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Oritavancin Activity against *S. aureus* Causing Invasive Infections in USA and European Hospitals: A Five-year International Surveillance Program

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Abstract

Background: Oritavancin has been developed for the treatment of serious Gram-positive infections. This study assessed the *in vitro* activity of oritavancin tested against *S. aureus*.

Methods: 9,115 *S. aureus* (5,382 and 3,733 from the USA and Europe, respectively) recovered from blood specimens over a 5-year period (2008-2012) were included. Identification was performed by standard algorithms and Vitek® 2. Susceptibility testing was performed by CLSI methods (M07-A9) and interpretations (M100-S23). *S. aureus* resistant (CLSI criteria) to ≥4 drug classes were defined as multidrug-resistant (MDR).

Results: Analysis was performed according to the methicillin (oxacillin), vancomycin, daptomycin and MDR phenotypes. Most MRSA (72.3%) and MDR isolates (72.0%), and those with elevated MIC results for vancomycin (72.2%) and daptomycin (76.0%) were from USA sites. Oritavancin was highly active against all *S. aureus* and exhibited modal MIC, MIC_{50} and MIC_{90} values of 0.03, 0.03 and 0.06 μg/mL, respectively. Oritavancin showed modal MIC and MIC_{50} values of 0.03 μg/mL when tested against all resistant subsets, except against *S. aureus* with vancomycin MIC = 2 μg/mL and daptomycin MIC values of ≥1 μg/mL ($MIC_{50/90}$, 0.06/0.12 μg/mL, for both). Oritavancin had MIC results 16- to 32- and 8-fold lower than vancomycin ($MIC_{50/90}$, 1/1 μg/mL) and daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL), respectively, when tested against MRSA. Oritavancin MIC_{50} and MIC_{90} values were also 8-fold lower than daptomycin ($MIC_{50/90}$, 0.5/1 μg/mL) when tested against isolates with vancomycin MIC = 2 μg/mL. Vancomycin ($MIC_{50/90}$, 1/1 μg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and linezolid ($MIC_{50/90}$, 1/2 μg/mL) were active against MDR isolates (≥99.4% susceptible); however, oritavancin showed MIC results eight- to 32-fold lower than these comparators.

Conclusions: Oritavancin exhibited potent *in vitro* activity when tested against *S. aureus* causing bacteremia, and oritavancin activity results were greater than the comparators clinically available for treating serious infections. Oritavancin was slightly less active when tested against *S. aureus* exhibiting vancomycin MIC values = 2 μg/mL and daptomycin MIC values of ≥1 μg/mL, but still inhibiting these strain subsets at ≤0.25 μg/mL.

Introduction

Bacteremia or bloodstream infections (BSI) are significant causes of mortality among hospitalized patients worldwide. Gram-positive isolates are frequently isolated from bacteremia; *Staphylococcus aureus* and *S. epidermidis* are the most common causative pathogens. In addition, BSI remain a major cause of life-threatening complications in patients with cancer. The Infectious Diseases Society of America (IDSA) guidelines for methicillin-resistant *S. aureus* (MRSA) infections recommend vancomycin or daptomycin for uncomplicated bacteremia, higher doses of daptomycin for complicated bacteremia, and higher doses of daptomycin in combination with either gentamicin, rifampin, linezolid, trimethoprim/sulfamethoxazole (TMP/SMX) or a β-lactam agent for persistent MRSA bacteremia and for cases that have not responded to vancomycin treatment.

Introduction-continued

These life-threatening situations require the prescription of efficient and potent agents; additional options for treating such serious Gram-positive infections should be well received. Oritavancin is a semisynthetic bactericidal lipoglycopeptide in final clinical development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). 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 was assessed through Phase 3 clinical trials (SOLO-1 and SOLO-2). Preliminary data showed oritavancin to be non-inferior to vancomycin in the efficacy analyses for the early clinical evaluation endpoints (48 - 72 hour; Food and Drug Administration [FDA] endpoint criteria) and the later endpoints (7-14 days after end of treatment; European Medicines Agency [EMA] endpoint criteria). This study reports the *in vitro* activity of oritavancin and other agents tested against a large collection of *S. aureus* recovered from blood specimens in hospitalized patients in USA and European centers.

Methods

Bacterial strain collection. A total of 9,115 *S. aureus* (5,382 and 3,733 from the USA and Europe, respectively) were included in the study. These isolates were collected from hospitalized patients in 31 and 34 medical centers in the USA and Europe, respectively. Isolates were recovered from blood specimens over a five-year period (2008-2012) and submitted to 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 laboratory (JMI Laboratories) 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 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 panels provide 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 and *Enterococcus faecalis* ATCC 29212). All QC results were within published acceptable ranges. MIC interpretations were based on the CLSI M100-S23 (2013) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2013) breakpoint criteria, as available. *S. aureus* resistant (CLSI criteria) to at least four drug classes were defined as multidrug-resistant (MDR).

Results

- Analysis was performed according to the methicillin (oxacillin), vancomycin, daptomycin and MDR phenotypes. Most MRSA (72.3%) and MDR isolates (72.0%), and those with elevated MIC results for vancomycin (MIC = 2 μg/mL; 72.2%) and daptomycin (MIC, ≥1 μg/mL; 76.0%) originated from USA sites.
- Oritavancin was highly active against all *S. aureus* and exhibited modal MIC, MIC_{50} and MIC_{90} values of 0.03, 0.03 and 0.06 μg/mL, respectively (Table 1). Oritavancin showed modal MIC and MIC_{50} values of 0.03 μg/mL when tested against susceptible and selected subsets of MRSA and MDR isolates (Table 1).
- When oritavancin was analyzed against subsets of *S. aureus* isolates exhibiting elevated MIC results for vancomycin (i.e. 2 μg/mL) and daptomycin (i.e. ≥1 μg/mL), MIC values ($MIC_{50/90}$, 0.06/0.12 μg/mL, for both) slightly higher (two-fold) were obtained when compared with the respective control groups ($MIC_{50/90}$, 0.03/0.06 μg/mL for both; Table 1).
- Overall, 37.8% of all tested isolates were MRSA. Among comparator agents, erythromycin, clindamycin and levofloxacin demonstrated limited antimicrobial coverage (≤83.3% susceptible) when tested against *S. aureus* (Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was equally active when tested against MRSA from the USA and Europe. This drug was eight-fold more active than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL) and 16- to 32-fold more active than vancomycin ($MIC_{50/90}$, 1/1 μg/mL) and linezolid ($MIC_{50/90}$, 1/2 μg/mL) against MRSA, regardless of geographic region (Table 2).
- The vast majority of MDR strains (98.4%) defined by the established criteria were MRSA (Table 2). Vancomycin ($MIC_{50/90}$, 1/1 μg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL), linezolid ($MIC_{50/90}$, 1/2 μg/mL) and TMP/SMX ($MIC_{50/90}$, ≤0.5/≤0.5 μg/mL) were also active against MDR isolates and showed susceptibility rates ≥94.2% (Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) showed MIC results eight- to 32-fold lower than active comparators, such as vancomycin, daptomycin and linezolid when tested against the MDR subset of isolates (Table 2).

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against *S. aureus* clinical isolates, including resistant subsets causing bacteremia as part of the 2008–2012 international oritavancin surveillance program.

Organism/subset[a] (number tested) / Antimicrobial agent	Range	MIC (μg/mL) 50%	MIC (μg/mL) 90%	% Susceptible/Resistant[b] CLSI	% Susceptible/Resistant[b] EUCAST
***S. aureus* (9,115)**					
Oritavancin	≤0.008 – 0.5	0.03	0.06	–[c] / – / –	– / – / –
Oxacillin	≤0.25 – >2	0.5	>2	62.2 / 0.0 / 37.8	62.2 / 0.0 / 37.8
Vancomycin	≤0.12 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0 / 0.0	99.6 / 0.0 / 0.4
Erythromycin	≤0.25 – >2	0.5	>2	53.3 / 1.6 / 45.1	53.8 / 0.5 / 45.7
Clindamycin	≤0.25 – >2	≤0.25	>2	83.3 / 0.3 / 16.4	82.8 / 0.5 / 16.7
Tetracycline	≤2 – >8	≤2	≤2	93.7 / 0.7 / 5.6	92.6 / 0.5 / 6.9
Levofloxacin	≤0.5 – >4	≤0.5	>4	63.8 / 0.9 / 35.3	63.8 / 0.9 / 35.3
Daptomycin	≤0.06 – 4	0.25	0.5	99.9 / - / -	99.9 / 0.0 / 0.1
Linezolid	≤0.12 – >8	1	2	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
TMP/SMX[d]	≤0.5 – >2	≤0.5	≤0.5	98.6 / 0.0 / 1.4	98.6 / 0.1 / 1.3
MRSA (USA; 2,492)					
Oritavancin	≤0.008 – 0.25	0.03	0.06	– / – / –	– / – / –
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0 / 0.0	99.5 / 0.0 / 0.5
Erythromycin	≤0.25 – >2	>2	>2	9.0 / 1.1 / 89.9	9.3 / 0.4 / 90.3
Clindamycin	≤0.25 – >2	≤0.25	>2	61.9 / 0.3 / 37.8	61.2 / 0.7 / 38.1
Tetracycline	≤2 – >8	≤2	≤2	95.0 / 0.5 / 4.5	92.5 / 1.6 / 5.9
Levofloxacin	≤0.5 – >4	>4	>4	22.4 / 1.2 / 76.4	22.4 / 1.2 / 76.4
Daptomycin	≤0.06 – 4	0.25	0.5	99.6 / - / -	99.6 / 0.0 / 0.4
Linezolid	0.25 – >8	1	2	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
TMP/SMX	≤0.5 – >2	≤0.5	≤0.5	97.7 / 0.0 / 2.3	97.7 / 0.3 / 2.0
MRSA (Europe; 956)					
Oritavancin	≤0.008 – 0.5	0.03	0.06	– / – / –	– / – / –
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0 / 0.0	98.6 / 0.0 / 1.4
Erythromycin	≤0.25 – >2	>2	>2	29.8 / 2.2 / 68.0	30.6 / 0.6 / 68.8
Clindamycin	≤0.25 – >2	≤0.25	>2	62.0 / 0.7 / 37.3	61.3 / 0.7 / 38.0
Tetracycline	≤2 – >8	≤2	>8	81.5 / 1.1 / 17.4	80.8 / 0.2 / 19.0
Levofloxacin	≤0.5 – >4	>4	>4	10.6 / 1.1 / 88.3	10.6 / 1.1 / 88.3
Daptomycin	0.12 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 2	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
TMP/SMX	≤0.5 – >2	≤0.5	≤0.5	97.7 / 0.0 / 2.3	97.7 / 0.0 / 2.3
MDR (1,345)					
Oritavancin	≤0.008 – 0.5	0.03	0.06	– / – / –	– / – / –
Oxacillin	≤0.25 – >2	>2	>2	1.6 / 0.0 / 98.4	1.6 / 0.0 / 98.4
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0 / 0.0	98.7 / 0.0 / 1.3
Erythromycin	≤0.25 – >2	>2	>2	0.1 / 0.2 / 99.7	0.1 / 0.1 / 99.8
Clindamycin	≤0.25 – >2	>2	>2	4.4 / 0.1 / 95.5	4.3 / 0.1 / 95.6
Tetracycline	≤2 – >8	≤2	>8	85.9 / 0.6 / 13.5	82.1 / 2.6 / 15.3
Levofloxacin	≤0.5 – >4	>4	>4	0.6 / 0.1 / 99.3	0.6 / 0.1 / 99.3
Daptomycin	0.12 – 4	0.25	0.5	99.4 / - / -	99.4 / 0.0 / 0.6
Linezolid	0.25 – >8	1	2	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
TMP/SMX	≤0.5 – >2	≤0.5	≤0.5	94.2 / 0.0 / 5.8	94.2 / 0.4 / 5.4

a. MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant isolates displaying a resistance phenotype (CLSI criteria) to at least four anti-gram-positive agents.
b. Breakpoint criteria according to CLSI (M100-S23, 2013) and EUCAST (2013).
c. Breakpoints not available.
d. TMP/SMX = trimethoprim/sulfamethoxazole.

Table 1. Antimicrobial activity and MIC distribution for oritavancin when tested against 9,115 clinical isolates of *S. aureus*, including resistant subsets causing bacteremia as part of the 2008 – 2012 international oritavancin surveillance program.

S. aureus[a] (no. tested) / Subset	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Number (cumulative %) inhibited at MIC (μg/mL)[b] ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All (9,115)	0.03	0.06	330(3.5)	2484(30.8)	**4032(75.0)**	1788(94.6)	413(99.1)	77(99.9)	1(100.0)
MSSA (5,667)	0.03	0.06	215(3.8)	1578(31.6)	**2469(75.2)**	1118(94.9)	240(99.2)	47(100.0)	
MRSA (3,448)	0.03	0.06	105(3.0)	906(29.3)	**1563(74.7)**	670(94.1)	173(99.1)	30(>99.9)	1(100.0)
Vancomycin ≤1 μg/mL (8,910)	0.03	0.06	318(3.6)	2468(31.3)	**3959(75.7)**	1711(94.9)	383(99.2)	70(>99.9)	1(100.0)
Vancomycin = 2 μg/mL (205)	0.06	0.12	2(1.0)	16(8.8)	73(44.4)	**77(82.0)**	30(96.6)	7(100.0)	
Daptomycin ≤0.5 μg/mL (9,014)[c]	0.03	0.06	318(3.5)	2474(31.0)	**3996(75.3)**	1751(94.7)	403(99.2)	71(>99.9)	1(100.0)
Daptomycin ≥1 μg/mL (100)	0.06	0.12	2(2.0)	10(12.0)	36(48.0)	**37(85.0)**	9(94.0)	6(100)	
MDR (1,345)	0.03	0.06	25(1.9)	304(24.5)	**650(72.8)**	283(93.8)	72(99.2)	10(99.9)	1(100.0)
Non-MDR (7,770)	0.03	0.06	295(3.8)	2180(31.9)	**3382(75.4)**	1505(94.7)	341(99.1)	67(100.0)	

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant isolates displaying a resistance phenotype (CLSI criteria) to at least four anti-gram-positive agents. Isolates exhibiting elevated MIC values for daptomycin include results at 1 (91 isolates), 2 (eight isolates) and 4 μg/mL (one isolate).
b. Modal MIC values are shown in bold.
c. One daptomycin MIC result not available.

Conclusions

- Oritavancin exhibited potent *in vitro* activity when tested against a large and clinically relevant collection of *S. aureus* causing bacteremia (five-year collection; 2008-2012). The oritavancin *in vitro* potency was greater than the clinically available comparators for treating *S. aureus* infections and inhibited >99.9% of *S. aureus* at ≤0.25 μg/mL.
- The analysis of oritavancin tested against *S. aureus* resistant subsets (MRSA and MDR) showed equivalent activity (MIC_{50}) results when compared with the respective counterpart isolates. However, for *S. aureus* exhibiting elevated MIC values for vancomycin (i.e. 2 μg/mL) and daptomycin (i.e. ≥1 μg/mL), the oritavancin MIC_{50} values were two-fold higher than respective counterpart isolates.
- This study documents important and potent *in vitro* activity for oritavancin against *S. aureus* causing bacteremia, regardless of geographic region or resistance phenotype, including those with decreased susceptibility to vancomycin and daptomycin. These results warrant further investigations to determine the oritavancin role for difficult-to-treat *S. aureus* infections.

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