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Evaluation of Oritavancin Antimicrobial Activity Tested against *Staphylococcus aureus* Associated with Skin and Skin-Structure Infections (2008 - 2009)

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Abstract

Background: Oritavancin is under clinical development for therapy of acute bacterial skin and skin-structure infections (ABSSSI). This study provides a comprehensive evaluation of the activities of oritavancin and comparators tested against contemporary (2008 – 2009) *S. aureus* from documented ABSSSI. The analysis includes categorization of methicillin-resistant *S. aureus* (MRSA) according to drug resistance patterns.

Methods: 1,789 and 2,085 *S. aureus* isolates were collected from 14 European countries (27 sites), including Israel and Turkey, and USA (27 sites), respectively. Identification was performed by standard algorithms and Vitek 2. *S. aureus* were tested for susceptibility by CLSI methods (M07-A8 and M100-S20-U). MRSA were categorized based on resistance patterns. Multidrug resistance (MDR) was defined when a resistance phenotype was noted for at least four antimicrobial classes.

Results: Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was 8- to 64-fold more active than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 100.0% susceptible), vancomycin ($MIC_{50/90}$, 1/1 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 2/2 μg/mL; >99.9% susceptible). Trimethoprim/sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 μg/mL; 99.0% susceptible) and tetracycline ($MIC_{50/90}$, ≤2/2 μg/mL; 93.2% susceptible) also showed acceptable coverage (≥90% susceptible) against all *S. aureus*. A total of 1,661 (42.9%) strains were MRSA (Table), which displayed four main resistance patterns, including MDR (24.7%). Oritavancin showed modal and MIC_{50} values of 0.03 μg/mL across nearly all resistant subsets. The activity of daptomycin (MIC_{50}, 0.25 μg/mL), vancomycin (MIC_{50}, 1 μg/mL) and linezolid (MIC_{50}, 2 μg/mL) against MRSA was not affected by methicillin susceptibility phenotype. Clindamycin (96.5% susceptible) and levofloxacin (94.0% susceptible) were only active against methicillin-susceptible *S. aureus*. Oritavancin was 2-fold less active against MRSA with vancomycin MIC of 2 μg/mL (n=41; $MIC_{50/90}$, 0.06/0.12 μg/mL) compared to strains with vancomycin MIC at ≤1 μg/mL ($MIC_{50/90}$, 0.03/0.06 μg/mL).

Conclusion: Oritavancin demonstrated potent activity against this collection of *S. aureus* causing ABSSSI. Oritavancin was slightly (2-fold) less active against MRSA with elevated vancomycin MICs (2 μg/mL), although inhibiting all tested strains at ≤0.25 μg/mL.

Introduction

Acute bacterial skin and skin-structure infections (ABSSSIs) encompass a wide spectrum of clinical entities, which range in severity. Most cases of ABSSSIs are mild and may be treated in an outpatient basis with local care and/or oral antibiotics. However, moderate or severe cases of ABSSSIs involving the deeper soft tissues, such as infected ulcers, burns, and major abscesses, require surgical intervention and may require hospitalization and parenteral therapy. Gram-positive organisms, predominantly *Staphylococcus aureus*, are among the most common pathogens responsible for ABSSSI, with an increasing prevalence of methicillin-resistant *S. aureus* (MRSA).

Introduction-continued

Oritavancin is a semisynthetic bactericidal lipoglycopeptide that is being developed for the treatment of ABSSSI caused by several Gram-positive organisms, including multidrug-resistant (MDR) staphylococci, enterococci and streptococci. This study was conducted to evaluate the oritavancin activity against *S. aureus* responsible for documented ABSSSI collected from hospitalized patients in the USA and Europe within the SENTRY Antimicrobial Surveillance Program. Furthermore, this analysis includes an evaluation of oritavancin actitivity tested against MRSA displaying a variety of MDR patterns.

Methods

Bacterial strain collection:
A total of 2,085 and 1,789 *S. aureus* were collected from USA (27 sites) and European (27 sites) medical centers, respectively. Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) as part of the SENTRY Program. The primary medical center provided the species identification and the monitoring laboratory confirmed the speciation using BactiStaph latex and tube coagulase agglutination tests (Remel, Lenxa, Kansas, USA), and the Vitek 2 Microbial Identification Systems (bioMérieux, Hazelwood, Missouri, USA), when necessary.

Antimicrobial susceptibility testing:
Isolates were tested for susceptibility by the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) recommendations (M07-A8, 2009). Susceptibility testing was performed by using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains: *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213. Interpretation of comparator (ten) MIC results was in accordance with published CLSI (M100-S20-U) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2010) criteria.

Analysis of oritavancin activity was performed against groups of *S. aureus* displaying different antibiogram resistance patterns (intermediate susceptibility was grouped as resistant using CLSI criteria). Among these patterns, a set of MDR strains (i.e. isolates displaying resistance to at least three classes of drugs in addition to β-lactams [oxacillin]) and a group of MRSA strains with elevated vancomycin MIC results (2 μg/mL) were included.

Results-1

- Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL; modal MIC, 0.03 μg/mL) demonstrated consistent antimicrobial activity when tested against *S. aureus,* regardless of geographic origin and antimicrobial resistance phenotypes (Table 1).
- Oritavancin MIC results were slightly higher when tested against MRSA displaying vancomycin MIC of 2 μg/mL (46.3% inhibited at ≤0.03 μg/mL; $MIC_{50/90}$, 0.06/0.12 μg/mL) compared to strains with vancomycin MIC at ≤1 μg/mL (82.1% inhibited at ≤0.03 μg/mL; $MIC_{50/90}$, 0.03/0.06 μg/mL; Table 1).
- Methicillin-susceptible *S. aureus* (MSSA) recovered from USA and European medical centers were very susceptible (≥90.5%) to all comparator agents tested, except for erythromycin (62.4 − 84.1% susceptible; Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was 32- to 64-fold more active than other clinically available comparators for the treatment of ABSSSI (i.e. vancomycin [$MIC_{50/90}$, 1/1 μg/mL; 100.0% susceptible] and linezolid [$MIC_{50/90}$, 2/2 μg/mL; 100.0% susceptible]; Table 2) when tested against MSSA.
- Daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 100.0% susceptible), clindamycin ($MIC_{50/90}$, ≤0.25/≤0.25 μg/mL; 94.6 – 97.5% susceptible), levofloxacin ($MIC_{50/90}$, ≤0.5/1 μg/mL; 90.5 – 96.2% susceptible) and trimethoprim/sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 μg/mL; 98.9 – 99.6% susceptible) were active against MSSA isolates (Table 2).
- When tested against MRSA clinical isolates, oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was 32- and 64-fold more active than vancomycin ($MIC_{50/90}$, 1/1 μg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 2/2 μg/mL; ≥99.8% susceptible; Table 2), respectively.
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) inhibited all MDR isolates at ≤0.25 μg/mL (Tables 1 and 2). In addition, oritavancin was 32-fold more active than vancomycin ($MIC_{50/90}$, 1/1 μg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; 99.5% susceptible), and eight-fold more active than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 100.0% susceptible) when tested against MDR strains (Table 2).

Results-2

Table 1. MIC frequency distribution for oritavancin tested against *S. aureus* and resistant subsets of MRSA isolates submitted as part of the 2008 – 2009 international surveillance program.

Resistance pattern[a] (no. tested/% of total[b])	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Number (cumulative %) inhibited at MIC (μg/mL) ≤0.008	0.015	0.03	0.06	0.12	0.25
All *S. aureus* (3,874)	0.03	0.06	107(2.8)	1113(31.5)	**2000(83.1)**[c]	582(98.1)	65(99.8)	7(100.0)
S. aureus USA (2,085/53.8)	0.03	0.06	43(2.1)	600(30.8)	**1075(82.4)**	328(98.1)	35(99.8)	4(100.0)
S. aureus Europe (1,789/46.2)	0.03	0.06	64(3.6)	513(32.3)	**925(84.0)**	254(98.2)	30(99.8)	3(100.0)
MSSA (2,213/57.1)	0.03	0.06	76(3.4)	670(33.7)	**1125(84.5)**	302(98.2)	36(99.8)	4(100.0)
MRSA (1,661/42.9)	0.03	0.06	31(1.9)	443(28.5)	**875(81.2)**	280(98.1)	29(99.8)	3(100.0)
OX, LE, ER (506/30.5[d])	0.03	0.06	7(1.4)	134(27.9)	**274(82.0)**	86(99.0)	4(99.8)	1(100.0)
OX, ER (420/25.3[d])	0.03	0.06	5(1.2)	128(31.7)	**211(81.9)**	70(98.6)	6(100.0)	–
OX, ER, LE, CL (313/18.8[d])	0.03	0.06	8(2.6)	68(24.3)	**169(78.3)**	60(97.4)	7(99.7)	1(100.0)
OX, LE, (143/8.6[d])	0.03	0.06	3(2.1)	39(29.4)	**72(79.7)**	24(96.5)	4(99.3)	1(100.0)
OX (90/5.4[d])	0.03	0.06	3(3.3)	24(30.0)	**43(77.8)**	16(95.6)	4(100.0)	–
OX, LE, CL, ER, TC (40/2.4[d])	0.03	0.03	1(2.5)	14(37.5)	**21(90.0)**	4(100.0)	–	–
OX, CL, ER (30/1.8[d])	0.03	0.06	0(0.0)	5(16.7)	**20(83.3)**	5(100.0)	–	–
OX, TC (27/1.6[d])	0.03	0.06	1(3.7)	7(29.6)	**14(81.5)**	3(92.6)	2(100.0)	–
OX, LE, ER, TC (24/1.4[d])	0.03	0.06	0(0.0)	2(8.3)	**17(79.2)**	4(95.8)	1(100.0)	–
MDR (411/24.7[d])	0.03	0.06	11(2.7)	95(25.8)	**223(80.0)**	73(97.8)	8(99.8)	1(100.0)
VA MIC ≤1 μg/mL (1,620/97.5[d])	0.03	0.06	31(1.9)	440(29.1)	**859(82.1)**	263(98.3)	25(99.9)	2(100.0)
VA MIC = 2 μg/mL (41/2.5[d])	0.06	0.12	0(0.0)	3(7.3)	16(46.3)	**17(87.8)**	4(97.6)	1(100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*. Most prevalent resistance patterns noted among MRSA. Intermediate and resistant results grouped as resistant. Criteria for susceptibility were those published by CLSI (2010). CL, clindamycin; ER, erythromycin; LE, levofloxacin; OX, oxacillin; VA, vancomycin; and TC, tetracycline. MDR = resistance to at least three classes of drugs in addition to β-lactams (oxacillin).
b. Percentage of total number of *S. aureus*, unless otherwise indicated.
c. Modal MIC values are shown in bold.
d. Percentage of total number of MRSA strains.

Table 2. Antimicrobial activity of oritavancin and comparator antimicrobial agents tested against *S. aureus* from USA and European hospitals (2008 – 2009).

Organism (no. tested)/ Antimicrobial agent	MIC (μg/mL) 50%	90%	Range	Susceptibility category[a] % Susceptible / % Resistant CLSI	EUCAST
MSSA USA (857)					
Oritavancin	0.03	0.06	≤0.008 – 0.25	–[b] / –	– / –
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	99.6 / 0.4
Erythromycin	0.5	>2	≤0.25 – >2	62.4 / 37.2	62.5 / 37.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	94.9 / 4.9	94.6 / 5.1
Tetracycline	≤2	≤2	≤2 – >8	95.3 / 3.9	94.9 / 5.1
Levofloxacin	≤0.5	1	≤0.5 – >4	90.5 / 9.0	90.5 / 9.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / –	100.0 / 0.0
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.9 / 1.1	98.9 / 1.1
MSSA Europe (1,356)					
Oritavancin	0.03	0.06	≤0.008 – 0.25	– / –	– / –
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.7 / 0.3
Erythromycin	≤0.25	>2	≤0.25 – >2	82.7 / 15.7	84.1 / 15.7
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.5 / 2.4	97.2 / 2.5
Tetracycline	≤2	≤2	≤2 – >8	94.2 / 5.2	93.7 / 6.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	96.2 / 3.5	96.2 / 3.5
Daptomycin	0.25	0.5	0.12 – 1	100.0 / –	100.0 / 0.0
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	99.6 / 0.4	99.6 / 0.4
MRSA USA (1,228)					
Oritavancin	0.03	0.06	≤0.008 – 0.25	– / –	– / –
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	99.5 / 0.5
Erythromycin	>2	>2	≤0.25 – >2	8.4 / 91.1	8.6 / 91.1
Clindamycin	≤0.25	>2	≤0.25 – >2	78.1 / 21.7	77.7 / 21.9
Tetracycline	≤2	≤2	≤2 – >8	94.9 / 4.5	94.0 / 6.0
Levofloxacin	4	>4	≤0.5 – >4	42.8 / 56.4	42.8 / 56.4
Daptomycin	0.25	0.5	0.12 – 1	100.0 / –	100.0 / 0.0
Linezolid	2	2	0.5 – 8	99.8 / 0.2	99.8 / 0.2
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.9 / 1.1	98.9 / 1.1
MRSA Europe (433)					
Oritavancin	0.03	0.06	≤0.008 – 0.12	– / –	– / –
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	98.6 / 1.4
Erythromycin	>2	>2	≤0.25 – >2	40.2 / 59.1	40.9 / 59.1
Clindamycin	≤0.25	>2	≤0.25 – >2	67.9 / 31.6	67.2 / 32.1
Tetracycline	≤2	>8	≤2 – >8	81.1 / 18.2	80.4 / 19.6
Levofloxacin	>4	>4	≤0.5 – >4	16.6 / 83.4	16.6 / 83.4
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / –	100.0 / 0.0
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	97.5 / 2.5	97.5 / 2.5
MDR MRSA (411)					
Oritavancin	0.03	0.06	≤0.008 – 0.25	– / –	– / –
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	98.3 / 1.7
Erythromycin	>2	>2	1 – >2	0.0 / 99.8	0.2 / 99.8
Clindamycin	>2	>2	≤0.25 – >2	8.3 / 91.0	8.0 / 91.7
Tetracycline	≤2	>8	≤2 – >8	78.8 / 20.0	77.1 / 22.9
Levofloxacin	>4	>4	≤0.5 – >4	2.7 / 96.8	2.7 / 96.8
Daptomycin	0.25	0.5	0.12 – 1	100.0 / –	100.0 / 0.0
Linezolid	1	2	0.5 – 8	99.5 / 0.5	99.5 / 0.5
TMP/SMX	≤0.5	1	≤0.5 – >2	94.9 / 5.1	94.9 / 5.1

MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug-resistant; TMP/SMX, trimethoprim/sulfamethoxazole.

a. Criteria for susceptibility as published by the CLSI (M100-S20-U; Update June 2010) and EUCAST (2010).
b. –, no breakpoint available.

Conclusions

- When tested against *S. aureus* from documented ABSSSI, oritavancin exhibited potent activity, which was not affected by geographic regions or different resistance phenotypes. Oritavancin activity was slightly affected (two-fold in the $MIC_{50/90}$ values) when tested against MRSA exhibiting vancomycin MIC values of 2 μg/mL compared with those with lower vancomycin MIC results (≤1 μg/mL).
- Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was 32- to 64-fold more active than comparator agents with approved clinical indication for ABSSSI (vancomycin [$MIC_{50/90}$, 1/1 μg/mL] and linezolid [$MIC_{50/90}$, 2/2 μg/mL]) when tested against *S. aureus*, including MDR strains.
- This in vitro activity data demonstrates that, once clinically approved, oritavancin will be a promising addition to the therapeutic armamentarium for treating ABSSSI infections caused by *S. aureus*.

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