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Oritavancin Activity Tested against *Staphylococcus aureus* Responsible for Documented Infections in European Hospitals (2008-2011)

Contact info:
Rodrigo Mendes, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre
Suite A
North Liberty, Iowa
USA 52317
Tel: 319-665-3370 ext 218
Email: rodrigo-mendes@jmilabs.com

RE MENDES, *HS SADER, DJ FARRELL, RN JONES*

JMI Laboratories, North Liberty, Iowa, USA

Abstract

Objectives: To assess the activity of oritavancin, a lipoglycopeptide under late-stage clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Oritavancin potency has been continuously monitored against Gram-positive clinical organisms from hospitals in the USA and Europe for four years. The aim of this study was to compare the activity of oritavancin with that of other marketed ABSSSI agents tested against *Staphylococcus aureus* from Europe.

Methods: *S. aureus* isolates (9,274) were collected (2008-2011) from 38 hospitals in 14 European countries, including Turkey and Israel, as part of the SENTRY Antimicrobial Surveillance Program. Isolates were submitted to a central laboratory where bacterial identifications were confirmed using standard algorithms and Vitek 2. Isolates were tested for susceptibility against oritavancin and comparators by CLSI methods (M07-A9, 2012). EUCAST (2012) and CLSI (2012) interpretative criteria were applied, when available. Isolates displaying resistance to oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline were considered multidrug-resistant (MDR).

Results: Isolates were mostly from SSSI (37.9%) and bloodstream infections (35.7%). The potent activity of oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was consistent across all subsets analyzed. Moreover, oritavancin inhibited 99.1% of *S. aureus* at ≤0.12 mg/L. Vancomycin (100% susceptible; EUCAST) and daptomycin (>99.9% susceptible) also showed stable $MIC_{50/90}$ results, except for daptomycin, which had a MIC_{50} value against MDR strains slightly higher (two-fold) than that obtained against the susceptible control group. Overall, comparator agents showed adequate antimicrobial coverage (≥90% susceptible) when tested against all *S. aureus*. However, erythromycin (71.6% susceptible), clindamycin (89.1% susceptible), levofloxacin (73.0% susceptible) and β-lactams (oxacillin, 74.3% susceptible) displayed suboptimal coverage when EUCAST criteria were applied. When tested against methicillin-resistant *S. aureus* and MDR strains, oritavancin was at least eight-fold more potent than daptomycin, and at least 16-fold more potent than both vancomycin and linezolid. Vancomycin (100% susceptible), teicoplanin (95.4% susceptible), daptomycin (100% susceptible) and linezolid (100% susceptible) were active (EUCAST) against MDR isolates.

Conclusions: Oritavancin continues to demonstrate potent *in vitro* activity when tested against a contemporary (2008-2011) collection of *S. aureus* recovered from European hospitals. In addition, oritavancin exhibited activity greater (≥eight-fold) than comparator agents, including when tested against selected MDR strains.

Introduction

Oritavancin is a semisynthetic bactericidal lipoglycopeptide in late-stage clinical development. This drug has demonstrated broad *in vitro* activity against Gram-positive pathogens, including multidrug-resistant (MDR) strains of methicillin-resistant *Staphylococcus aureus* (MRSA), other staphylococci and streptococci associated with skin and bloodstream infections, and *Enterococcus* spp. strains including those strains resistant to vancomycin. Oritavancin possesses three distinct mechanisms of action, which consist of (1) disruption of bacterial membrane integrity; (2) inhibition of the transglycosylation step of the bacterial cell wall synthesis; and (3) inhibition of the transpeptidation step of cell wall synthesis. The multiple mechanisms of action confer on oritavancin a potent, concentration-dependent bactericidal activity against Gram-positive pathogens.

The efficacy and safety of a single-dose of intravenous oritavancin therapy compared with multiple doses of vancomycin for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) is currently being assessed through Phase 3 clinical trials (SOLO-1 and SOLO-2). Moreover, oritavancin *in vitro* activity has been continuously monitored since 2008 against Gram-positive clinical isolates collected from United States (USA) and European hospitals as part of the SENTRY Antimicrobial Surveillance Program. This study reports the *in vitro* activity of oritavancin and other marketed ABSSSI agents tested against *S. aureus* from Europe.

Methods

Bacterial strain collection. *S. aureus* isolates (9,274) collected (2008-2011) from unique hospitalized patients with documented infections in 38 hospitals in 14 European countries, including Turkey and Israel, were included in this study. Isolates included in this evaluation were mostly from SSSI (37.9%) and bacteraemia (35.7%), and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) following previously established protocols. Bacterial species identification was performed by using an automated system (Vitek®2; bioMérieux, Hazelwood, Missouri, USA) or conventional biochemical algorithms, as required.

Antimicrobial susceptibility test methods. 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 ThermoFisher Scientific (formerly TREK Diagnostics Systems/Sensititre) (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-S22, 2012) strains: *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213. Interpretation of comparator MIC results was in accordance with published CLSI (M100-S22) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2012) criteria.

S. aureus isolates were stratified based on the antimicrobial susceptibility profile, as follows: wildtype (WT) multidrug-susceptible (control group), methicillin (oxacillin)-susceptible and -resistant, and MDR isolates. The multidrug-susceptible group is represented by wildtype isolates susceptible to all comparator agents tested, while the MDR group is comprised of those displaying resistance to oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline.

Results – 1

- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was highly active against all *S. aureus*. When tested against MRSA and MDR clinical isolates this agent demonstrated modal MIC results (47.6 - 52.3% of MIC values at 0.03 mg/L) equivalent to that observed for the WT susceptible control group (41.6% of MIC values at 0.03 mg/L; Table 1).
- Overall, 25.7, 28.0, 10.4 and 26.4% of *S. aureus* strains were resistant to methicillin, erythromycin, clindamycin and levofloxacin, respectively, according to EUCAST criteria (Table 2). Vancomycin, teicoplanin, daptomycin, linezolid and trimethoprim/sulfamethoxazole demonstrated highest coverage (≥99.1% susceptible; EUCAST).
- Vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible), teicoplanin ($MIC_{50/90}$, ≤2/≤2 mg/L; ≥95.4% susceptible), daptomycin ($MIC_{50/90}$, 0.25 - 0.5/0.5 mg/L; >99.9% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; 100% susceptible) demonstrated high susceptibility rates when tested against subsets of MRSA and MDR clinical strains (Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L), vancomycin ($MIC_{50/90}$, 1/1 mg/L) and linezolid ($MIC_{50/90}$, 1/2 mg/L) showed stable MIC_{50} results when tested against MRSA and MDR isolates compared with the multidrug-susceptible control group (Table 2). In contrast, daptomycin tested against MDR isolates exhibited MIC_{50} values ($MIC_{50/90}$, 0.5/0.5 mg/L) slightly higher (two-fold) than that obtained against the WT control group ($MIC_{50/90}$, 0.25/0.5 mg/L).
- A total of 38 (0.4%) *S. aureus* exhibited a resistance phenotype to teicoplanin (MIC values, >2 mg/L) according to the EUCAST criteria. When tested against this select group of strains, oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) demonstrated MIC_{50} and MIC_{90} values equivalent to those obtained against the WT control group ($MIC_{50/90}$, 0.03/0.06 mg/L; data not shown).
- When tested against the MRSA and MDR group of strains, oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was eight- to 16-fold more potent than daptomycin ($MIC_{50/90}$, 0.25 - 0.5/0.5 mg/L), and 16- to 32-fold more potent than both vancomycin ($MIC_{50/90}$, 1/1 mg/L) and linezolid ($MIC_{50/90}$, 1/2 mg/L).

Results – 3

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against *S. aureus* (overall), resistant subsets and a wildtype susceptible control group as part of the 2008 – 2011 international oritavancin surveillance program.

Organism[a] (number tested) Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% Susceptible/Resistant[b] CLSI	EUCAST
All (9,274)					
Oritavancin	0.03	0.06	≤0.008 – 0.5	–[c] / –	– / –
Oxacillin	0.5	>2	≤0.25 – >2	74.3 / 25.7	74.3 / 25.7
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.6 / 0.4
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	0.12 – 4	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	71.0 / 27.5	71.6 / 28.0
Clindamycin	≤0.25	>2	≤0.25 – >2	89.6 / 10.2	89.1 / 10.4
Tetracycline	≤2	≤2	≤2 – >8	92.7 / 6.6	92.3 / 7.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	73.0 / 26.4	73.0 / 26.4
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >2	99.1 / 0.9	99.1 / 0.8
Multidrug-susceptible (2,588)					
Oritavancin	0.03	0.06	≤0.008 – 0.25	– / –	– / –
Oxacillin	0.5	0.5	≤0.25 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Methicillin-resistant (2,384)					
Oritavancin	0.03	0.06	≤0.008 – 0.5	– / –	– / –
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	98.9 / 1.1
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Linezolid	1	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	≤0.25 – >2	32.9 / 65.6	33.6 / 65.9
Clindamycin	≤0.25	>2	≤0.25 – >2	66.3 / 33.5	65.4 / 33.7
Tetracycline	≤2	>8	≤2 – >8	85.9 / 13.1	85.3 / 14.4
Levofloxacin	>4	>4	≤0.5 – >4	12.1 / 87.0	12.1 / 87.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.0 / 2.0	98.0 / 1.9
Multidrug-resistant (151)					
Oritavancin	0.03	0.06	≤0.008 – 0.25	– / –	– / –
Oxacillin	>2	>2	>2	0.0 / 100.0	0.0 / 100.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	95.4 / 4.6
Daptomycin	0.5	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	>2	0.0 / 100.0	0.0 / 100.0
Clindamycin	>2	>2	1 – >2	0.0 / 98.0	0.0 / 100.0
Tetracycline	>8	>8	4 – >8	1.3 / 97.4	0.0 / 100.0
Levofloxacin	>4	>4	4 – >4	0.0 / 100.0	0.0 / 100.0
TMP/SMX	2	>2	≤0.5 – >2	76.8 / 23.2	76.8 / 23.2

a. Multidrug-susceptible group is represented by wildtype isolates susceptible to all comparator agents tested. Multidrug-resistant strains are represented by isolates displaying resistance to oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline.
b. Breakpoint criteria according to CLSI (M100-S22, 2012) and EUCAST (2012).
c. Breakpoints not available.
d. Trimethoprim/sulfamethoxazole.

Conclusions

- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) demonstrated potent activity against this contemporary (2008 - 2011) collection of *S. aureus* clinical isolates collected from Europe, including a subset of MDR strains. In addition, oritavancin inhibited 99.1% of *S. aureus* at ≤0.12 mg/L (all strains inhibited at ≤0.5 mg/L).
- The *in vitro* data presented here demonstrated that oritavancin has an antimicrobial activity eight- to 32-fold greater than marketed anti-gram-positive agents currently available for managing serious infections caused by *S. aureus.*
- Oritavancin continues to exhibit potent antimicrobial activity against *S. aureus,* the main pathogen responsible for ABSSSI. These *in vitro* surveillance results will provide a benchmark for oritavancin against current *S. aureus* pathogens as this drug continues in late-stage clinical development.

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Results – 2

Table 1. MIC distribution of oritavancin tested against *S. aureus* (overall), resistant subsets and a wildtype susceptible control group as part of the 2008 – 2011 international oritavancin surveillance program.

Organism (number tested)[a]	MIC (mg/L) 50%	90%	Number (cumulative %) inhibited at each oritavancin MIC (mg/L)[b] ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All (9,274)	0.03	0.06	262(2.8)	2292(27.5)	**4321(74.1)**	1880(94.4)	440(99.1)	78(>99.9)	1(100.0)
Methicillin-susceptible (6,890)	0.03	0.06	204(3.0)	1712(27.8)	**3187(74.1)**	1424(94.7)	302(99.1)	61(100.0)	–
Methicillin-resistant (2,384)	0.03	0.06	58(2.4)	580(26.8)	**1134(74.3)**	456(93.5)	138(99.2)	17(>99.9)	1(100.0)
Wildtype multidrug-susceptible (2,588)	0.03	0.06	53(2.0)	520(22.1)	**1077(63.8)**	690(90.4)	197(98.0)	51(100.0)	–
Non-wildtype/non-multidrug-resistant (6,535)	0.03	0.06	204(3.1)	1728(29.6	**3165(78.0)**	1174(96.0)	237(99.6)	26(>99.9)	1(100.0)
Multidrug-resistant (151)	0.03	0.06	5(3.3)	44(32.5)	**79(84.8)**	16(95.4)	6(99.3)	1(100.0)	–

a. Multidrug-susceptible group is represented by wildtype isolates susceptible to all comparator agents tested. Multidrug-resistant (MDR) strains are represented by isolates displaying resistance to oxacillin, erythromycin, clindamycin, levofloxacin and tetracycline.
b. Modal MIC results are in bold.