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Activity of Oritavancin Tested against Gram-positive Clinical Isolates Responsible for Documented Skin and Soft Tissue Infections in European Hospitals (2011-2013)

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Introduction

Acute skin and soft-tissue infections (SSTIs) are often caused by aerobic Gram-positive cocci, including *Staphylococcus aureus* and β-haemolytic streptococci. In the past decade, new strains of methicillin-resistant *S. aureus* (MRSA; USA300, sequence type 8) have emerged as the predominant cause of community-associated (CA) SSTIs in many areas of North America and other parts of the world. MRSA isolates were shown to be responsible for as many as 60% (98% of MRSA isolates are USA300-like) of the acute purulent SSTI in the USA emergency departments. The epidemiology of SSTIs in European countries differs from that of the USA and it is represented by a more heterogeneous *S. aureus* population. Although USA300-like isolates have been detected in some European countries, ST80 isolates are often responsible for CA-MRSA, among others.

The high incidence of MRSA causing SSTI has complicated the management of such infections and the selection of empirical therapy. These MRSA isolates are usually susceptible to other agents, such as clindamycin, tetracycline and trimethoprim-sulfamethoxazole, which have been considered as therapeutic options for uncomplicated SSTIs. However, although still rare, resistant phenotypes to these drugs have been reported and have brought difficulties for the management of such uncomplicated infections even further. Moreover, complicated SSTIs, which typically involve deep soft tissue and occur in patients with underlying disease, often require intravenous antibiotic therapy, surgical intervention, or both.

Several antimicrobial drugs targeting Gram-positive organisms have become clinically available or are undergoing clinical development. Oritavancin is a lipoglycopeptide in final clinical development for the treatment of patients with acute SSTI. This drug has completed two multicentre clinical trials (SOLO I and II) which assessed the efficacy and safety of a single dose of oritavancin compared to 7 to 10-day daily doses of vancomycin for the treatment of acute SSTI caused by susceptible Gram-positive bacteria, including MRSA. Oritavancin is currently under regulatory review by the US-Food and Drug Administration and European Medicines Agency. This study was conducted to update the *in vitro* activity of oritavancin against pathogens responsible for SSTI in European and Israeli hospitals.

Materials and Methods

Bacterial strain collection. A total of 3,004 *S. aureus*, 478 β-haemolytic streptococci and 149 viridans group streptococci were included in the study. These isolates were recovered from clinical specimens associated with SSTI, per local guidelines, in hospitalised patients in Europe (28 sites in 14 countries) and Israel (one site) between 2011 and 2013. 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 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 ThermoFisher 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, *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.

Results

- Oritavancin had modal MIC and MIC_{50} results of 0.03 mg/L for both methicillin-susceptible *S. aureus* (MSSA) and MRSA, and inhibited all isolates at ≤0.25 mg/L, except for one MSSA strain (MIC, 0.5 mg/L; Table 1). The oritavancin MIC_{50} value obtained against MRSA was eight-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), and 32-fold lower than vancomycin ($MIC_{50/90}$, 1/1 mg/L) and linezolid ($MIC_{50/90}$, 1/1 mg/L; Table 2).
- The comparator agents vancomycin, daptomycin and linezolid demonstrated susceptibility rates ≥99.6% against MRSA when the CLSI or EUCAST breakpoint criteria were applied (Table 2). Teicoplanin and trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L; 98.8 % susceptible) were also active *in vitro* against this collection of MRSA isolates (Table 2).
- Overall, MSSA clinical isolates showed low MIC values for oritavancin and were very susceptible to the comparator agents (≥94.0% susceptible), except for erythromycin that demonstrated limited antimicrobial coverage ($MIC_{50/90}$, 0.25/>16 mg/L; 84.8% susceptible).
- Oritavancin ($MIC_{50/90}$, 0.03/0.25 mg/L), daptomycin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100.0% susceptible) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100.0% susceptible) were the most active agents tested against *S. pyogenes*, while oritavancin ($MIC_{50/90}$, 0.015/0.06 mg/L) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 100.0% susceptible) were the most active tested agents against *S. agalactiae* (Tables 1 and 2).
- Overall, comparator agents demonstrated substantial coverage (≥93.8% susceptible) when tested against clinical isolates of *S. pyogenes* and *S. agalactiae*, except for erythromycin and tetracycline (≤86.4% susceptible) against *S. pyogenes* and erythromycin, clindamycin and tetracycline (≤87.6% susceptible) against *S. agalactiae* (Table 2).
- Oritavancin displayed overall MIC_{50} and MIC_{90} values of ≤0.08 and 0.03 mg/L, respectively, against Viridans group streptococcal isolates (Table 1). Similar MIC results were obtained for the *S. anginosus* and *S. mitis* groups (Table 2). When compared to those of other agents, oritavancin MIC_{90} values against Viridans group streptococci were at least 16-fold lower (Table 2).
- Isolates of the *S. anginosus* group showed low MIC results for oritavancin (MIC_{100}, 0.03 mg/L) and penicillin (MIC_{100}, 0.25 mg/L), followed by vancomycin (MIC_{100}, 1 mg/L), daptomycin (MIC_{100}, 1 mg/L) and linezolid (MIC_{100}, 2 mg/L; Table 2).

Table 1. Antimicrobial activity and MIC distribution for oritavancin against contemporary (2011 – 2013) clinical isolates from European countries and Israel as part of the SENTRY Antimicrobial Surveillance Programme.

Organism[a] (no. tested)	MIC (mg/L): 50%	90%	Number (cumulative %) inhibited at oritavancin MIC (mg/L)[b]: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
***S. aureus* (3,004)**	0.03	0.06	53 (1.8)	552 (20.1)	**1,299 (63.4)**	821 (90.7)	250 (99.0)	28 (100.0)	1 (100.0)
MSSA (2,245)	0.03	0.06	43 (1.9)	416 (20.4)	**976 (63.9)**	617 (91.4)	174 (99.2)	18 (100.0)	1 (100.0)
MRSA (759)	0.03	0.12	10 (1.3)	136 (19.2)	**323 (61.8)**	204 (88.7)	76 (98.7)	10 (100.0)	
βHS (478)	0.03	0.25	53 (11.1)	117 (35.6)	**133 (63.4)**	60 (75.9)	58 (88.1)	40 (96.4)	17 (100.0)
S. pyogenes (273)	0.03	0.25	33 (12.1)	59 (33.7)	**84 (64.5)**	36 (77.7)	32 (89.4)	24 (98.2)	5 (100.0)
S. agalactiae (97)	0.015	0.06	11 (11.3)	**39 (51.5)**	33 (85.6)	5 (90.7)	4 (94.8)	2 (96.9)	3 (100.0)
Other species[c] (108)	0.06	0.25	9 (8.3)	19 (25.9)	16 (40.7)	19 (58.3)	**22 (78.7)**	14 (91.7)	9 (100.0)
VGS (149)	≤0.008	0.03	**107 (71.8)**	26 (89.3)	6 (93.3)	6 (97.3)	4 (100.0)		
S. anginosus group[d] (78)	≤0.008	0.015	**70 (89.7)**	6 (97.4)	2 (100.0)				
S. mitis group[e] (42)	≤0.008	0.06	**22 (52.4)**	13 (83.3)	2 (88.1)	2 (92.9)	3 (100.0)		

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; βHS = β-haemolytic streptococci; VGS = viridans group streptococci.
b. Modal MIC values are shown in bold.
c. Includes *S. dysgalactiae* (25 strains), *S. equi* (one strain), *S. equisimilis* (five strains), Group C streptococci (18 strains), Group F streptococci (one strain), and Group G streptococci (58 strains).
d. Includes *S. anginosus* (51 strains), *S. anginosus* group (nine strains), *S. constellatus* (17 strains) and *S. intermedius* (one strain).
e. Includes *S. gordonii* (one strain), *S. mitis/oralis* (seven strains), *S. mitis* group (13 strains), *S. oralis* (13 strains), *S. parasanguinis* (five strains), and *S. sanguinis* (three strains).

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against Gram-positive clinical isolates from European countries and Israel as part of the 2011 – 2013 SENTRY Antimicrobial Surveillance Programme.

Organism[a] (no. tested) / Antimicrobial agent	MIC (mg/L): Range	50%	90%	%Susceptible/%Intermediate/%Resistant[b]: CLSI	EUCAST
MRSA (759)					
Oritavancin	≤0.008 – 0.25	0.03	0.12	-/ - / -	- / - / -
Vancomycin	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	≤2	≤2	99.9 / 0.1 / 0.0	99.1 / 0.0 / 0.9
Daptomycin	0.12 – 2	0.25	0.5	99.6 / - / -	99.6 / 0.0 / 0.4
Linezolid	≤0.12 – 8	1	1	99.7 / 0.0 / 0.3	99.7 / 0.0 / 0.3
Erythromycin	≤0.12 – >16	>16	>16	33.4 / 2.7 / 63.9	34.2 / 0.5 / 65.3
Clindamycin	≤0.25 – >2	≤0.25	>2	70.4 / 0.1 / 29.5	69.7 / 0.7 / 29.6
Tetracycline	≤0.25 – >8	≤0.25	>8	82.3 / 1.8 / 15.9	82.1 / 0.1 / 17.8
Levofloxacin	≤0.12 – >4	>4	>4	15.9 / 1.4 / 82.7	15.9 / 1.4 / 82.7
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	≤0.5	98.8 / 0.0 / 1.2	98.8 / 0.3 / 0.9
MSSA (2,245)					
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	≤2	≤2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 2	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	0.25	>16	84.8 / 0.9 / 14.3	84.8 / 0.2 / 15.0
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	97.0 / 0.1 / 2.9	96.6 / 0.4 / 3.0
Tetracycline	≤0.25 – >8	≤0.25	≤0.25	94.3 / 0.6 / 5.1	94.0 / 0.2 / 5.8
Levofloxacin	≤0.12 – >4	≤0.12	0.25	95.4 / 0.4 / 4.2	95.4 / 0.4 / 4.2
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	≤0.5	99.6 / 0.0 / 0.4	99.6 / 0.2 / 0.2
***S. pyogenes* (273)**					
Oritavancin	≤0.008 – 0.5	0.03	0.25	- / - / -	- / - / -
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	0.25 – 0.5	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 0.25	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 1	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	≤0.12	2	86.4 / 0.7 / 12.9	86.4 / 0.7 / 12.9
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	97.1 / 0.0 / 2.9	97.1 / 0.0 / 2.9
Tetracycline	≤0.25 – >8	≤0.25	>8	73.1 / 0.7 / 26.2	72.7 / 0.4 / 26.9
Levofloxacin	≤0.12 – 2	0.5	1	100.0 / 0.0 / 0.0	93.8 / 6.2 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	≤0.5	- / - / -	96.3 / 0.8 / 2.9
***S. agalactiae* (97)**					
Oritavancin	≤0.008 – 0.5	0.015	0.06	- / - / -	- / - / -
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	0.12 – 0.5	0.25	0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25 – 1	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Erythromycin	≤0.12 – >16	≤0.12	>16	73.2 / 3.1 / 23.7	73.2 / 3.1 / 23.7
Clindamycin	≤0.25 – >2	≤0.25	>2	87.6 / 0.0 / 12.4	87.6 / 0.0 / 12.4
Tetracycline	≤0.25 – >8	>8	>8	21.9 / 1.0 / 77.1	21.9 / 0.0 / 78.1
Levofloxacin	0.5 – >4	0.5	1	99.0 / 0.0 / 1.0	95.9 / 3.1 / 1.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	- / - / -	100.0 / 0.0 / 0.0
VGS[d] (149)					
Oritavancin	≤0.008 – 0.12	≤0.008	0.03	- / - / -	- / - / -
Penicillin	≤0.06 – >8	≤0.06	1	74.5 / 20.8 / 4.7	82.6 / 12.7 / 4.7
Vancomycin	0.25 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 2	0.25	0.5	99.3 / - / -	- / - / -
Linezolid	≤0.12 – 2	1	1	100.0 / - / -	- / - / -
Erythromycin	≤0.12 – >16	≤0.12	>16	61.1 / 1.3 / 37.6	- / - / -
Clindamycin	≤0.25 – >2	≤0.25	>2	83.2 / 0.0 / 16.8	83.2 / 0.0 / 16.8
Tetracycline	≤0.25 – >8	0.5	>8	65.1 / 1.3 / 33.6	- / - / -
Levofloxacin	≤0.12 – >4	1	1	98.0 / 0.0 / 2.0	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	2	- / - / -	- / - / -
***S. anginosus* group[e] (78)**					
Oritavancin	≤0.008 – 0.03	≤0.008	0.015	- / - / -	- / - / -
Penicillin	≤0.06 – 0.25	≤0.06	≤0.06	94.9 / 5.1 / 0.0	100.0 / 0.0 / 0.0
Vancomycin	0.25 – 1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06 – 1	0.25	0.5	100.0 / - / -	- / - / -
Linezolid	≤0.12 – 2	1	1	100.0 / - / -	- / - / -
Erythromycin	≤0.12 – >16	≤0.12	4	79.5 / 1.3 / 19.2	- / - / -
Clindamycin	≤0.25 – >2	≤0.25	>2	87.2 / 0.0 / 12.8	87.2 / 0.0 / 12.8
Tetracycline	≤0.25 – >8	0.5	>8	70.5 / 0.0 / 29.5	- / - / -
Levofloxacin	≤0.12 – >4	0.5	1	98.7 / 0.0 / 1.3	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	≤0.5	- / - / -	- / - / -

a. MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; VGS = viridans group streptococci.
b. Breakpoint criteria for comparator agents were those from CLSI (M100-S24, 2014) and EUCAST (2014), as available.
c. Breakpoint not available.
d. Includes *S. anginosus* (51 strains), *S. anginosus* group (nine strains), *S. bovis* group (three strains), *S. constellatus* (17 strains), *S. gallolyticus* (two strains), *S. gordonii* (one strain), *S. infantis* (one strain), *S. intermedius* (one strain), *S. mitis/oralis* (seven strains), *S. mitis* group (13 strains), *S. oralis* (13 strains), *S. parasanguinis* (five strains), *S. salivarius* (six strains), *S. sanguinis* (three strains), *S. vestibularis* (one strain), and other species (16 strains).
e. Includes *S. anginosus* (51 strains), *S. anginosus* group (nine strains), *S. constellatus* (17 strains) and *S. intermedius* (one strain).

Conclusions

- Overall, oritavancin *in vitro* potency was greater than comparator agents when tested against this recent (2011 2013) collection of *S. aureus*, and viridans and β-haemolytic streptococci. Oritavancin inhibited all isolates at ≤0.5 mg/L.
- Oritavancin continues to exhibit potent antimicrobial activity against *S. aureus*, and viridans and β-haemolytic streptococcal clinical isolates, the main pathogens responsible for SSTI. These *in vitro* surveillance results benchmark oritavancin activity against current pathogens as this agent progresses through clinical development.

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