	**12(74.3)**	3(82.9)	5(97.1)	1(100.0)	-

a. Multidrug-resistant (MDR) strains of *S. aureus* are represented by those displaying methicillin resistance (oxacillin) in addition to a non-susceptible phenotype to at least three of the following drugs: erythromycin, clindamycin, levofloxacin, tetracycline and trimethoprim/sulfamethoxazole. MDR β-hemolytic streptococcal strains were those showing a non-susceptible phenotype to at least three of the following drugs: erythromycin, clindamycin, levofloxacin or tetracycline.
b. Modal MIC values are in bold.

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against key pathogens responsible for SSSI in the USA as part of the 2010 – 2012 international oritavancin surveillance program.

Organism[a] (no. tested) Antimicrobial agent	Range	MIC (μg/mL) 50%	MIC (μg/mL) 90%	% Susceptible/Resistant[b] CLSI	% Susceptible/Resistant[b] EUCAST
S. aureus (3,061)					
Methicillin-susceptible (1,460)					
Oritavancin	≤0.008 – 0.25	0.03	0.12	–[c] / –	– / –
Vancomycin	0.25 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Daptomycin	≤0.06 – 2	0.25	0.5	99.9 / –	99.9 / 0.1
Linezolid	≤0.12 – 2	1	2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25 – >4	≤0.25	>4	64.7 / 32.6	65.0 / 34.2
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	96.2 / 3.8	95.8 / 3.8
Tetracycline	≤0.25 – >8	≤0.25	≤0.25	96.2 / 3.4	95.4 / 4.5
Levofloxacin	≤0.5 – >4	≤0.5	4	87.5 / 10.9	87.5 / 10.9
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	99.2 / 0.8	99.2 / 0.8
Methicillin-resistant (1,601)					
Oritavancin	≤0.008 – 0.25	0.03	0.12	– / –	– / –
Vancomycin	0.5 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0	99.9 / 0.1
Daptomycin	0.12 – 1	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	≤0.12 – 8	1	1	99.9 / 0.1	99.9 / 0.1
Erythromycin	≤0.25 – >4	>4	>4	10.6 / 88.2	10.7 / 89.0
Clindamycin	≤0.25 – >2	≤0.25	>2	79.6 / 20.2	79.3 / 20.4
Tetracycline	≤0.25 – >8	≤0.25	0.5	95.9 / 3.7	94.0 / 4.2
Levofloxacin	≤0.5 – >4	4	>4	41.3 / 55.7	41.3 / 55.7
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	98.4 / 1.6	98.4 / 1.5
Multidrug-resistant (320)					
Oritavancin	≤0.008 – 0.25	0.03	0.12	– / –	– / –
Oxacillin	>2	>2	>2	0.0 / 100.0	0.0 / 100.0
Vancomycin	0.5 – 2	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0	99.4 / 0.6
Daptomycin	0.12 – 1	0.25	0.5	100.0 / –	100.0 / 0.0
Linezolid	≤0.12 – 8	1	1	99.7 / 0.3	99.7 / 0.3
Erythromycin	0.25 – >4	>4	>4	0.3 / 98.8	0.3 / 99.7
Clindamycin	≤0.25 – >2	>2	>2	7.2 / 92.8	7.2 / 92.8
Tetracycline	≤0.25 – >8	≤0.25	>8	87.8 / 11.9	80.6 / 12.2
Levofloxacin	≤0.5 – >4	>4	>4	0.6 / 98.8	0.6 / 98.8
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	92.5 / 7.5	92.5 / 6.9
β-hemolytic streptococci (301)					
Group A (197)					
Oritavancin	≤0.008 – 0.5	0.03	0.12	– / –	– / –
Penicillin	≤0.06 – 0.12	≤0.06	≤0.06	100.0 / –	100.0 / 0.0
Vancomycin	0.25 – 0.5	0.25	0.5	100.0 / –	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	– / –	100.0 / 0.0
Daptomycin	≤0.06 – 0.25	≤0.06	≤0.06	100.0 / –	100.0 / 0.0
Linezolid	0.25 – 1	1	1	100.0 / –	100.0 / 0.0
Erythromycin	≤0.25 – >4	≤0.25	1	89.8 / 10.2	89.8 / 10.2
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	95.4 / 4.6	95.4 / 4.6
Tetracycline	≤0.25 – >8	≤0.25	0.5	90.9 / 9.1	90.9 / 9.1
Levofloxacin	≤0.5 – >4	≤0.5	1	99.5 / 0.5	91.9 / 0.5
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	– / –	97.5 / 1.5
Group B (104)					
Oritavancin	≤0.008 – 0.5	0.03	0.12	– / –	– / –
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Vancomycin	0.25 – 0.5	0.5	0.5	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	– / –	100.0 / 0.0
Daptomycin	0.12 – 0.5	0.25	0.25	100.0 / –	100.0 / 0.0
Linezolid	0.5 – 1	1	1	100.0 / –	100.0 / 0.0
Erythromycin	≤0.25 – >4	1	>4	48.1 / 51.9	48.1 / 51.9
Clindamycin	≤0.25 – >2	≤0.25	>2	68.3 / 30.8	69.2 / 30.8
Tetracycline	≤0.25 – >8	>8	>8	11.5 / 87.5	11.5 / 88.5
Levofloxacin	≤0.5 – 4	≤0.5	1	99.0 / 0.0	97.1 / 1.0
TMP/SMX	≤0.5 – 1	≤0.5	≤0.5	– / –	100.0 / 0.0

a. Multidrug-resistant (MDR) strains of *S. aureus* are represented by those displaying methicillin resistance (oxacillin) in addition to a non-susceptible phenotype to at least three of the following drugs: erythromycin, clindamycin, levofloxacin, tetracycline and trimethoprim/sulfamethoxazole (TMP/SMX).
b. Breakpoint criteria according to CLSI (M100-S22, 2012) and EUCAST (2012).
c. Breakpoints not available.

Conclusions

- Oritavancin ($MIC_{50/90}$, 0.03/0.06-0.12 μg/mL) demonstrated potent activity against this contemporary (2010 - 2012) collection of *S. aureus* and BHS isolates, including resistant subsets, causing SSSI in USA hospitals. In addition, oritavancin inhibited 99.8% of SSSI organisms at ≤0.25 μg/mL.
- These *in vitro* data demonstrate that oritavancin has an antimicrobial activity greater than direct comparators available for managing SSSI caused by *S. aureus* and potency similar to that of penicillin against BHS.
- Oritavancin continues to exhibit potent antimicrobial activity against key pathogens responsible for ABSSSI. These *in vitro* surveillance results provide a benchmark for oritavancin against current clinical pathogens as this agent completes clinical development.

References

Arhin FF, Sarmiento I, Parr TR Jr, Moeck G (2012). Activity of oritavancin and comparators in vitro against standard and high inocula of *Staphylococcus aureus*. Int J Antimicrob Agents 39: 159-162.

Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition.* Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement.* Wayne, PA: CLSI.

European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed: January 1, 2012.

Mendes RE, Woosley LN, Farrell DJ, Sader HS, Jones RN (2012). Oritavancin activity against vancomycin-susceptible and vancomycin-resistant Enterococci with molecularly characterized glycopeptide resistance genes recovered from bacteremic patients, 2009-2010. Antimicrob Agents Chemother 5: 1639-1642.

52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, CA, September 9-12, 2012