Oritavancin *In vitro* Activity Against the Most Prevalent Antibiogram Resistance Patterns Among Methicillin-resistant *Staphylococcus aureus*, Including Multidrug-resistant Strains from Patients in European Hospitals (2010-2013)

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Abstract

Objectives: Oritavancin was approved (August, 2014) by the United States FDA for the treatment of acute bacterial skin and skin structure infections. This study assessed the *in vitro* activity of oritavancin and comparator agents against methicillin-resistant *S. aureus* (MRSA) recovered from hospitalised patients in Europe and adjacent regions between 2010 and 2013.

Methods: A total of 9,603 *S. aureus* clinical isolates 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 Programme. Identification was confirmed and susceptibility testing was performed by CLSI methods. MIC interpretation used the FDA (oritavancin), and CLSI (2014) and/or EUCAST (2014) criteria. Oritavancin activity was evaluated according to antibiogram resistance patterns (CLSI criteria). *S. aureus* displaying phenotypic resistance to methicillin and to at least three other classes of drugs (except for daptomycin; non-susceptible [MIC >1 mg/L] phenotypes were included) were considered as multidrug-resistant (MDR).

Results: 74.2% (7,127/9,603) of isolates were methicillin-susceptible (MSSA), against which oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) inhibited 99.2% at ≤0.12 mg/L (US FDA breakpoint for *S. aureus*). A total of 30 resistance patterns were observed among the MRSA population; three profiles were predominant (21.8 – 29.0% of total) and encompassed 75.7% of the MRSA isolates. The MDR phenotype was noted in 33.6% of MRSA. Oritavancin MIC_{50} was 0.03 mg/L against the MSSA and MRSA overall populations, and against each observed resistance pattern, including MDR. Vancomycin ($MIC_{50/90}$, 0.5-1/1 mg/L; 100.0% susceptible), teicoplanin (96.4 – 100.0% susceptible), daptomycin ($MIC_{50/90}$, 0.25-0.5/0.5 mg/L; 99.6 – 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/1-2 mg/L; 99.6 – 100.0% susceptible) also showed consistent activity against each resistance pattern that had greater than 10 isolates each. Oritavancin had an MIC_{50} value 8-fold lower than daptomycin (0.25-0.5 mg/L), and at least 16-fold lower than vancomycin (MIC_{50}, 0.5-1 mg/L) and linezolid (MIC_{50}, 1 mg/L) against each resistance subset. Trimethoprim-sulfamethoxazole (95.6 – 100.0% susceptible) was also active against these resistance subsets, except against 40 MRSA isolates displaying a resistance phenotype to this agent (10 patterns included; $MIC_{50/90}$, >4/>4 mg/L; 0.0% susceptible).

Conclusions: Oritavancin demonstrated consistent and potent *in vitro* activity against this contemporary collection of MRSA displaying several resistance phenotypes, including MDR, from European and adjacent countries, with all isolates inhibited at ≤0.25 mg/L. In addition, oritavancin was at least eight-fold more potent than comparator agents with similar therapeutic indications.

Introduction

Antimicrobial resistance in bacterial pathogens has been described as a growing problem worldwide, and the resistance rates observed in common pathogens are reaching elevated levels in many countries. These factors have compromised the empirical use of previously reliable agents. Resistant Gram-positive and -negative isolates have become commonplace in both hospital and community settings, affecting usual prescribing practices. As an example, 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).

Oritavancin (ORBACTIV™, oritavancin for injection) is a semisynthetic bactericidal lipoglycopeptide recently approved by the United States Food and Drug Administration (US-FDA) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs) caused by *S. aureus* (including methicillin-susceptible [MSSA] and MRSA isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only). The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion in January 2015, recommending the granting of a marketing authorisation for oritavancin for the treatment of ABSSSI in adults. This study assessed the *in vitro* activity of oritavancin and comparator agents against MRSA and resistant subsets recovered from hospitalised patients in Europe and adjacent regions between 2010 and 2013.

Methods

Bacterial strain collection. A total of 9,603 *S. aureus* clinical isolates were collected from 12 European countries (39 sites), Russia (three sites), Turkey (three sites) and Israel (one site). 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 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 (Cleveland, 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 *E. faecalis* ATCC 29212). All QC results were within published acceptable ranges (M100-S25). MIC interpretations were based on the FDA (oritavancin), and CLSI M100-S25 (2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2015) breakpoint criteria, as available. The *in vitro* activities of oritavancin and comparator agents were evaluated according to antibiogram resistance patterns (CLSI criteria). *S. aureus* displaying phenotypic resistance to methicillin and to at least three other classes of drugs (except for daptomycin; non-susceptible [MIC >1 mg/L] phenotypes were included) were considered as multidrug-resistant (MDR).

Results

- A total of 74.2% (7,127/9,603) and 25.8% (2,476/9,603) of isolates were MSSA and MRSA, respectively. Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L for both) inhibited 99.2 and 98.9% of the MSSA and MRSA isolates at ≤0.12 mg/L (US-FDA breakpoint for *S. aureus*), respectively (Table 1).
- A total of 30 resistance patterns were observed among the MRSA population. Three profiles were predominant (21.8 – 29.0% of total; Table 1) and encompassed 75.7% of the MRSA isolates included in this study.
- Oritavancin demonstrated MIC_{50} results of 0.03 mg/L against the MSSA and MRSA overall populations, as well as against each of the most predominant antibiogram resistance profiles (97.7 – 100.0% susceptible; Table 1).
- The comparator agents, vancomycin (MIC_{50}, 0.5 – 1 mg/L), daptomycin (MIC_{50}, 0.25 – 0.5 mg/L) and linezolid (MIC_{50}, 1 mg/L) also showed overall consistent MIC_{50} values, regardless of methicillin susceptibility or antibiogram resistance profile (Table 2).
- Trimethoprim-sulfamethoxazole (98.4% susceptible) exhibited a high degree of coverage against *S. aureus*, including MRSA isolates, while other agents, such as clindamycin (Table 2) and tetracycline (data not shown) were active only against MSSA or MRSA isolates associated with certain antibiogram profiles.
- The MDR phenotype was noted in 33.6% of the MRSA population. The oritavancin MIC_{50} results against MDR and non-MDR MRSA were equivalent (i.e. 0.03 mg/L; Tables 1 and 2). Vancomycin (MIC_{50}, 1 mg/L), daptomycin (MIC_{50}, 0.25 mg/L) and linezolid (MIC_{50}, 1 mg/L) also showed similar MIC_{50} values against both populations.
- Teicoplanin (98.9 – 99.8% susceptible) and trimethoprim-sulfamethoxazole (95.6 – 99.8% susceptible) also demonstrated a high degree of antimicrobial coverage against the MDR and non-MDR MRSA populations. Among other tested agents, only clindamycin had acceptable (>90% susceptible) coverage against non-MDR isolates (Table 2).

Table 1. Antimicrobial activity and MIC distribution for oritavancin against contemporary (2010 – 2013) *S. aureus* clinical isolates displaying several antimicrobial susceptibility phenotypes.

Phenotype[a] (no. tested/%)	MIC (mg/L)		Number (cumulative %) inhibited at oritavancin MIC (mg/L) of[b]:					
	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25
MSSA (7,127)	0.03	0.06	188 (2.6)	1702 (26.5)	**3071 (69.6)**	1676 (93.1)	431 (99.2)	59 (100.0)
MRSA (2,476/25.8)	0.03	0.06	49 (2.0)	583 (25.5)	**1055 (68.1)**	577 (91.4)	184 (98.9)	28 (100.0)
OX, LE, ER (718/29.0)	0.03	0.06	10 (1.4)	165 (24.4)	**298 (65.9)**	185 (91.6)	49 (98.5)	11 (100.0)
OX, LE, CL, ER (617/24.9)	0.03	0.12	13 (2.1)	143 (25.3)	**247 (65.3)**	145 (88.8)	61 (98.7)	8 (100.0)
OX, LE (539/21.8)	0.03	0.06	14 (2.6)	116 (24.1)	**250 (70.5)**	118 (92.4)	37 (99.3)	4 (100.0)
OX alone (164/6.6)	0.03	0.06	2 (1.2)	37 (23.8)	**76 (70.1)**	37 (92.7)	11 (99.4)	1 (100.0)
OX, LE, CL, ER, TC (111/4.5)	0.03	0.06	2 (1.8)	25 (24.3)	**54 (73.0)**	25 (95.5)	5 (100.0)	
OX, LE, TC (95/3.8)	0.03	0.06	3 (3.2)	**44 (49.5)**	28 (78.9)	18 (97.9)	2 (100.0)	
OX, LE, ER, TC (45/1.8)	0.03	0.06	0 (0.0)	16 (35.6)	**21 (82.2)**	5 (93.3)	2 (97.8)	1 (100.0)
OX, ER (44/1.8)	0.03	0.12	0 (0.0)	9 (20.5)	**20 (65.9)**	10 (88.6)	4 (97.7)	1 (100.0)
OX, TC (35/1.4)	0.03	0.06	2 (5.7)	7 (25.7)	**17 (74.3)**	8 (97.1)	1 (100.0)	
OX LE, CL, ER, TC, T/S (21/0.8)	0.03	0.06	1 (4.8)	3 (19.0)	**13 (81.0)**	3 (95.2)	1 (100.0)	
MDR (832/33.6)	0.03	0.12	17 (2.0)	197 (25.7)	**348 (67.5)**	185 (89.8)	74 (98.7)	11 (100.0)
Non-MDR (1,644/66.4)	0.03	0.06	32 (1.9)	386 (25.4)	**707 (68.4)**	392 (92.3)	110 (99.0)	17 (100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*. Criteria for susceptibility were those published by CLSI (2015). OX = oxacillin, ER = erythromycin, CL = clindamycin (constitutive), LE = levofloxacin, TC = tetracycline and T/S = trimethoprim-sulfamethoxazole. MDR = phenotypic resistance to methicillin and to at least three other classes of drugs. All isolates were susceptible to vancomycin at CLSI and EUCAST breakpoints.
b. Bolded values represent the Modal MIC results. Underlined rates represent percentages of susceptibility for oritavancin according to the US FDA labelling supplement for the product ORBACTIV™ (i.e. ≤0.12 mg/L for susceptible).

Table 2. Antimicrobial activity of oritavancin and comparator agents against contemporary (2010 – 2013) *S. aureus* clinical isolates displaying several antimicrobial susceptibility phenotypes.

Phenotype[a] (no. tested/%)	MIC_{50}, MIC_{90} (mg/L) and % susceptible[b] for each agent														
	Oritavancin			Vancomycin			Daptomycin			Linezolid			Clindamycin		
	50%	90%	%S	50%	90%	%S	50%	90%	%S	50%	90%	%S	50%	90%	%S
MSSA (7,127)	0.03	0.06	99.2	1	1	100.0	0.25	0.5	100.0	1	1	100.0	≤0.25	≤0.25	97.2
MRSA (2,476/25.8)	0.03	0.06	98.9	1	1	100.0	0.25	0.5	99.8	1	1	99.9	≤0.25	>2	67.4
OX, LE, ER (718/29.0)	0.03	0.06	98.5	0.5	1	100.0	0.25	0.5	100.0	1	1	100.0	≤0.25	≤0.25	99.3
OX, LE, CL, ER (617/24.9)	0.03	0.12	98.7	1	1	100.0	0.25	0.5	100.0	1	1	100.0	>2	>2	0.0
OX, LE (539/21.8)	0.03	0.06	99.3	1	1	100.0	0.25	0.5	100.0	1	1	100.0	≤0.25	≤0.25	99.4
OX alone (164/6.6)	0.03	0.06	99.4	1	1	100.0	0.25	0.5	100.0	1	2	100.0	≤0.25	≤0.25	100.0
OX, LE, CL, ER, TC (111/4.5)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	1	1	100.0	>2	>2	0.0
OX, LE, TC (95/3.8)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	1	1	100.0	≤0.25	≤0.25	100.0
OX, LE, ER, TE (45/1.8)	0.03	0.06	97.8	1	1	100.0	0.25	0.5	100.0	1	1	100.0	≤0.25	≤0.25	97.8
OX, ER (44/1.8)	0.03	0.12	97.7	1	1	100.0	0.25	0.5	100.0	1	1	100.0	≤0.25	≤0.25	90.9
OX, TC (35/1.4)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	1	2	100.0	≤0.25	≤0.25	100.0
OX, LE, CL, ER, TC, T/S (21/0.8)	0.03	0.06	100.0	1	1	100.0	0.5	0.5	100.0	1	1	100.0	>2	>2	0.0
MDR (832/33.6)	0.03	0.12	98.7	1	1	100.0	0.25	0.5	99.6	1	1	99.6	>2	>2	7.3
Non-MDR (1,644/66.4)	0.03	0.06	99.0	1	1	100.0	0.25	0.5	99.9	1	1	100.0	≤0.25	≤0.25	97.7

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*. Criteria for susceptibility were those published by CLSI (2015). OX = oxacillin, ER = erythromycin, CL = clindamycin (constitutive), LE = levofloxacin, TC = tetracycline and T/S = trimethoprim-sulfamethoxazole. MDR = phenotypic resistance to methicillin and to at least three other classes of drugs. All isolates were susceptible to vancomycin at CLSI and EUCAST breakpoints.
b. Breakpoint criteria for oritavancin according to the US FDA labelling supplement for the product ORBACTIV™ (i.e. ≤0.12 mg/L for susceptible). Breakpoint criteria for comparator agents were those from EUCAST (2015).

Conclusions

- Oritavancin demonstrated consistent *in vitro* activity against this contemporary collection of MRSA displaying several resistance phenotypes, including MDR, from European and adjacent countries, with all isolates inhibited at ≤0.25 mg/L.
- Oritavancin had MIC_{50} values that were eight-fold lower than daptomycin (0.25-0.5 mg/L), and at least 16-fold lower than vancomycin (MIC_{50}, 0.5-1 mg/L) and linezolid (MIC_{50}, 1 mg/L) against *S. aureus*, regardless of antimicrobial phenotype.
- These *in vitro* results indicate potent activity of oritavancin against *S. aureus*, including clinical isolates displaying a MDR phenotype. Moreover, this *in vitro* potency was consistently greater than comparator agents with similar therapeutic indications.

Disclosures

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