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Analysis of Oritavancin Activity Against Gram-Positive Clinical Isolates Responsible for Bacterial Endocarditis in United States and European Hospitals (2008–2016)

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Introduction

- Infective endocarditis (IE) is a life-threatening infectious disease
- Despite recent diagnostic and treatment advances, mortality by IE remains high, with more than 30% of patients affected dying within 1 year after diagnosis
- Presently, staphylococci and streptococci combined cause approximately 80% of IE cases
  - *Staphylococcus aureus* remains the dominant pathogen, accounting for 25–30% of cases
    - About 30% of all *S. aureus* causing IE are methicillin-resistant (MRSA)
    - Vancomycin is an agent of choice for MRSA IE despite poor penetration into vegetations and slow bactericidal activity
    - Clinical failures are frequently observed
  - Coagulase-negative staphylococci (CoNS) account for ~11% of cases
  - Viridans group streptococci (VGS) cause ~30% of cases
  - Enterococci cause ~10% of cases
- Oritavancin belongs to the lipoglycopeptide class of antimicrobial agents. It interrupts bacterial cell wall synthesis in addition to disrupting cell membrane integrity. Together, these mechanisms result in rapid bactericidal activity
- Oritavancin demonstrates potent *in vitro* activity against *S. aureus* (including MRSA), streptococci, and vancomycin–susceptible (VSE) and -resistant (VRE) enterococci, and its potency has remained stable over time
- This study analyzed the *in vitro* activity of oritavancin against gram-positive organisms causing endocarditis. Isolates were collected from United States (US) and European (EU) sites

Materials and Methods

Bacterial isolates

- A total of 424 organisms recovered from patients with a diagnosis of bacterial endocarditis at US and EU sites during the SENTRY Antimicrobial Surveillance Program (2008–2016) were included (Table 1)
- Isolates were determined to be clinically significant based on local guidelines and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA)
- Participating laboratories initially identified isolates and JMI confirmed bacterial identifications by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07–A10 document
- Testing used reference 96-well panels manufactured by JMI Laboratories
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619)

Breakpoint criteria for comparator agents were from CLSI (M100-S27) and EUCAST (Breakpoint tables v7.1)

Results

- Among the 424 isolates, 212 (50.0%) were *S. aureus* (31.6% MRSA), 47 (11.1%) were CoNS, 81 (19.1%) were *Enterococcus faecalis*, 21 (5.0%) were *Enterococcus faecium*, 24 (5.7%) were beta-hemolytic streptococci (BHS), and 39 (9.2%) were VGS (Table 1)
- Oritavancin had similar MIC_{90} values (0.06 μg/mL) against *S. aureus* and CoNS, inhibiting 98.8% of these isolates at ≤0.12 μg/mL
- Oritavancin MIC_{50} values were 8- to 32-fold lower than those for vancomycin, daptomycin, and ceftaroline against staphylococci
- Oritavancin showed MIC values against *E. faecium* ($MIC_{50/90}$, ≤0.008/0.03 μg/mL) that were 2-fold lower than against *E. faecalis* ($MIC_{50/90}$, 0.015/0.03 μg/mL; 97.5% susceptible against all or 100% susceptible against indicated vancomycin-susceptible isolates)
- Oritavancin inhibited 98.1% of all enterococci, including vancomycin-resistant isolates at ≤0.12 μg/mL
- Vancomycin, daptomycin, linezolid ($MIC_{50/90}$, 1/2 μg/mL), and ampicillin ($MIC_{50/90}$, ≤1/2 μg/mL) were similarly active against *E. faecalis*, while daptomycin and linezolid had coverage (100.0% susceptibility) against *E. faecium*
- Overall, BHS isolates were highly susceptible to all agents tested, except for erythromycin (70.8% susceptible), clindamycin (75.0% susceptible), and tetracycline (43.5% susceptible)
- Oritavancin was the most active agent (MIC_{90}, 0.12 μg/mL; 100.0% susceptible) tested against VGS

Table 1 Antimicrobial activity of oritavancin tested against the main organisms and organism groups of isolates

Organism / organism group (number of isolates)	No. of isolates at MIC (μg/mL; *cumulative %*)								
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
***S. aureus* (212)**	7 *3.3*	74 *38.2*	73 *72.6*	42 *92.5*	14 *99.1*	2 *100.0*		0.03	0.06
MRSA (67)	2 *3.0*	21 *34.3*	25 *71.6*	13 *91.0*	4 *97.0*	2 *100.0*		0.03	0.06
MSSA (145)	5 *3.4*	53 *40.0*	48 *73.1*	29 *93.1*	10 *100.0*			0.03	0.06
CoNS (47)	11 *23.4*	6 *36.2*	14 *66.0*	13 *93.6*	2 *97.9*	1 *100.0*		0.03	0.06
***E. faecalis* (81)**	37 *45.7*	33 *86.4*	8 *96.3*	0 *96.3*	1 *97.5*	0 *97.5*	2 *100.0*	0.015	0.03
***E. faecium* (21)**	13 *61.9*	3 *76.2*	4 *95.2*	0 *95.2*	1 *100.0*			≤0.008	0.03
Vancomycin-susceptible (12)	11 *91.7*	0 *91.7*	1 *100.0*					≤0.008	0.008
VanA-phenotype (9)	2 *22.2*	3 *55.6*	3 *88.9*	0 *88.9*	1 *100.0*			0.015	
β-hemolytic streptococci (24)	1 *4.2*	6 *29.2*	6 *54.2*	8 *87.5*	2 *95.8*	1 *100.0*		0.03	0.12
Viridans group streptococci (39)	19 *48.7*	5 *61.5*	5 *74.4*	3 *82.1*	4 *92.3*	3 *100.0*		0.015	0.12

Table 2. Comparative antimicrobial activity of oritavancin and comparator agents tested against the main organisms and organism groups of isolates causing IE in Europe and the United States

Organism / resistance group (no tested) Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI/ EUCAST[a] %S
MSSA (145)				
Oritavancin	0.03	0.06	0.008 – 0.12	100.0/100.0
Ceftaroline	0.25	0.5	0.06 – 0.5	100.0/100.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	96.6/96.6
Daptomycin	0.25	0.5	≤0.12 – 1	100.0/100.0
Erythromycin	≤0.25	>2	≤0.25 – >2	80.0/80.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	95.2/95.2
Linezolid	1	2	0.5 – 2	100.0/100.0
TMX	≤0.5	≤0.5	≤0.5	100.0/100.0
Vancomycin	1	1	0.25 – 2	100.0/100.0
Teicoplanin	≤2	≤2	≤2	100.0/100.0
MRSA (67)				
Oritavancin	0.03	0.06	0.008 – 0.25	97.0/97.0
Ceftaroline	1	2	0.25 – 2	80.6/80.6
Clindamycin	≤0.25	>2	≤0.25 – >2	60.6/60.6
Daptomycin	0.25	0.5	0.25 – 1	100.0/100.0
Erythromycin	>2	>2	≤0.25 – >2	20.9/20.9
Levofloxacin	>4	>4	≤0.5 – >4	31.3/31.3
Linezolid	1	2	0.25 – 2	100.0/100.0
TMX	≤0.5	≤0.5	≤0.5– 2	100.0/100.0
Vancomycin	1	1	0.5 – 2	100.0/100.0
Teicoplanin	≤2	≤2	≤2 – 4	100.0/98.5
CoNS (47)[b]				
Oritavancin	0.03	0.06	≤0.008 – 0.25	– / –
Ceftaroline	0.25	0.5	≤0.06 – 2	– / –
Clindamycin	≤0.25	>2	≤0.25 – >2	78.7/78.7
Daptomycin	0.25	0.5	≤0.12 – 0.5	100.0/100.0
Erythromycin	>2	>2	≤0.25 – >2	46.8/46.8
Levofloxacin	2	>4	≤0.5 – >4	46.8/46.8
Linezolid	0.5	1	≤0.12 – 8	97.9/97.9
Oxacillin	2	>2	≤0.25 – >2	25.5/25.5
Teicoplanin	≤2	8	≤2 – 16	97.9/85.1
Vancomycin	1	2	0.25 – 2	100.0/100.0
***E. faecalis* (81)**				
Oritavancin	0.015	0.03	≤0.008 – 0.5	97.5/-
Ampicillin	≤1	2	≤1 – 4	100.0/100.0
Ceftaroline	2	8	0.12 – >8	– / –
Daptomycin	1	2	0.25 – 2	100.0 / –
Erythromycin	2	>2	≤0.25 – >2	13.7 / –
Levofloxacin	2	>4	≤0.5 – >4	70.4/72.8
Linezolid	1	2	0.5 – 2	100.0/100.0
Teicoplanin	≤2	≤2	≤2 – >16	97.5/97.5
Vancomycin	1	2	≤0.5 – >16	96.3/96.3

Organism / resistance group (number tested/ antimicrobial agent)	MIC_{50}	MIC_{90}	Range	CLSI/ EUCAST[a] %S
***E. faecium* (21)**				
Oritavancin	≤0.008	0.03	≤0.008 – 0.12	– / –
Ampicillin	>8	>8	1 – >8	4.8/4.8
Ceftaroline	>8	>8	2 – >8	– / –
Daptomycin	2	2	0.12 – 4	100.0 / –
Erythromycin	>2	>2	0.5 – >2	5.3 / –
Levofloxacin	>4	>4	1 – >4	4.8/4.8
Linezolid	1	2	0.5 – 2	100.0/100.0
Teicoplanin	≤2	>16	≤2 – >16	57.1/57.1
Vancomycin	1	>16	≤0.5 – >16	57.1/57.1
Beta-hemolytic streptococci (24)[c]				
Oritavancin	0.03	0.12	≤0.008 – 0.25	100.0/100.0
Ceftaroline	≤0.015	≤0.015	≤0.015 – 0.03	100.0/100.0
Clindamycin	≤0.25	>2	≤0.25 – >2	75.0/75.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0/100.0
Erythromycin	≤0.25	>2	≤0.25 – >2	70.8/70.8
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0/100.0
Linezolid	1	1	0.5 – 1	100.0/100.0
Penicillin	≤0.06	≤0.06	≤0.06	100.0/100.0
Teicoplanin	≤2	≤2	≤2	– /100.0
Tetracycline	8	>8	≤2 – >8	43.5/38.1
Vancomycin	0.25	0.5	0.25 – 0.5	100.0/100.0
Viridans group streptococci (39)[d]				
Oritavancin	0.015	0.12	≤0.008 – 0.25	100.0/100.0
Ceftaroline	≤0.015	0.12	≤0.015 – 2	– / –
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.3/92.3
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / –
Erythromycin	2	>2	≤0.25 – >2	41.0 / –
Levofloxacin	1	2	0.25 – 2	100.0 / –
Linezolid	0.5	1	0.25 – 1	100.0 / –
Penicillin	0.12	2	≤0.06 – >8	71.8/76.9
Teicoplanin	≤2	≤2	≤2	– / 100.0
Tetracycline	≤2	>8	≤2 – >8	79.5 / –
Vancomycin	0.5	0.5	0.25 – 1	100.0/100.0

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci

[a] Criteria as published by CLSI (2017) and EUCAST (2017).Oritavancin breakpoint for vancomycin-susceptible *E. faecalis* applied to all isolates, including 2 vancomycin-resistant isolates. All vancomycin-susceptible *E. faecalis* were susceptible to oritavancin.

[b] Organisms include: *Staphylococcus capitis* (2), *S. epidermidis* (28), *S. haemolyticus* (3), *S. hominis* (3), *S. lugdunensis* (4), *S. pasteuri* (1), unspeciated coagulase-negative staphylococci (6)

[c] Organisms include: *Streptococcus agalactiae* (11), *S. dysgalactiae* (1), *S. equisimilis* (2), *S. pyogenes* (10)

[d] Organisms include: *Streptococcus anginosus* (3), *S. bovis* group (1), *S. gallolyticus* (4), *S. gordonii* (2), *S. mitis* group (6), *S. mitis/oralis* (4), *S. mutans* (1), *S. oralis* (5), *S. parasanguinis* (2), *S. salivarius* group (1), *S. sanguinis* (8), *S. sinensis* (1), *S. vestibularis* (1)

Conclusions

- Oritavancin showed potent *in vitro* activity against isolates recovered from patients with IE in US and EU sites
- Oritavancin coverage against this gram-positive collection was comparable to that of other anti-gram-positive agents, including daptomycin, linezolid, teicoplanin, and vancomycin
  - Oritavancin, daptomycin, and linezolid demonstrated activity against VRE, including VanA-type organisms
- Results presented here provide invaluable information on the antimicrobial resistance profile of gram-positive isolates that cause infections in patients with IE and indicate that oritavancin exhibits potent *in vitro* activity against these organisms, including MRSA and VRE, isolated from IE patients hospitalized in EU and US medical centers

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