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Spectrum of Activity of Oritavancin and Comparison Agents Tested against Contemporary Staphylococcus aureus Collected in European Hospitals

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Amended Abstract

Objectives: To assess the spectrum of activity and potency of oritavancin and comparators tested against *Staphylococcus aureus* recovered from hospitalized patients in Europe during the 2008 – 2009 International Oritavancin Surveillance Program, as part of the SENTRY Antimicrobial Surveillance Program. This analysis includes categorization of methicillin-resistant *S. aureus* (MRSA) based on antimicrobial resistance patterns.

Methods: 3,788 consecutive, non-duplicate *S. aureus* were collected from medical centres located in 13 European countries. Isolates were submitted to a central monitoring laboratory and species identification performed by Gram stain, biochemical tests and Vitek 2, when needed. Susceptibility testing was performed using CLSI methods (M07-A8, 2009). CLSI (M100-S20, 2010) and regional interpretive criteria (EUCAST, 2009) were applied, when available. Oritavancin activity was also evaluated according to resistance patterns. MRSA displaying resistance phenotypes to at least four classes of drugs were considered as multidrug-resistant (MDR).

Results: The majority of isolates were from bacteremia (39.9%) and skin and skin structure infections (35.8%). The overall MRSA rate was 25.6% and highest in Greece (59.5%), followed by Poland (40.9%), Belgium (38.5%), Ireland (36.0%) and the United Kingdom (30.6%). MRSA rates in other European countries were <30.0%. Among MRSA, 30 resistance patterns were noted and MDR strains comprised 39.3%. *S. aureus* were very susceptible to vancomycin (100.0%), daptomycin (100.0%), linezolid (100.0%), teicoplanin (99.3%) and trimethoprim/sulfamethoxazole (99.2%). Levofloxacin, erythromycin and clindamycin (71.7 – 87.9% susceptible) showed suboptimal activity. Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) was eight-fold more potent than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and 16- to 32-fold more active than vancomycin ($MIC_{50/90}$, 1/1 mg/L) and linezolid ($MIC_{50/90}$, 2/2 mg/L). Oritavancin exhibited stable and potent activity (based on $MIC_{50/90}$ results) against *S. aureus*, regardless of MRSA categorization, sampling year, country of origin and resistance patterns, including a MDR phenotype (see Table 1).

Conclusions: Oritavancin demonstrated consistent and potent in vitro activity against this contemporary collection of European *S. aureus* strains. The oritavancin $MIC_{50/90}$ values did not vary when tested against *S. aureus* from different countries, sampling years or resistance phenotype. In addition, oritavancin was at least eight-fold more potent than comparators. Continued longitudinal surveillance of new and currently marketed agents against this important clinical pathogen is a prudent practice to monitor for emergence of resistance.

Introduction

Infections caused by multidrug-resistant (MDR) Gram-positive bacteria represent a major public health problem, not only increasing morbidity and mortality, but also causing higher costs for patient management and implementation of infection control measures. *Staphylococcus aureus* has long been established as an important nosocomial pathogen, and frequently presents a MDR phenotype, complicating antimicrobial therapy.

Occurrences of methicillin-resistant *S. aureus* (MRSA) have been especially problematic in intensive care units (ICU), where these organisms account for up to 70% of all *S. aureus*. In addition, a remarkable spread of community-acquired (CA) MRSA isolates (especially USA300) has been reported during the last decade in the United States (USA) and elsewhere. These CA organisms are currently responsible for approximately 80 – 90% of skin and skin structure infections (SSSI). Furthermore, MRSA lineages usually associated with CA infections, have entered the nosocomial environment and are now responsible for 30% of invasive infections in USA hospitals.

The increased rates of methicillin resistance among *S. aureus* and the fact that the MRSA epidemiology is constantly evolving, have challenged empiric therapies and traditional infection control practices. The aim of this study was to assess the spectrum of activity and potency of oritavancin and comparator agents tested against *S. aureus* recovered from hospitalized patients in Europe during the 2008 – 2009 International Oritavancin Surveillance Program, as a component of the SENTRY Antimicrobial Surveillance Program. This analysis includes categorization of MRSA based on antimicrobial resistance patterns.

Methods

Bacterial isolates. A total of 3,788 consecutive, non-duplicate *S. aureus* were collected from medical centres (29) located in 13 European countries, including Turkey and Israel. Isolates were collected from bacteremia (40%), SSSI (36%) or pneumonia (12%). Local bacterial species identifications were confirmed by Gram stains, standard biochemical tests and the automated Vitek 2 System (bioMérieux, Hazelwood, Missouri, USA).

Antimicrobial susceptibility testing. All isolates were tested for susceptibility by reference broth microdilution methods following Clinical Laboratory Standards Institute (CLSI; M07-A8, 2009). Susceptibility testing was performed in validated panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Interpretations of comparator MIC values were performed using the CLSI (M100-S20, 2010) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2009) criteria, when available.

Analysis of oritavancin activity was performed against several groups of *S. aureus* displaying various antibiogram resistance patterns (intermediate susceptibility was grouped as resistant). In addition, a MDR set of *S. aureus* (defined as isolates displaying resistance to at least three classes of drugs in addition to β-lactams [oxacillin]) was evaluated.

Quality assurance of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20, 2010) quality control (QC) strains: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. MIC ranges for oritavancin (with polysorbate-80) and comparators tested against ATCC QC strains were those recently published in the CLSI M100-S20 (2010) document.

Results-1

- The overall methicillin resistance rate among *S. aureus* included in this investigation was 25.6%. Higher resistance rates were noted in Greece (59.5%), followed by Poland (40.9%), Belgium (38.5%), Ireland (36.0%) and the United Kingdom (30.6%).
- Oritavancin was very potent when tested against *S. aureus* ($MIC_{50/90}$, 0.03/0.06 mg/L), regardless of resistance phenotype to other comparator agents (Table 1).
- A total of 30 antimicrobial resistance patterns were recognized among MRSA. Three resistance profiles predominated and accounted for 71.1% of tested MRSA; while a MDR phenotype was noted among 39.3% of MRSA isolates (Table 1).
- Resistances to glycopeptides was not observed in the population tested (CLSI criteria; Table 2). However, 15 MRSA with teicoplanin MIC values at ≥4 mg/L (oritavancin $MIC_{50/90}$, 0.03/0.06 mg/L) were categorized as resistant when using the EUCAST (2009) breakpoint criteria. The vast majority (86.7%) of these isolates showed a MDR phenotype.
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) tested against MRSA strains exhibited MIC_{90} values eight- to 32-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), vancomycin ($MIC_{50/90}$, 1/1 mg/L) and linezolid ($MIC_{50/90}$, 2/2 mg/L; Table 2).
- Vancomycin, teicoplanin, daptomycin, linezolid and trimethoprim/sulfamethoxazole were very active (≥96.6% susceptible) when tested against MRSA or other groups of strains displaying various resistance phenotypes (Table 2).

Results-2

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

Resistance pattern[a] (no tested; %)	MIC (mg/L)		Number (cumulative %) inhibited at oritavancin MIC (mg/L) of:					
	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5
Overall (3,788)	0.03	0.06	972 (25.7)	2019 (79.0)	704 (97.5)	86 (99.8)	6 (>99.9)	1 (100.0)
MSSA (2,816; 74.3)	0.03	0.06	748 (26.6)	1493 (79.6)	511 (97.7)	59 (99.8)	5 (100.0)	
MRSA (972; 25.6)	0.03	0.06	224 (23.1)	526 (77.2)	193 (97.0)	27 (99.8)	1 (99.9)	1 (100.0)
OX, LE, CL, ER (254; 26.1)	0.03	0.06	54 (21.3)	131 (72.8)	59 (96.1)	9 (99.6)	0 (99.6)	1 (100.0)
OX, LE, ER (236; 24.3)	0.03	0.06	54 (22.9)	135 (80.1)	44 (98.7)	3 (100.0)		
OX, LE (201; 20.7)	0.03	0.06	46 (22.9)	109 (77.1)	38 (96.0)	8 (100.0)		
OX, LE, CL, ER, TC (81; 8.3)	0.03	0.06	26 (32.1)	46 (88.9)	5 (95.1)	3 (98.8)	1 (100.0)	
OX (51; 5.2)	0.03	0.06	12 (23.5)	25 (72.5)	13 (98.0)	1 (100.0)		
OX, TC (46; 4.7)	0.03	0.06	7 (15.2)	24 (67.4)	14 (97.8)	1 (100.0)		
OX, LE, TC (20; 2.1)	0.03	0.06	5 (25.0)	12 (85.0)	2 (95.0)	1 (100.0)		
OX, ER (15; 1.5)	0.03	0.06	7 (46.7)	5 (80.0)	3 (100.0)			
OX, ER, LE, TC (12; 1.2)	0.03	0.06	1 (8.3)	8 (75.0)	3 (100.0)			
MDR (382; 39.3)	0.03	0.06	87 (22.8)	205 (76.4)	76 (96.3)	12 (99.5)	1 (99.7)	1 (100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*. Most prevalent resistance patterns observed among MRSA. Intermediate and resistant results grouped as resistant. Criteria for susceptibility were those published by EUCAST (2009). OX = oxacillin, ER = erythromycin, CL = clindamycin, LE = levofloxacin and TC = tetracycline. MDR = resistance phenotype to at least three classes of drugs in addition to β-lactams (methicillin [oxacillin]).

Table 2. Antimicrobial activity of oritavancin and comparators tested against *S. aureus* and resistant subsets collected as part of the 2008 – 2009 international oritavancin surveillance program.

Resistance pattern[a] (no. tested) Antimicrobial agent	MIC (mg/L)		% susceptible / % resistant[b]		Resistance pattern[a] (no. tested) Antimicrobial agent	MIC (mg/L)		% susceptible / % resistant[b]	
	50%	90%	CLSI	EUCAST		50%	90%	CLSI	EUCAST
MSSA (2,816)					**OX, LE, ER (236)**				
Oritavancin	0.03	0.06	–[c] / –	– / –	Oritavancin	0.03	0.06	– / –	– / –
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0	Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0	Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	83.8 / 14.8	84.8 / 14.8	Erythromycin	>2	>2	0.0 / 100.0	0.0 / 100.0
Clindamycin	≤0.25	≤0.25	97.7 / 2.2	97.2 / 2.3	Clindamycin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	94.2 / 5.3	93.8 / 6.2	Tetracycline	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	94.0 / 5.6	94.0 / 5.6	Levofloxacin	>4	>4	0.0 / 99.2	0.0 / 99.2
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0	Daptomycin	0.25	0.5	100.0 / 0.0	100.0 / 0.0
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0	Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
TMP/SMX[d]	≤0.5	≤0.5	99.4 / 0.6	99.4 / 0.6	TMP/SMX	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
MRSA (972)					**OX, LE (201)**				
Oritavancin	0.03	0.06	– / –	– / –	Oritavancin	0.03	0.06	– / –	– / –
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0	Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	99.8 / 0.0	Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	32.7 / 66.3	33.6 / 66.3	Erythromycin	≤0.25	0.5	99.5 / 0.0	100.0 / 0.0
Clindamycin	≤0.25	>2	62.2 / 37.1	61.1 / 37.8	Clindamycin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	>8	80.9 / 18.3	80.6 / 19.4	Tetracycline	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	>4	>4	13.7 / 85.5	13.7 / 85.5	Levofloxacin	>4	>4	0.0 / 99.9	0.0 / 99.9
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0	Daptomycin	0.25	0.5	100.0 / 0.0	100.0 / 0.0
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0	Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	98.6 / 1.4	98.6 / 1.4	TMP/SMX	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
OX, LE, CL, ER (254)					**MDR (382)**				
Oritavancin	0.03	0.06	– / –	– / –	Oritavancin	0.03	0.06	– / –	– / –
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0	Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0	Teicoplanin	≤2	≤2	100.0 / 0.0	96.6 / 3.4
Erythromycin	>2	>2	0.0 / 100.0	0.0 / 100.0	Erythromycin	>2	>2	0.8 / 99.0	0.8 / 99.0
Clindamycin	>2	>2	0.0 / 100.0	0.0 / 100.0	Clindamycin	>2	>2	6.8 / 91.9	5.2 / 93.2
Tetracycline	≤2	≤2	0.0 / 100.0	0.0 / 100.0	Tetracycline	≤2	>8	69.7 / 29.8	69.2 / 30.8
Levofloxacin	>4	>4	0.0 / 100.0	0.0 / 100.0	Levofloxacin	>4	>4	1.3 / 97.7	1.3 / 97.7
Daptomycin	0.5	0.5	100.0 / 0.0	100.0 / 0.0	Daptomycin	0.5	0.5	100.0 / 0.0	100.0 / 0.0
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0	Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0	TMP/SMX	≤0.5	2	97.1 / 2.9	97.1 / 2.9

a. Most prevalent resistance patterns observed among MRSA. Intermediate and resistant results grouped as resistant. Criteria for susceptibility were those published by EUCAST (2009). MSSA = methicillin-susceptible *S. aureus*. MRSA = methicillin-resistant *S. aureus*. OX = oxacillin, ER = erythromycin, CL = clindamycin, LE = levofloxacin and TC = tetracycline. MDR = resistance phenotype to at least three classes of drugs in addition to β-lactams (methicillin [oxacillin]).
b. Breakpoint susceptibility criteria as published by CLSI M100-S20 (2010) and EUCAST (2009).
c. –, indicates no susceptibility and/or resistant breakpoints are available for the respective drug/organism combination.
d. Trimethoprim/sulfamethoxazole.

Conclusions

- Oritavancin demonstrated consistent and potent in vitro activity against this contemporary (2008 – 2009) collection of European *S. aureus* strains. In addition, the activity of oritavancin ($MIC_{50/90}$ at 0.03/0.06 mg/L) was not adversely affected by resistance phenotypes to other agents.
- Overall, oritavancin displayed greater potency (≥eight-fold) than several other antimicrobial agents tested against *S. aureus*, and inhibited all isolates at ≤0.5 mg/L.
- The oritavancin in vitro data presented here are promising and warrant continued longitudinal surveillance to monitor for sustained oritavancin activity against *S. aureus* in Europe.

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