Oritavancin activity tested against European staphylococcal clinical isolates and resistant subsets including those with reduced susceptibility to daptomycin, teicoplanin or vancomycin (2010–2014)

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Abstract

Background: Oritavancin was approved by the United States FDA (2014) and European Medicines Agency (2015) for the treatment of acute bacterial skin and skin structure infections. This study assessed the *in vitro* activity of oritavancin and comparator agents against staphylococcal clinical isolates (2010 – 2014), including subsets of isolates exhibiting decreased susceptibility to other agents.

Material/Methods: A total of 3,285 methicillin-resistant *S. aureus* (MRSA) and 1,358 methicillin-resistant coagulase-negative staphylococci (CoNS) were collected from 12 European countries (39 sites), Russia (three sites), Turkey (three sites) and Israel (one site). Isolates were submitted to a monitoring laboratory as part of the SENTRY Antimicrobial Surveillance Program. Identification was confirmed and susceptibility testing was performed by reference broth microdilution methods. MIC interpretation used EUCAST criteria. Isolates were stratified according to daptomycin, teicoplanin and vancomycin MIC results. Isolates displaying phenotypic resistance to at least three classes of antibacterial agents (in addition to methicillin) were considered as multidrug-resistant (MDR).

Results: Oritavancin inhibited 99.8% of all MRSA at the susceptible breakpoint (≤0.12 mg/L). A total of 30.1% and 1.9% of MRSA displayed a MDR phenotype and decreased susceptibility to vancomycin (vancomycin MIC = 2 mg/L), respectively; only 0.2% of MRSA were daptomycin non-susceptible. *S. aureus* with decreased susceptibility to vancomycin or non-susceptible to daptomycin had oritavancin MIC_{50} results (MIC_{50}, 0.06 mg/L) two-fold higher than the susceptible counterparts (MIC_{50}, 0.03 mg/L). All eight isolates of MRSA with decreased susceptibility to daptomycin were susceptible to oritavancin, linezolid, teicoplanin and vancomycin. Oritavancin and linezolid (93.7 - 98.4% susceptible) were active against MRSA displaying a vancomycin MIC of 2 mg/L, while teicoplanin (79.4% susceptible, EUCAST criteria) and daptomycin (88.9% susceptible) had marginal coverage. Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was the most potent agent against CoNS, followed by daptomycin ($MIC_{50/90}$, 0.5/0.5 mg/L; 99.9% susceptible), linezolid ($MIC_{50/90}$, 0.5/1 mg/L; 99.2% susceptible) and vancomycin ($MIC_{50/90}$, 2/2 mg/L; 100.0% susceptible). Whereas teicoplanin-resistant CoNS had oritavancin MIC values ($MIC_{50/90}$, 0.06/0.12 mg/L) that were two-fold higher than those of teicoplanin-susceptible isolates ($MIC_{50/90}$, 0.03/0.06 mg/L), oritavancin inhibited 99.5% of CoNS at ≤0.12 mg/L and all isolates at 0.25 mg/L. Oritavancin ($MIC_{50/90}$, 0.06/0.12 mg/L), daptomycin ($MIC_{50/90}$, 0.5/0.5 mg/L; 100.0% susceptible), linezolid ($MIC_{50/90}$, 0.5/1 mg/L; 98.5% susceptible) and vancomycin ($MIC_{50/90}$, 2/2 mg/L; 100.0% susceptible) had *in vitro* activity against teicoplanin-resistant CoNS. Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L), linezolid (98.8 - 99.7% susceptible) and vancomycin (100.0% susceptible) were active against staphylococcal isolates showing a MDR phenotype.

Conclusions: Oritavancin demonstrated potent *in vitro* activity against this large collection of MRSA and CoNS (including MDR isolates and those displaying decreased susceptibility to clinically available agents) from Europe and adjacent regions. Oritavancin was consistently more potent than the tested comparator agents.

Introduction

Antimicrobial resistance in bacterial pathogens remains a growing problem worldwide. However, there has been an overall decrease in the incidence rate of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in many European countries. In contrast, species of coagulase-negative staphylococci (CoNS), previously regarded as contaminants, have gained considerable attention in the last decade as an important pathogen, which often exhibits a multidrug-resistant (MDR) phenotype (see **Tables 1 and 2**). In fact, *Staphylococcus epidermidis* isolates from Greece demonstrating a linezolid dependence phenotype have been recently reported, as well as outbreaks of linezolid-resistant isolates in European countries.

Oritavancin (ORBACTIV™, oritavancin for injection) is approved by the Food and Drug Administration (FDA) and European Medicines Agency for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs). Oritavancin has demonstrated potent *in vitro* activity against staphylococci, enterococci and streptococci. In this study, the *in vitro* activity of oritavancin and comparator agents was assessed against a contemporary (2010 – 2014) collection of staphylococcal clinical isolates, including subsets of isolates exhibiting a MDR phenotype or decreased susceptibility to vancomycin, teicoplanin or daptomycin.

Methods

Bacterial strain collection. A total of 3,285 MRSA and 1,358 methicillin-resistant CoNS (MRCoNS) were collected from 12 European countries (39 sites), Russia (three sites), Turkey (three sites) and Israel (one site) during 2010 - 2014. These 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 supported by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) (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-A10 document. Testing was performed using panels manufactured by Thermo Fisher Scientific (Oakwood Village, Ohio, USA). These panels provide oritavancin 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 (M100-S26).

MIC interpretations were based on the CLSI (M100-S26) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2016) breakpoint criteria, as available. The *in vitro* activities of oritavancin and comparator agents were evaluated according to the daptomycin, teicoplanin and vancomycin MIC results (EUCAST criteria). Moreover, MRSA and MRCoNS isolates displaying phenotypic resistance to at least three other classes of drugs (except for daptomycin; non-susceptible [MIC >1 mg/L] phenotypes were included) were considered as MDR.

Results

- The collection utilized in this study consisted of 3,285 MRSA collected from various clinical specimen types in hospitalised patients in Europe and the USA. A total of 0.2% of isolates were daptomycin-non-susceptible and 1.9% had elevated vancomycin MIC results (i.e. 2 mg/L). In addition, 30.1% of MRSA isolates exhibited a MDR phenotype (**Table 1**).
- Among the 1,358 MRCoNS, 19.3% were teicoplanin-resistant and 65.0% demonstrated a MDR phenotype (**Tables 1 and 2**).
- MRSA isolates with decreased susceptibility to vancomycin or non-susceptibility to daptomycin had oritavancin MIC_{50} results (MIC_{50}, 0.06 mg/L) two-fold higher than those obtained from the more susceptible counterparts ($MIC_{50/90}$, 0.03/0.06 mg/L; **Table 1**).
- All eight MRSA with decreased susceptibility to daptomycin were susceptible to oritavancin (MIC, 0.06 - 0.12 mg/L), linezolid (MIC, 0.5 - 2 mg/L) and vancomycin (MIC, 1 - 2 mg/L). Teicoplanin (MIC, ≤4 mg/L) had a low susceptibility rate result against this strain set (62.5% susceptible [EUCAST]; data not shown).
- Oritavancin (all MRSA inhibited at ≤0.25 mg/L; 93.7% susceptible) and linezolid (98.4% susceptible) were active against MRSA displaying a vancomycin MIC of 2 mg/L, while teicoplanin (79.4% susceptible, EUCAST criteria) and daptomycin (88.9% susceptible) had marginal coverage (**Table 2**).
- Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was the most potent agent against MRCoNS, followed by daptomycin ($MIC_{50/90}$, 0.25 - 0.5/0.5 mg/L), linezolid ($MIC_{50/90}$, 0.5/1 mg/L) and vancomycin ($MIC_{50/90}$, 2/2 mg/L; data not shown).
- Teicoplanin-resistant MRCoNS had oritavancin MIC values ($MIC_{50/90}$, 0.06/0.12 mg/L) that were two-fold higher than those of teicoplanin-susceptible isolates ($MIC_{50/90}$, 0.03/0.06 mg/L); however, oritavancin inhibited 99.5% of the MRCoNS population at ≤0.12 mg/L and all isolates at ≤0.25 mg/L (**Tables 1 and 2**).
- Oritavancin ($MIC_{50/90}$, 0.06/0.12 mg/L), daptomycin ($MIC_{50/90}$, 0.5/0.5 mg/L; 100.0% susceptible), linezolid ($MIC_{50/90}$, 0.5/1 mg/L; 98.5% susceptible) and vancomycin ($MIC_{50/90}$, 2/2 mg/L; 100.0% susceptible) demonstrated *in vitro* activity against teicoplanin-resistant MRCoNS.
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L), linezolid (98.8 - 99.7% susceptible), daptomycin (99.4 - 100.0% susceptible) and vancomycin (100.0% susceptible) were as active against staphylococcal isolates showing a MDR phenotype as they were against non-MDR isolates (**Table 2**).

Table 1. Antimicrobial activity and MIC distribution for oritavancin against contemporary (2010 – 2014) staphylococcal clinical isolates displaying several antimicrobial susceptibility phenotypes.

Phenotype[a] (no tested)	MIC (mg/L) 50%	90%	Number (cumulative %) inhibited at oritavancin MIC (mg/L) of[b]: ≤0.008	0.015	0.03	0.06	0.12	0.25
MRSA (3,285)	0.03	0.06	78 (2.4)	847 (28.2)	1401 (70.8)	727 (92.9)	224 (99.8)	8 (100.0)
DAP-S (MIC ≤1 mg/L; 3,274)	0.03	0.06	78 (2.4)	847 (28.3)	1,399 (71.0)	722 (93.0)	220 (99.8)	8 (100.0)
DAP-NS (MIC = 2 mg/L; 8)	0.06	-	0 (0.0)	0 (0.0)	0 (0.0)	5 (62.5)	3 (100.0)	
VAN MIC ≤1 mg/L; 3,222)	0.03	0.06	78 (2.4)	846 (28.7)	1,386 (71.7)	698 (93.4)	210 (99.9)	4 (100.0)
VAN MIC = 2 mg/L; 63)	0.06	0.12	0 (0.0)	1 (1.6)	15 (25.4)	29 (71.4)	14 (93.7)	4 (100.0)
Non-MDR (2,297)	0.03	0.06	49 (2.1)	614 (28.9)	989 (71.9)	504 (93.9)	138 (99.9)	3 (100.0)
MDR (988)	0.03	0.06	29 (2.9)	233 (26.5)	412 (68.2)	223 (90.8)	86 (99.5)	5 (100.0)
MRCoNS (1,358)	0.03	0.06	174 (12.8)	173 (25.6)	518 (63.7)	407 (93.7)	79 (99.5)	7 (100.0)
TEC-S (MIC, ≤4 mg/L; 1,096)	0.03	0.06	173 (15.8)	162 (30.6)	453 (71.9)	269 (96.4)	39 (100.0)	
TEC-R (MIC, >4 mg/L; 262)	0.06	0.12	2 (0.8)	11 (5.0)	65 (29.8)	137 (82.1)	40 (97.3)	7 (100.0)
Non-MDR (476)	0.03	0.06	84 (17.6)	77 (33.8)	181 (71.8)	114 (95.8)	18 (99.6)	2 (100.0)
MDR (883)	0.03	0.06	91 (10.3)	96 (21.2)	337 (59.3)	293 (92.5)	61 (99.4)	5 (100.0)

a. MRSA = methicillin-resistant *S. aureus*; DAP = daptomycin; VAN = vancomycin; TEC = teicoplanin; S = susceptible; NS = non-susceptible; R = resistant; MRCoNS = methicillin-resistant coagulase-negative staphylococci; MDR = resistance to at least three other classes of drugs (except for daptomycin; non-susceptible [MIC >1 mg/L] phenotypes were included) in addition to methicillin; criteria for susceptibility were those published by EUCAST (2016).
b. Underlined rates represent percentages of susceptibility for oritavancin considering EUCAST breakpoints.

Table 2. Antimicrobial activity of oritavancin and comparator agents against contemporary (2010 – 2014) clinical isolates displaying several antimicrobial susceptibility phenotypes.

Organism (no. tested) Antimicrobial agent[a]	Range	MIC (mg/L) 50%	90%	%Susceptible / %Intermediate / %Resistant[b] CLSI			EUCAST		
MRSA with vancomycin MIC of ≤1 mg/L (3,222)									
Oritavancin	≤0.008 — 0.25	0.03	0.06	99.9	-	-[b]	-	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	70.2	0.2	29.6	69.8	0.4	29.8
Daptomycin	≤0.06 — 2	0.25	0.5	>99.9	-	-	>99.9	-	<0.1
Erythromycin	≤0.25 — >4	>4	>4	33.2	3.3	63.5	33.5	1.1	65.4
Levofloxacin	≤0.5 — >4	>4	>4	14.2	1.1	84.7	14.2	1.1	84.7
Linezolid	≤0.12 — 8	1	1	99.9	-	0.1	99.9	-	0.1
Teicoplanin	≤2 — 4	≤2	≤2	100.0	0.0	0.0	99.8	-	0.2
Tetracycline	≤0.5 — >8	≤0.5	>8	85.4	1.5	13.1	84.7	0.4	14.8
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	98.5	-	1.5	98.5	0.3	1.2
Vancomycin	0.25 — 1	1	1	100.0	0.0	0.0	100.0	-	0.0
MRSA with vancomycin MIC of 2 mg/L (63)									
Oritavancin	0.015 — 0.25	0.06	0.12	93.7	-	-[b]	-	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	53.2	1.6	45.2	51.6	1.6	46.8
Daptomycin	0.25 — 2	0.5	2	88.9	-	-	88.9	-	11.1
Erythromycin	≤0.25 — >4	>4	>4	25.4	7.9	66.7	25.4	4.8	69.8
Levofloxacin	≤0.12 — >4	>4	>4	4.8	0.0	95.2	4.8	0.0	95.2
Linezolid	0.25 — 8	1	1	98.4	-	1.6	98.4	-	1.6
Teicoplanin	≤2 — 16	≤2	4	98.4	1.6	0.0	79.4	-	20.6
Tetracycline	≤0.5 — >8	≤0.5	>8	76.2	1.6	22.2	71.4	4.8	23.8
TMP-SMX	≤0.5 — >4	≤0.5	1	95.2	-	4.8	95.2	0.0	4.8
Vancomycin	2 — 2	2	2	100.0	0.0	0.0	100.0	-	0.0
MDR MRSA (988)									
Oritavancin	≤0.008 — 0.25	0.03	0.06	99.5	-	-[b]	-	-	-
Clindamycin	≤0.25 — >2	>2	>2	4.7	0.3	95.0	3.9	0.8	95.3
Daptomycin	≤0.06 — 2	0.25	0.5	99.4	-	-	99.4	-	0.6
Erythromycin	≤0.12 — >4	>4	>4	0.4	1.4	98.2	0.4	0.2	99.4
Levofloxacin	0.5 — >4	>4	>4	0.1	1.3	98.6	0.1	1.3	98.6
Linezolid	≤0.12 — 8	1	1	99.7	-	0.3	99.7	-	0.3
Teicoplanin	≤2 — 16	≤2	≤2	99.9	0.1	0.0	98.2	-	1.8
Tetracycline	≤0.5 — >8	≤0.5	>8	81.8	0.4	17.8	80.3	1.2	18.4
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	95.2	-	4.8	95.2	0.8	3.9
Vancomycin	0.25 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
Teicoplanin-susceptible MRCoNS (1,096)									
Oritavancin	≤0.008 — 0.12	0.03	0.06	-	-	-	-	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	62.9	0.8	36.3	60.5	2.4	37.1
Daptomycin	≤0.06 — 2	0.25	0.5	99.9	-	-	99.9	-	0.1
Erythromycin	≤0.25 — >4	>4	>4	23.5	0.8	75.7	23.7	0.4	76.0
Levofloxacin	≤0.5 — >4	4	>4	24.3	6.6	69.2	24.3	6.6	69.2
Linezolid	≤0.12 — >8	0.5	1	99.5	-	0.5	99.5	-	0.5
Teicoplanin	≤2 — 4	≤2	4	100.0	0.0	0.0	100.0	-	0.0
Tetracycline	≤0.5 — >8	1	>8	81.9	2.5	15.6	70.1	9.5	20.4
TMP-SMX	≤0.5 — >4	4	>4	49.5	-	50.5	49.5	22.4	28.0
Vancomycin	≤0.12 — 2	2	2	100.0	0.0	0.0	100.0	-	0.0
Teicoplanin-resistant MRCoNS (262)									
Oritavancin	≤0.008 — 0.25	0.06	0.12	-	-	-	-	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	59.4	1.1	39.5	54.8	4.6	40.6
Daptomycin	0.12 — 1	0.5	0.5	100.0	-	-	100.0	-	0.0
Erythromycin	≤0.25 — >4	>4	>4	17.2	0.0	82.8	17.2	0.0	82.8
Levofloxacin	≤0.5 — >4	>4	>4	14.5	2.3	83.2	14.5	2.3	83.2
Linezolid	0.25 — >8	0.5	1	98.5	-	1.5	98.5	-	1.5
Teicoplanin	8 — >8	8	>8	88.3	11.7	0.0	0.0	-	100.0
Tetracycline	≤0.5 — >8	1	>8	84.4	3.1	12.6	65.6	13.4	21.0
TMP-SMX	≤0.5 — >4	4	>4	45.8	-	54.2	45.8	23.3	30.9
Vancomycin	1 — 4	2	2	100.0	0.0	0.0	100.0	-	0.0
MDR MRCoNS (883)									
Oritavancin	≤0.008 — 0.25	0.03	0.06	-	-	-	-	-	-
Clindamycin	≤0.25 — >2	>2	>2	44.2	0.6	55.2	40.4	3.9	55.8
Daptomycin	≤0.06 — 1	0.5	0.5	100.0	-	-	100.0	-	0.0
Erythromycin	≤0.25 — >4	>4	>4	6.9	0.8	92.3	7.2	0.5	92.4
Levofloxacin	≤0.5 — >4	>4	>4	2.9	6.7	90.4	2.9	6.7	90.4
Linezolid	≤0.12 — >8	0.5	1	98.8	-	1.2	98.8	-	1.2
Teicoplanin	≤2 — >8	4	8	97.0	3.0	0.0	74.9	-	25.1
Tetracycline	≤0.5 — >8	1	>8	84.4	1.7	13.9	70.2	10.1	19.7
TMP-SMX	≤0.5 — >4	4	>4	30.6	-	69.4	30.6	30.5	39.0
Vancomycin	≤0.12 — 4	2	2	100.0	0.0	0.0	100.0	-	0.0

a. MRSA = methicillin-resistant *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole; MRCoNS = methicillin-resistant coagulase-negative staphylococci; MDR = resistance to at least three other classes of drugs (except for daptomycin; non-susceptible [MIC >1 mg/L] phenotypes were included) in addition to methicillin.
b. Breakpoint criteria for oritavancin according to the CLSI (M100-S26, 2016) and EUCAST (2016), as available. "-" = breakpoint not available.

Conclusions

- Oritavancin inhibited 99.7% (4,628/4,643) of all MRSA and MRCoNS at the susceptible breakpoint for *S. aureus* (≤0.12 mg/L) (**Table 1**). In addition, oritavancin was consistently more potent than the tested comparator agents.
- Oritavancin demonstrated potent *in vitro* activity against this large collection of MRSA and MRCoNS, including MDR isolates and those displaying decreased susceptibility to clinically available agents, from Europe and adjacent regions.

Disclosures

This study was sponsored by an educational/research grant from the Medicines Company (Parsippany, New Jersey, United States) via the SENTRY Antimicrobial Surveillance Programme platform.

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Presented at ECCMID 2016 (26th European Congress of Clinical Microbiology and Infectious Diseases) 9-12 April 2016, Amsterdam, The Netherlands

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