205 Oritavancin Activity Tested Against Resistant Subsets of Gram-Positive Pathogens

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Abstract

Background: Oritavancin, a semi-synthetic lipoglycopeptide, has demonstrated activity against Gram-positive organisms. The activities of oritavancin and other potent marketed agents were evaluated against resistant subsets of Gram-positive isolates recovered from USA and European sites during the SENTRY Antimicrobial Surveillance Program.

Methods: Unique Gram-positive isolates (11,650) were collected from 62 hospitals in 14 countries during 2008 and 2009, and sent to a central monitor. Identification was confirmed by standard algorithms and Vitek 2. Isolates were tested for susceptibility by CLSI methods (M07-A8 and M100-S19). Organisms displaying linezolid MIC at ≥8 μg/ml were screened for 23S rRNA mutations and *cfr* by PCR/sequencing.

Results: Oritavancin (MIC_{90}, 0.06 μg/ml) was eight-fold more active than daptomycin (MIC_{90}, 0.5 μg/ml) and between 16- and 32-fold more active than vancomycin and linezolid (MIC_{90}, 1-2 μg/ml) against methicillin-resistant staphylococci. Oritavancin, vancomycin and daptomycin maintained potency against linezolid-nonsusceptible staphylococci, where the majority (88%) had 23S rRNA alterations and two strains harbored *cfr*. Oritavancin, vancomycin and linezolid demonstrated sustained activity against daptomycin-nonsusceptible staphylococci. Oritavancin (MIC_{90}, 0.12 μg/ml) was 16-fold more active than daptomycin and linezolid (MIC_{90}, 2 μg/ml; ≥98.5 susceptible) against vancomycin-resistant enterococci (VRE). Although only oritavancin and daptomycin exhibited activity against linezolid-resistant enterococci, oritavancin (MIC_{90}, 0.06 μg/ml) was 32-fold more active than daptomycin (MIC_{90}, 2 μg/ml). When tested against *S. pneumoniae*, oritavancin showed MIC_{90} values (0.008 μg/ml) 128-fold lower than linezolid or levofloxacin (MIC_{90}, 1 μg/ml), regardless of penicillin phenotype. Oritavancin was eight- and 16-fold more active than vancomycin or daptomycin (MIC_{90}, 0.5 μg/ml) and linezolid or levofloxacin (MIC_{90}, 1 μg/ml), respectively, against penicillin-resistant viridans group streptococci.

Susceptible/resistant subsets[a] (no. tested)	MIC_{90} (μg/ml) of susceptible/resistant subsets against[b]: ORI	VAN	DAP	LZD	CLI	LEV
MSSA/MRSA (3,711/3,020)	0.06/0.06	1/1	0.5/0.5	2/2	≤0.25/>2	≤0.5/>4
MS/RCoNS (290/801)	0.06/0.06	2/2	0.5/0.5	1/1	0.5/>2	>4/>4
LZD-S/-non-S staph (7,798/24)	0.06/0.06	1/2	0.5/0.5	2/>8	>2/>2	>4/>4
DAP-S/-non-S staph (7,811/11)	0.06/0.12	1/2	0.5/4	2/2	>2/>2	>4/>4
VSE/VRE (1,438/461)	0.03/0.12	>16	2/2	2/2	>4/>4	>4/>4
LZD-S/-RE (1,896/10)	0.06/0.06	>16/>16	2/2	2/>8	>4/>4	>4/>4
PEN-S/-R SPN (745/254)	≤0.004/0.008	≤1/≤1	NT[c]	1/1	≤0.25/>2	1/1
PEN-S/-R VGS (147/15)	≤0.004/0.06	0.5/0.5	0.5/0.5	1/1	≤0.25/>2	2/1

a. MSSA/MRSA = methicillin-susceptible/-resistant *S. aureus*; MS/RCoNS = methicillin-susceptible/-resistant coagulase-negative staphylococci; LZD-S/-non-S = linezolid-susceptible/-nonsusceptible; DAP-S/-non-S = daptomycin-susceptible/-nonsusceptible; VS/RE = vancomycin-susceptible/-resistant enterococci; LZD-S/-RE = linezolid-susceptible/-resistant enterococci; PEN-S/-R SPN = penicillin-susceptible/-resistant *S. pneumoniae*; PEN-S/-R VGS = penicillin-susceptible/-resistant Viridans group streptococci.
b. ORI = oritavancin; VAN = vancomycin; DAP = daptomycin; LZD = linezolid; CLI = clindamycin; LEV = levofloxacin.
c. NT = not tested.

Conclusions: Oritavancin displayed great potency against these recent resistant subsets of Gram-positive organisms from USA and Europe. The oritavancin MIC_{90} values were only slightly affected (four-fold) by VRE subsets.

Introduction

Antimicrobial resistance, presently a major public health problem worldwide, is not limited to only certain pathogenic species or healthcare settings. Multidrug-resistant (MDR) Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and pneumococci resistant to penicillin and macrolides, continue to challenge the antimicrobial therapies available. Most alarming, however, are reports of MRSA in the community, and isolates with decreased susceptibility to vancomycin as well as ongoing reports of unfavorable clinical responses to this glycopeptide.

This challenging clinical scenario has had a major impact on antimicrobial policies and prompted the pharmaceutical industry to develop new effective agents. Oritavancin is an investigational semi-synthetic lipoglycopeptide with potent activity against MDR Gram-positive pathogens. Oritavancin exhibits a rapid bactericidal and concentration-dependent in vitro activity. In this study, the activity of oritavancin and other potent agents were evaluated against resistant subsets of Gram-positive isolates recovered from medical centers in the United States (USA) and Europe through the SENTRY Antimicrobial Surveillance Program (2008-2009).

Methods

Bacterial isolate collection: A total of 11,650 unique Gram-positive clinically significant isolates were submitted to a central monitoring laboratory (JMI Laboratories, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program (2008 – 2009). The isolates were collected from 34 medical centers located in the United States (USA) and 28 centers in 13 countries in Europe. Bacterial identification was performed by the local submitting sites and confirmed by the central monitor using conventional algorithms and the Vitek® 2 Microbial Identification Systems (bioMérieux, Missouri, USA).

Susceptibility testing: The isolates were tested for susceptibility according to the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A8) using Mueller-Hinton media. Interpretation of MIC results for comparator compounds were in accordance with published CLSI (M100-S19) criteria. Quality control (QC) ranges were those established by CLSI M100-S19; QC strains included *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212, among others. Categories of susceptible and resistant subsets of Gram-positive isolates were established according to the breakpoints provided by the CLSI M100-S19 document.

Characterization of mechanisms for linezolid-nonsusceptible phenotype: Isolates were screened for mutations in the central loop of domain V region of 23S rRNA and presence of the *cfr*-encoding gene using standard PCR reactions and sequencing.

Results-1

- Overall, oritavancin was very active (MIC_{90}, 0.06 μg/ml) against staphylococci, regardless of methicillin or linezolid resistance phenotype, inhibiting all isolates at ≤0.25 μg/ml (Table 1).
- MRSA strains with elevated vancomycin MIC values (2 μg/ml) exhibited oritavancin MIC results slightly higher ($MIC_{50/90}$, 0.06/0.12 μg/ml) when compared to strains with vancomycin MIC values at ≤1 μg/ml ($MIC_{50/90}$, 0.03/0.06 μg/ml; Table 1).
- Daptomycin-nonsusceptible staphylococci showed oritavancin MIC_{90} values (0.12 μg/ml) two-fold higher than their susceptible counterparts (MIC_{90}, 0.06 μg/ml; Table 1).
- Oritavancin (MIC_{90}, 0.06 μg/ml) was eight-fold more active than daptomycin (MIC_{90}, 0.5 μg/ml) and 16- to 32-fold more active than vancomycin (MIC_{90}, 1 μg/ml) and linezolid (MIC_{90}, 2 μg/ml) when tested against methicillin-resistant staphylococci (Table 2).
- Vancomycin, teicoplanin, daptomycin and linezolid were also very activity against MRSA and methicillin-resistant coagulase-negative staphylococci (≥94.1% susceptible; Table 2).
- Oritavancin ($MIC_{50/90}$, 0.06/0.06 μg/ml), vancomycin ($MIC_{50/90}$, 2/2 μg/ml; 100.0% susceptible) and daptomycin ($MIC_{50/90}$, 0.5/0.5 μg/ml; 100.0% susceptible) were active against linezolid-nonsusceptible staphylococci. The vast majority (88%) of these isolates had 23S rRNA alterations and two (12%) strains harbored *cfr*.
- Vancomycin-susceptible *E. faecium* showed oritavancin MIC_{90} values (0.008 μg/ml) four-fold lower than vancomycin-susceptible *E. faecalis* (MIC_{90}, 0.03 μg/ml; Table 1). Similarly, vancomycin-resistant *E. faecium* exhibited oritavancin MIC_{90} values (0.12 μg/ml) four-fold lower than vancomycin-resistant *E. faecalis* (MIC_{90}, 0.5 μg/ml; Tables 1 and 2).
- Oritavancin demonstrated elevated MIC_{90} values (16-fold higher) against vancomycin-resistant *E. faecalis* (0.5 μg/ml) or *E. faecium* (0.12 μg/ml) when compared to vancomycin-susceptible strains (MIC_{90}, 0.03 and 0.008 μg/ml, respectively; Tables 1 and 2).
- Vancomycin-resistant *E. faecium* showed oritavancin $MIC_{50/90}$ values (0.03/0.12 μg/ml) eight- to 64-fold lower than quinupristin/dalfopristin ($MIC_{50/90}$, 1/1 μg/ml), daptomycin ($MIC_{50/90}$, 2/2 μg/ml and linezolid ($MIC_{50/90}$, 1/2 μg/ml; Table 2).
- Penicillin-resistant *S. pneumoniae* exhibited oritavancin MIC_{90} values (0.008 μg/ml) 128-fold lower than linezolid (MIC_{90}, 1 μg/ml) or levofloxacin (MIC_{90}, 1 μg/ml; Table 2).
- Oritavancin (MIC_{90}, 0.06 μg/ml) was eight- and 16-fold more active than vancomycin or daptomycin (MIC_{90}, 0.5 μg/ml) and linezolid or levofloxacin (MIC_{90}, 1 μg/ml), respectively, against penicillin-resistant viridans group streptococci (Table 2).

Results-2

Table 1. Activity of oritavancin against susceptible and resistant organism species/groups recovered from hospitalized patients during the SENTRY Antimicrobial Surveillance Program (2008-2009).

Organism[a] (number tested)	MIC (μg/ml) 50%	MIC (μg/ml) 90%	Number (%) inhibited at each oritavancin concentration (μg/ml) ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
MSSA (3,711)	0.03	0.06	73 (1.2)	770 (20.7)	2037 (54.9)	741 (20.0)	84 (2.3)	6 (0.2)	–	–
MRSA (3,020)	0.03	0.06	45 (1.5)	554 (18.3)	1701 (56.3)	632 (20.9)	79 (2.6)	9 (0.3)	–	–
MRSA with vancomycin ≤1 μg/ml (2640)	0.03	0.06	22 (0.8)	430 (16.3)	1528 (57.9)	578 (21.9)	73 (2.8)	9 (0.3)	–	–
MRSA with vancomycin of 2 μg/ml (88)	0.06	0.12	–	3 (3.4)	23 (26.1)	49 (55.7)	11 (12.5)	2 (2.3)	–	–
MSCoNS (290)	0.03	0.06	76 (26.2)	57 (19.7)	104 (35.9)	49 (16.9)	4 (1.4)	–	–	–
MRCoNS (801)	0.03	0.06	113 (14.1)	89 (11.1)	307 (38.3)	251 (31.3)	36 (4.5)	5 (0.6)	–	–
Linezolid-susceptible staphylococci (7,798)	0.03	0.06	307 (3.9)	1468 (18.8)	4140 (53.1)	1662 (21.3)	203 (2.6)	18 (0.2)	–	–
Linezolid-nonsusceptible staphylococci (24)	0.06	0.06	–	2 (8.3)	9 (37.5)	11 (45.8)	–	2 (8.3)	–	–
Daptomycin-susceptible staphylococci (7,811)	0.03	0.06	307 (3.9)	1466 (18.8)	4149 (53.1)	1668 (21.4)	202 (2.6)	19 (0.2)	–	–
Daptomycin-nonsusceptible staphylococci (11)	0.06	0.12	–	4 (36.4)	–	5 (45.5)	1 (9.1)	1 (9.1)	–	–
Vancomycin-susceptible *E. faecium* (261)	≤0.004	0.008	255 (97.7)	6 (2.3)	–	–	–	–	–	–
Vancomycin-resistant *E. faecium* (407)	0.03	0.12	40 (9.8)	28 (6.9)	150 (36.9)	134 (32.9)	47 (11.5)	6 (1.5)	2 (0.5)	–
Vancomycin-susceptible *E. faecalis* (1,128)	0.015	0.03	279 (24.7)	475 (42.1)	304 (26.9)	65 (5.8)	4 (0.3)	1 (<0.1)	–	–
Vancomycin-resistant *E. faecalis* (50)	0.25	0.5	6 (12.0)	4 (8.0)	4 (8.0)	1 (2.0)	4 (8.0)	14 (28.0)	15 (30.0)	2 (4.0)
Linezolid-susceptible enterococci (1,896)	0.015	0.06	624 (32.9)	519 (27.4)	459 (24.2)	202 (10.6)	53 (2.8)	20 (1.0)	17 (0.9)	1 (0.1)
Linezolid-resistant enterococci (10)	0.03	0.12	1 (10.0)	–	5 (50.0)	1 (10.0)	2 (20.0)	1 (10.0)	–	–
Penicillin-susceptible *S. pneumoniae* (745)	≤0.004	≤0.004	737 (98.9)	3 (0.4)	5 (0.7)	–	–	–	–	–
Penicillin-resistant *S. pneumoniae* (254)	≤0.004	0.008	247 (97.2)	3 (1.2)	3 (1.2)	1 (0.4)	–	–	–	–
Erythromycin-susceptible *S. pneumoniae* (744)	≤0.004	0.008	736 (98.9)	3 (0.4)	5 (0.7)	–	–	–	–	–
Erythromycin-resistant *S. pneumoniae* (452)	≤0.004	0.008	444 (98.2)	3 (0.7)	4 (0.9)	1 (0.2)	–	–	–	–
Penicillin-susceptible VGS (147)	≤0.004	0.03	107 (72.8)	19 (12.9)	13 (8.8)	6 (4.1)	1 (0.7)	1 (0.7)	–	–
Penicillin-resistant VGS (15)	0.008	0.06	8 (53.3)	2 (13.3)	1 (6.7)	1 (6.7)	–	1 (6.7)	–	–

a. MSSA, methicillin (oxacillin)-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSCoNS, methicillin-susceptible coagulase-negative staphylococci (CoNS); MRCoNS, methicillin-resistant CoNS; VGS, viridans group streptococci.

Table 2. Activity of oritavancin and comparator antimicrobial agents tested against Gram-positive isolates recovered from hospitalized patients during the SENTRY Antimicrobial Surveillance Program (2008-2009).

Organism[a] (no. tested)/ antimicrobial agent	MIC (μg/ml)[b] Range	50%	90%	% by category[c]: Susceptible/Resistant
MRSA (3,020)				
Oritavancin	≤0.004 – 0.5	0.03	0.06	- / -
Vancomycin	0.25 – 2	1	1	100.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0
Daptomycin	0.12 – 4	0.25	0.5	99.8 / -
Linezolid	0.25 – >8	2	2	99.9 / -
Erythromycin	≤0.25 – >2	>2	>2	12.7 / 86.5
Clindamycin	≤0.25 – >2	≤0.25	>2	63.7 / 35.8
Tetracycline	≤2 – >8	≤2	4	90.6 / 8.9
Levofloxacin	≤0.5 – >4	>4	>4	25.8 / 73.5
Trimethoprim/sulfamethoxazole	≤0.5 – >2	≤0.5	≤0.5	98.6 / 1.4
MRCoNS (1,359)				
Oritavancin	≤0.004 – 0.25	0.03	0.06	- / -
Vancomycin	≤0.12 – 4	2	2	100.0 / 0.0
Teicoplanin	≤2 – >16	≤2	8	94.1 / 1.1
Daptomycin	≤0.06 – 2	0.25	0.5	99.8 / -
Linezolid	0.12 – >8	1	1	97.5 / -
Erythromycin	≤0.25 – >2	>2	>2	24.1 / 75.0
Clindamycin	≤0.25 – >2	≤0.25	>2	56.3 / 40.9
Tetracycline	≤2 – >8	≤2	>8	84.9 / 14.1
Levofloxacin	≤0.5 – >4	>4	>4	29.3 / 68.0
Trimethoprim/sulfamethoxazole	≤0.5 – >2	2	>2	51.4 / 48.6
Linezolid-nonsusceptible staphylococci (24)				
Oritavancin	0.015 – 0.25	0.06	0.06	- / -
Oxacillin	≤0.25 – >2	>2	>2	4.2 / 95.8
Vancomycin	1 – 4	2	2	100.0 / 0.0
Teicoplanin	≤2 – 16	4	16	66.7 / 0.0
Daptomycin	0.25 – 1	0.5	0.5	100.0 / -
Linezolid	8 – >8	>8	>8	0.0 / -
Erythromycin	≤0.25 – >2	>2	>2	20.8 / 75.0
Clindamycin	≤0.25 – >2	2	>2	33.3 / 29.2
Tetracycline	≤2 – 4	≤2	≤2	100.0 / 0.0
Levofloxacin	>4	>4	>4	0.0 / 100.0
Trimethoprim/sulfamethoxazole	≤0.5 – >2	>2	>2	12.5 / 87.5
Daptomycin-nonsusceptible staphylococci (11)				
Oritavancin	0.015 – 0.25	0.06	0.12	- / -
Oxacillin	≤0.25 – >2	>2	>2	18.2 / 81.8
Vancomycin	1 – 4	2	2	100.0 / 0.0
Teicoplanin	≤2 – 8	≤2	≤2	100.0 / 0.0
Daptomycin	2 – 4	2	4	0.0 / -
Linezolid	0.5 – 2	1	2	100.0 / -
Erythromycin	≤0.25 – >2	>2	>2	36.4 / 63.6
Clindamycin	≤0.25 – >2	>2	>2	36.4 / 54.5
Tetracycline	≤2	≤2	≤2	100.0 / 0.0
Levofloxacin	≤0.5 – >4	>4	>4	45.5 / 54.5
Trimethoprim/sulfamethoxazole	≤0.5 – 2	≤0.5	≤0.5	100.0 / 0.0
Vancomycin-resistant *E. faecalis* (50)				
Oritavancin	≤0.004 – 1	0.25	0.5	- / -
Ampicillin	≤1 – 2	≤1	2	100.0 / 0.0
Vancomycin	>16	>16	>16	0.0 / 100.0
Teicoplanin	≤2 – >16	>16	>16	26.0 / 74.0
Daptomycin	≤0.06 – 2	1	1	100.0 / -
Linezolid	0.5 – 2	1	2	100.0 / 0.0
Quinupristin/dalfopristin	2 – >2	>2	>2	0.0 / 98.0
Erythromycin	2 – >2	>2	>2	0.0 / 94.0
Gentamicin (HL)[d]	≤500 – >1000	>1000	>1000	18.4 / 81.6
Tetracycline	≤2 – >8	>8	>8	12.0 / 88.0
Levofloxacin	1 – >4	>4	>4	2.0 / 98.0
Vancomycin-resistant *E. faecium* (407)				
Oritavancin	≤0.004 – 0.5	0.03	0.12	- / -
Ampicillin	>16	>16	>16	0.0 / 100.0
Vancomycin	>16	>16	>16	0.0 / 100.0
Teicoplanin	≤2 – >16	>16	>16	2.7 / 93.4
Daptomycin	≤0.06 – 8	2	2	99.5 / -
Linezolid	0.5 – >8	1	2	98.3 / 1.7
Quinupristin/dalfopristin	≤0.25 – >2	1	1	95.6 / 2.0
Erythromycin	≤0.25 – >2	>2	>2	2.9 / 95.3
Gentamicin (HL)	≤500 – >1000	≤500	>1000	82.2 / 17.8
Tetracycline	≤2 – >8	≤2	>8	58.5 / 41.0
Levofloxacin	1 – >4	>4	>4	2.0 / 97.8
Penicillin-resistant *S. pneumoniae* (254)				
Oritavancin	≤0.004 – 0.06	≤0.004	0.008	- / -
Penicillin[e]	2 – >4	4	4	42.5 / 3.1
Penicillin[f]	2 – >4	4	4	0.0 / 100.0
Vancomycin	≤1	≤1	≤1	100.0 / -
Linezolid	0.25 – 2	0.5	1	100.0 / -
Ceftriaxone	≤0.25 – 8	1	2	55.9 / 7.5
Levofloxacin	≤0.5 – >4	1	1	98.0 / 1.6
Erythromycin	≤0.06 – >2	>2	>2	13.8 / 86.2
Clindamycin	≤0.25 – >2	>2	>2	39.0 / 60.2
Tetracycline	≤2 – >8	>8	>8	32.7 / 67.3
Trimethoprim/sulfamethoxazole	≤0.5 – >2	>2	>2	21.3 / 65.7
Penicillin-resistant viridans group streptococci (15)				
Oritavancin	≤0.004 – 0.25	0.008	0.06	- / -
Penicillin	4 – >32	8	16	0.0 / 100.0
Vancomycin	0.25 – 1	0.5	0.5	100.0 / -
Teicoplanin	≤2	≤2	≤2	- / -
Daptomycin	0.12 – 1	0.25	0.5	100.0 / -
Linezolid	0.25 – 1	0.5	1	100.0 / -
Levofloxacin	≤0.5 – >4	1	1	93.3 / 6.7
Erythromycin	≤0.25 – >2	>2	>2	6.7 / 93.3
Clindamycin	≤0.25 – >2	≤0.25	>2	86.7 / 13.3
Tetracycline	≤2 – >8	≤2	>8	66.7 / 20.0

a. MRSA, methicillin (oxacillin)-resistant *S. aureus*; MRCoNS, methicillin-resistant coagulase-negative staphylococci.
b. Range, 50% and 90% values of minimal inhibitory concentration (MIC).
c. Criteria for susceptible and resistant as published by CLSI (M100-S19, 2009). Dashes (–) indicate lack of CLSI interpretive criteria.
d. HL, high level aminoglycoside resistance.
e. Criteria as published by the CLSI [2009] for penicillin parenteral (non-meningitis).
f. Criteria as published by the CLSI [2009] for penicillin (oral penicillin V).

Conclusions

- Among the agents evaluated in this study, oritavancin displayed the greatest potency against the tested resistant subsets of Gram-positive organisms, regardless of resistance phenotype.
- MRSA were very susceptible to oritavancin (highest MIC value, 0.25 μg/ml). However, MRSA with decreased susceptibility to vancomycin (MIC, 2 μg/ml) showed oritavancin MIC_{90} values slightly higher (two-fold) than those more susceptible to vancomycin (MIC, ≤1 μg/ml).
- Oritavancin was very active against vancomycin-susceptible (highest MIC, 0.25 μg/ml) and vancomycin-resistant enterococci (highest MIC, 1 μg/ml).
- These in vitro activity results suggest oritavancin continues to be a promising agent for the treatment of serious infections caused by Gram-positive pathogens.

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