Activity of Oritavancin and Comparator Agents against Multidrug-resistant Staphylococcal and Streptococcal Isolates Responsible for Documented Infections in European Hospitals (2011-2013)

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Introduction

The use of β-lactam antibiotics to empirically treat skin and soft-tissue infections (SSTIs) in many regions of the world has been compromised by the widespread isolation of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Vancomycin remains the first-line antimicrobial therapy for invasive infections caused by MRSA. Some recent studies have correlated increased vancomycin MIC results with adverse clinical outcomes. However, a prospective study identified the same high vancomycin MIC results as predictor for poor outcomes even among patients receiving a directed therapy for treating a methicillin-susceptible *S. aureus* infection.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide currently under regulatory review by the US-Food and Drug Administration and European Medicines Agency for the treatment of patients with acute bacterial SSTIs. This study was performed to assess the activity of oritavancin against multidrug-resistant (MDR) staphylococcal and streptococcal pathogens recovered from European medical centres as part of the SENTRY Antimicrobial Surveillance Programme for 2011-2013.

Materials and Methods

Bacterial strain collection. A total of 9,039 isolates recovered from clinical specimens in hospitalised patients with documented infections in Europe (30 sites in 14 countries) and Israel (one site) were included. Selected isolates were submitted to the monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Programme. Isolates were primarily identified by the participating laboratory; their identity was 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. 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, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges (M100-S24). MIC interpretations were based on the CLSI M100-S24 (2014) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2014) breakpoint criteria, as available. Staphylococci and streptococci non-susceptible (based on CLSI criteria) to ≥4 and ≥3 drug classes, respectively, were defined as MDR.

Results

- A total of 584 (9.4%) of *S. aureus* isolates met the criteria for a MDR phenotype (Table). These isolates were mostly (99.3%) methicillin-resistant (MRSA) and demonstrated elevated resistance rates (33.1 – 97.9%) for erythromycin, clindamycin, tetracycline and levofloxacin (Table).
- Oritavancin exhibited MIC_{50} results of 0.03 mg/L when tested against MDR and non-MDR isolates of *S. aureus* (Table); this value was at least eight-fold lower than those of daptomycin, vancomycin or linezolid (Table).
- Oritavancin and daptomycin modal MIC, MIC_{50} and MIC_{90} results when tested against *S. aureus* isolates with vancomycin MIC = 2 mg/L were 2-fold higher than those obtained against isolates with vancomycin MIC at ≤1 mg/L.
- Overall, β-lactams (oxacillin), erythromycin, clindamycin, tetracycline and levofloxacin demonstrated marginal *in vitro* activity (53.2 – 84.0% susceptible) when tested against the subset of *S. aureus* isolates exhibiting vancomycin MIC = 2 mg/L (Table), while other comparators showed acceptable antimicrobial coverage (≥91.5% susceptible).
- Oritavancin $MIC_{50/90}$ (0.06/0.12 mg/L) was ≥8-fold lower than daptomycin and linezolid when tested against *S. aureus* isolates exhibiting vancomycin MIC = 2 mg/L (Table).
- A large proportion (37.0%; 477/1289) of coagulase-negative staphylococci (CoNS) met the MDR criteria. Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) and linezolid ($MIC_{50/90}$, 0.5/1 mg/L) had equivalent MIC_{50} and MIC_{90} results when tested against MDR and non-MDR CoNS, while all other agents tested against MDR CoNS showed MIC_{50} results at least two-fold higher than those obtained against non-MDR CoNS (data not shown).
- Comparator agents such as daptomycin, linezolid, teicoplanin and vancomycin had MIC results eight- to 128-fold higher than oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) when tested against MDR CoNS (Table).
- Only 6.3% of β-haemolytic streptococci had a MDR phenotype, which was mostly due to non-susceptibility to erythromycin, clindamycin and tetracycline. These MDR β-haemolytic streptococcal isolates had low $MIC_{50/90}$ values to oritavancin ($MIC_{50/90}$, 0.03/0.12 mg/L), which was equivalent to that obtained against the non-MDR group ($MIC_{50/90}$, 0.03/0.25 mg/L).
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 mg/L) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100% susceptible) were most active against β-haemolytic streptococci.
- Oritavancin $MIC_{50/90}$ (0.015/0.06 mg/L) was at least 16-fold lower than those obtained for the comparator agents demonstrating *in vitro* activity (≥91.4% susceptible) against the MDR population of Viridans group streptococci (Table).

Table. Antimicrobial activity of oritavancin and comparator agents against MDR subsets of Gram-positive clinical isolates from Europe and Israel as part of the 2011–2013 SENTRY Antimicrobial Surveillance Programme.

Organism (number tested)/ Antimicrobial agent	MIC (mg/L): Range	50%	90%	% Susceptible/%Intermediate/ % Resistant[a]: CLSI	EUCAST
S. aureus (6,219)					
MDR[b] (584)					
Oritavancin	≤0.008 – 0.25	0.03	0.12	-[c] / - / -	- / - / -
Oxacillin	≤0.25 – >2	>2	>2	0.7 / 0.0 / 99.3	0.7 / 0.0 / 99.3
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	≤2	≤2	99.8 / 0.2 / 0.0	99.0 / 0.0 / 1.0
Daptomycin	0.12 – 2	0.25	0.5	99.8 / - / -	99.8 / 0.0 / 0.2
Linezolid	0.25 – 8	1	1	99.5 / 0.0 / 0.5	99.5 / 0.0 / 0.5
Erythromycin	1 – >16	>16	>16	0.0 / 5.7 / 94.3	0.2 / 1.9 / 97.9
Clindamycin	≤0.25 – >2	>2	>2	14.4 / 0.3 / 85.3	14.2 / 0.2 / 85.6
Tetracycline	≤0.25 – >8	≤0.25	>8	65.9 / 1.0 / 33.1	65.5 / 0.2 / 34.3
Levofloxacin	≤0.12 – >4	>4	>4	2.2 / 1.9 / 95.9	2.2 / 1.9 / 95.9
TMP/SMX[d]	≤0.5 – >4	≤0.5	≤0.5	95.0 / 0.0 / 5.0	95.0 / 0.9 / 4.1
Vancomycin ≥2 mg/L (94)					
Oritavancin	≤0.008 – 0.25	0.06	0.12	- / - / -	- / - / -
Oxacillin	≤0.25 – >2	1	>2	56.4 / 0.0 / 43.6	56.4 / 0.0 / 43.6
Vancomycin	2	2	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	≤2	≤2	98.9 / 1.1 / 0.0	91.5 / 0.0 / 8.5
Daptomycin	0.25 – 2	0.5	1	96.8 / - / -	96.8 / 0.0 / 3.2
Linezolid	0.25 – 8	1	2	98.9 / 0.0 / 1.1	98.9 / 0.0 / 1.1
Erythromycin	≤0.12 – >16	0.5	>16	54.3 / 5.3 / 40.4	54.3 / 2.1 / 43.6
Clindamycin	≤0.25 – >2	≤0.25	>2	72.0 / 2.2 / 25.8	71.0 / 1.0 / 28.0
Tetracycline	≤0.25 – >8	≤0.25	>8	84.0 / 1.1 / 14.9	83.0 / 1.0 / 16.0
Levofloxacin	≤0.12 – >4	0.5	>4	53.2 / 2.1 / 44.7	53.2 / 2.1 / 44.7
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	97.9 / 0.0 / 2.1	97.9 / 0.0 / 2.1
CoNS (1,289)					
MDR (477)					
Oritavancin	≤0.008 – 0.25	0.03	0.06	- / - / -	- / - / -
Oxacillin	≤0.25 – >2	>2	>2	1.0 / 0.0 / 99.0	1.0 / 0.0 / 99.0
Vancomycin	≤0.12 – 4	2	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	4	8	95.4 / 4.6 / 0.0	74.0 / 0.0 / 26.0
Daptomycin	≤0.06 – 1	0.5	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – >8	0.5	1	98.3 / 0.0 / 1.7	98.3 / 0.0 / 1.7
Erythromycin	≤0.12 – >16	>16	>16	1.7 / 0.8 / 97.5	2.1 / 0.2 / 97.7
Clindamycin	≤0.25 – >2	>2	>2	39.5 / 0.8 / 59.7	37.0 / 2.5 / 60.5
Tetracycline	≤0.25 – >8	1	>8	73.2 / 2.7 / 24.1	60.8 / 9.2 / 30.0
Levofloxacin	≤0.12 – >4	>4	>4	4.8 / 4.6 / 90.6	4.8 / 4.6 / 90.6
TMP/SMX	≤0.5 – >4	4	>4	24.9 / 0.0 / 75.1	24.9 / 34.4 / 40.7
β-haemolytic streptococci (1,016)					
MDR (64)					
Oritavancin	≤0.008 – 0.5	0.03	0.12	- / - / -	- / - / -
Penicillin	≤0.06 – 0.12	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	0.25 – 0.5	0.5	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 0.5	0.25	0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	0.5 – >16	>16	>16	0.0 / 3.1 / 96.9	0.0 / 3.1 / 96.9
Clindamycin	≤0.25 – >2	>2	>2	4.7 / 0.0 / 95.3	4.7 / 0.0 / 95.3
Tetracycline	4 – >8	>8	>8	0.0 / 3.1 / 96.9	0.0 / 0.0 / 100.0
Levofloxacin	0.25 – >4	0.5	1	95.3 / 0.0 / 4.7	90.6 / 4.7 / 4.7
TMP/SMX	≤0.5 – >4	≤0.5	≤0.5	- / - / -	93.8 / 1.5 / 4.7
Viridans group streptococci (515)					
MDR (139)					
Oritavancin	≤0.008 – 0.25	0.015	0.06	- / - / -	- / - / -
Penicillin	≤0.06 – >8	0.25	8	31.7 / 49.6 / 18.7	51.1 / 30.2 / 18.7
Vancomycin	0.25 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 2	0.25	1	99.3 / - / -	- / - / -
Linezolid	≤0.12 – 2	0.5	1	100.0 / - / -	- / - / -
Erythromycin	0.5 – >16	8	>16	0.0 / 1.4 / 98.6	- / - / -
Clindamycin	≤0.25 – >2	≤0.25	>2	52.5 / 0.7 / 46.8	53.2 / 0.0 / 46.8
Tetracycline	≤0.25 – >8	>8	>8	33.1 / 5.7 / 61.2	- / - / -
Levofloxacin	0.5 – >4	1	2	91.4 / 0.7 / 7.9	- / - / -
TMP/SMX	≤0.5 – >4	≤0.5	4	- / - / -	- / - / -

a. Breakpoint criteria for comparator agents were those from CLSI (M100-S24, 2014) and EUCAST (2014), as available.
b. Staphylococci and streptococci non-susceptible (based on CLSI criteria) to four and three drug classes or more, respectively, were defined as multidrug-resistant (MDR).
c. Breakpoint not available.
d. TMP/SMX, trimethoprim/sulfamethoxazole.

Conclusions

- Oritavancin demonstrated potent *in vitro* activity against this contemporary challenge collection of MDR and non-MDR clinical isolates from Europe and Israel. Higher (2-fold) oritavancin MIC values were noted against *S. aureus* with borderline susceptibility to vancomycin (MIC = 2 mg/L). However, oritavancin inhibited all tested strains at ≤0.5 mg/L.
- The *in vitro* activity presented for oritavancin was uniformly greater than those obtained for the comparator agents tested. These results warrant further investigation to determine the potential of oritavancin for treating infections caused by MDR Gram-positive isolates.

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