C1- 142

48th Annual ICAAC/
IDSA 46th Annual Meeting,
Washington DC, October 25-28, 2008

Activity of Oritavancin Tested against Contemporary Gram-Positive Pathogens Submitted to a Global Surveillance Program (2008)

T.R. FRITSCHE, H.S. SADER and R.N. JONES, JMI Laboratories, North Liberty, IA, USA

Ronald Jones, M.D.
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370
fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background: Oritavancin (ORI), a novel lipoglycopeptide active against Gram-positive pathogens, is under USA-FDA review for complicated skin and skin structure infections. We evaluated ORI against contemporary Gram-positive isolates recovered from an international resistance surveillance program.

Methods: Consecutive, non-duplicate patient isolates (5,769) were submitted from medical centers in North America and Europe during the first quarter of 2008 to the monitoring laboratory, and susceptibility tested using CLSI methods (M7-A7 and M100-S18) against ORI and comparator agents. Isolates originated from bloodstream, skin and soft tissue and respiratory tract infections.

Results: ORI was highly active against all tested isolates including staphylococci (highest MIC value/MIC_{90}; 0.5/0.06 µg/ml), streptococci (0.25/0.12 µg/ml), and enterococci (1/0.06 µg/ml). ORI was equally active against *S. aureus* and coagulase-negative staphylococci (CoNS), including against oxacillin-susceptible and -resistant strains (all $MIC_{50/90}$ values, 0.03/0.06 µg/ml). Among vancomycin-resistant *E. faecalis* (4.0%) and *E. faecium* (58.1%), ORI was 16- and 8-fold less potent (MIC_{90}), respectively, than among vancomycin-susceptible strains, but all vancomycin-resistant strains had oritavancin MICs ≤1 µg/ml. Compared with vancomycin, ORI MIC_{90} potencies for all 3 organism groups were 4 to ≥512-fold lower.

	MIC (µg/ml)			
	Oritavancin		Vancomycin	
Organism (no. tested)	50%	90%	50%	90%
S. aureus (3214)	0.03	0.06	1	1
Coagulase-negative staphylococci (509)	0.03	0.06	2	2
E. faecalis (621)	0.015	0.03	1	2
E. faecium (322)	0.015	0.06	>16	>16
S. pneumoniae (701)	≤0.004	≤0.004	≤1	≤1
β-haemolytic streptococci (305)	0.03	0.12	0.5	0.5
Viridans group streptococci (97)	≤0.004	0.03	0.5	0.5

Conclusions: Among tested agents, oritavancin displayed highest potency against recent staphylococcal, enterococcal and streptococcal isolates, and retained modest activity against vancomycin-resistant enterococcal strains (MIC values, ≤1 µg/ml). Bactericidal activity combined with enhanced potency are key attributes of oritavancin. As with other antimicrobials, resistant emergence necessitates continued surveillance.

INTRODUCTION

The rapid and sustained emergence of antimicrobial resistance among Gram-positive pathogens is rendering existing empiric therapies less effective and more subject to failure, resulting in increased mortality, lengthened hospital stays and increased healthcare costs. Increases in prevalence of both nosocomial and community-acquired infections caused by *Staphylococcus aureus* is especially worrisome, and has driven increased use of expensive alternative agents. As usage of vancomycin has increased, so have cases of vancomycin-resistant enterococcal infections, especially the clonal spread of *Enterococcus faecium* (CC-17). Penicillin and macrolide resistance among *Streptococcus pneumoniae* and other streptococci has further driven the usage of other therapies, especially fluoroquinolones, with consequent bystander effects contributing to increased fluoroquinolone resistance among other bacterial species. The need for alternative therapies that are stable to these mutational events and/or exogenous acquisition of resistance determinants is urgent.

Oritavancin, a semisynthetic lipoglycopeptide active against many prevalent Gram-positive pathogens, has completed several Phase 3 clinical trials for complicated skin and skin structure infections, and is currently under United States Food and Drug Administration (USA-FDA) regulatory review. While previous *in vitro* studies have focused on limited populations of targeted species, particularly resistant subsets or from specific anatomic sites of infection, current surveillance data assessing regional resistance characteristics are limited and currently needed as the compound nears approval for clinical use.

In this report, we summarize the initial 2008 results of the North American and European surveillance testing program, comparing the activity of oritavancin and currently marketed glycopeptides with other antimicrobial agents against clinical isolates submitted for the first half of 2008 (5,769 strains).

METHODS

Bacterial strain collection: A total of 5,769 non-duplicate consecutive Gram-positive clinical isolates were submitted from more than 50 medical centers located in North America (56.5%) and Europe (43.5%) during the first half of 2008 as part of the longitudinal Oritavancin International Surveillance Program. Isolates originated from patients with documented bloodstream (39.6%), respiratory tract (25.1%), skin and skin structure (14.0%) and other infections (21.3%). The distribution of leading species and strains is presented in Table 1.

Susceptibility test methods: All strains were tested by the broth microdilution method using commercially prepared panels (TREK Diagnostics, OH) in cation-adjusted Mueller-Hinton broth containing 0.002% polysorbate-80 (for oritavancin only; with 2-5% lysed horse blood added for testing of streptococci) against a variety of antimicrobial agents representing the most common classes and examples of drugs used for the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with published CLSI criteria (2008). Quality control (QC) strains utilized included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. All QC results were within CLSI-specified ranges (2008).

RESULTS

- Oritavancin was highly active against all surveillance collection isolates, including staphylococci (highest MIC value/MIC_{90}; 0.5/0.06 µg/ml), streptococci (0.25/0.12 µg/ml), and enterococci (1/0.06 µg/ml; Table 1).
- Oritavancin was equally active against *S. aureus* (44.3% oxacillin-resistant) and coagulase-negative staphylococci (74.3%; Table 2); differences between oxacillin-susceptible and -resistant strains were not detected (all $MIC_{50/90}$ values, 0.03/0.06 µg/ml).
- All staphylococci were also susceptible to vancomycin and teicoplanin, and >99% were susceptible to daptomycin and linezolid. Macrolide and fluoroquinolone resistances were elevated, especially among oxacillin-resistant strains (74.1-87.9%; Table 2).
- By tested species, vancomycin resistance was highly prevalent among *E. faecium* (58.1%), but less so in *E. faecalis* (4.0%).
- Oritavancin was 16- and 8-fold less potent (MIC_{90}) against vancomycin-resistant *E. faecalis* and *E. faecium*, respectively, when compared to vancomycin-susceptible strains (data not shown); but all vancomycin-resistant strains had oritavancin MIC values at ≤1 µg/ml (Table 1).
- While enterococci were >99% susceptible to daptomycin and linezolid, oritavancin was 32-fold more active (MIC_{90} values, 0.06 versus 2 µg/ml) than these cited agents.
- Oritavancin was the most potent agent tested against *S. pneumoniae* and viridians group streptococci (MIC_{90} values, ≤0.008 µg/ml); only penicillin (MIC_{90}, 0.06) was more active against the tested β-haemolytic streptococci (two-fold; Table 4).

Table 1. Antimicrobial activity of oritavancin tested against commonly isolated Gram-positive pathogens and resistant organism subsets submitted as part of the 2008 international surveillance program.

	MIC (µg/ml)		Cumulative % inhibited at each oritavancin MIC (µg/ml)							
Organism (no. tested)	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2
S. aureus (3214)	0.03	0.06	21	76	97	>99	>99	100	-	-
Oxacillin-susceptible (1790)	0.03	0.06	22	76	97	>99	>99	100	-	-
Oxacillin-resistant (1424)	0.03	0.06	20	77	97	>99	>99	100	-	-
Coagulase-negative staphylococci (509)	0.03	0.06	29	67	95	>99	100	-	-	-
Oxacillin-susceptible (131)	0.03	0.06	42	79	>99	100	-	-	-	-
Oxacillin-resistant (378)	0.03	0.06	25	63	93	99	100	-	-	-
Enterococcus spp. (972)	0.015	0.06	61	87	97	98	>99	>99	100	-
Vancomycin-susceptible (754)	0.015	0.03	74	95	>99	>99	>99	>99	100	-
Vancomycin-resistant (214)	0.03	0.12	17	59	86	92	96	>99	100	-
E. faecalis (621)	0.015	0.03	65	91	97	97	98	>99	100	-
E. faecium (322)	0.015	0.06	52	79	97	>99	100	-	-	-
S. pneumoniae (701)	≤0.004	≤0.004	>99	>99	100	-	-	-	-	-
Penicillin-susceptible (450)	≤0.004	≤0.004	>99	100	-	-	-	-	-	-
Penicillin-non-susceptible (251)	≤0.004	0.008	>99	>99	100	-	-	-	-	-
Viridans group streptococci (97)	≤0.004	0.03	85	94	98	99	100	-	-	-
β-haemolytic streptococci (305)	0.03	0.12	26	59	89	98	100	-	-	-

Table 2. Antimicrobial activity of oritavancin and comparator agents when tested against year 2008 *S. aureus* and CoNS recovered as part of the oritavancin international surveillance study.

	MIC (µg/mL)		
Organism (no. tested)/Antimicrobial agent	50%	90%	% Susceptible/Resistant[a]
S. aureus (oxacillin-susceptible; 1,790)			
Oritavancin	0.03	0.06	- / -
Vancomycin	1	1	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0
Daptomycin	0.25	0.5	100.0 / -
Linezolid	2	2	100.0 / -
Levofloxacin	≤0.5	≤0.5	91.2 / 8.2
Erythromycin	≤0.25	>2	72.5 / 26.8
Clindamycin	≤0.25	≤0.25	95.0 / 4.9
Tetracycline	≤2	≤2	95.6 / 3.7
S. aureus (oxacillin-resistant; 1,424)			
Oritavancin	0.03	0.06	- / -
Vancomycin	1	1	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0
Daptomycin	0.25	0.5	99.6 / -
Linezolid	2	2	100.0 / -
Levofloxacin	>4	>4	25.4 / 74.1
Erythromycin	>2	>2	11.7 / 87.9
Clindamycin	≤0.25	>2	66.6 / 33.3
Tetracycline	≤2	≤2	93.5 / 6.1
CoNS (oxacillin-susceptible; 131)			
Oritavancin	0.03	0.06	- / -
Vancomycin	1	2	100.0 / 0.0
Teicoplanin	≤2	4	100.0 / 0.0
Daptomycin	0.25	0.5	99.2 / -
Linezolid	1	1	100.0 / -
Levofloxacin	≤0.5	>4	81.7 / 16.8
Erythromycin	≤0.25	>2	62.6 / 37.4
Clindamycin	≤0.25	≤0.25	91.6 / 7.6
Tetracycline	≤2	≤2	92.4 / 7.6
CoNS (oxacillin-resistant; 378)			
Oritavancin	0.03	0.06	- / -
Vancomycin	2	2	100.0 / 0.0
Teicoplanin	4	8	93.9 / 1.3
Daptomycin	0.25	0.5	99.7 / -
Linezolid	1	1	99.2 / -
Levofloxacin	>4	>4	30.2 / 67.7
Erythromycin	>2	>2	27.2 / 72.8
Clindamycin	≤0.25	>2	54.8 / 43.4
Tetracycline	≤2	>8	87.0 / 12.2

Table 3. Antimicrobial activity of oritavancin and comparator agents when tested against year 2008 *E. faecalis* and *E. faecium* recovered as part of the oritavancin international surveillance study.

	MIC (µg/mL)		
Organism (no. tested)/Antimicrobial agent	50%	90%	% Susceptible/Resistant[a]
E. faecalis (vancomycin-susceptible; 594)			
Oritavancin	0.015	0.03	- / -
Teicoplanin	≤2	≤2	100.0 / 0.0
Daptomycin	1	2	100.0 / -
Linezolid	1	2	100.0 / 0.0
Gentamicin (HL)	≤500	>1000	72.7 / 27.3
Streptomycin (HL)	≤1000	>2000	72.4 / 27.6
Ampicillin	≤1	2	100.0 / 0.0
E. faecalis (vancomycin-resistant; 25)			
Oritavancin	0.25	0.5	- / -
Teicoplanin	>16	>16	24.0 / 76.0
Daptomycin	1	1	100.0 / -
Linezolid	1	2	100.0 / 0.0
Gentamicin (HL)	>1000	>1000	29.2 / 70.8
Streptomycin (HL)	2000	>2000	40.0 / 60.0
Ampicillin	≤1	2	100.0 / 0.0
E. faecium (vancomycin-susceptible; 134)			
Oritavancin	≤0.004	0.008	- / -
Teicoplanin	≤2	≤2	100.0 / 0.0
Daptomycin	2	2	100.0 / -
Linezolid	1	2	100.0 / 0.0
Quinupristin/dalfopristin	1	>2	67.2 / 26.1
Gentamicin (HL)	≤500	>1000	74.6 / 25.4
Streptomycin (HL)	2000	>2000	48.5 / 51.5
Ampicillin	>16	>16	11.2 / 88.8
E. faecium (vancomycin-resistant; 187)			
Oritavancin	0.03	0.06	- / -
Teicoplanin	>16	>16	4.3 / 89.8
Daptomycin	2	2	100.0 / -
Linezolid	1	2	99.5 / 0.5
Quinupristin/dalfopristin	0.5	1	94.1 / 2.7
Gentamicin (HL)	≤500	>1000	85.6 / 14.4
Streptomycin (HL)	≤1000	>2000	50.3 / 49.7
Ampicillin	>16	>16	0.0 / 100.0

Table 4. Antimicrobial activity of oritavancin and comparator agents when tested against year 2008 *S. pneumoniae,* viridians group streptococci and β-haemolytic streptococci recovered as part of the oritavancin international surveillance study.

	MIC (µg/mL)		
Organism (no. tested)/Antimicrobial agent	50%	90%	% Susceptible/Resistant[a]
S. pneumoniae (penicillin-susceptible; 450)			
Oritavancin	≤0.004	≤0.004	- / -
Vancomycin	≤1	≤1	100.0 / -
Linezolid	1	1	100.0 / -
Levofloxacin	1	1	99.8 / 0.2
Erythromycin	≤0.06	>8	85.3 / 14.7
Clindamycin	≤0.25	≤0.25	93.1 / 6.7
Tetracycline	≤2	≤2	90.2 / 9.1
S. pneumoniae (penicillin-non-susceptible; 251)			
Oritavancin	≤0.004	0.008	- / -
Vancomycin	≤1	≤1	100.0 / -
Linezolid	1	1	100.0 / -
Levofloxacin	1	1	98.4 / 1.2
Erythromycin	>8	>8	21.9 / 77.7
Clindamycin	≤0.25	>2	55.0 / 45.0
Tetracycline	>8	>8	44.6 / 55.4
Viridans group streptococci (97)			
Oritavancin	≤0.004	0.03	- / -
Vancomycin	0.5	0.5	100.0 / -
Daptomycin	0.25	0.5	100.0 / -
Linezolid	1	1	100.0 / -
Levofloxacin	1	2	92.8 / 6.2
Erythromycin	≤0.25	>2	55.7 / 41.2
Clindamycin	≤0.25	≤0.25	91.8 / 8.2
Tetracycline	≤2	>8	73.2 / 21.6
Penicillin	0.06	1	77.3 / 5.2
β-haemolytic streptococci (305)			
Oritavancin	0.03	0.12	- / -
Vancomycin	0.5	0.5	100.0 / -
Daptomycin	≤0.06	0.25	100.0 / -
Linezolid	1	1	100.0 / -
Levofloxacin	≤0.5	1	99.3 / 0.7
Erythromycin	≤0.25	>2	78.7 / 20.7
Clindamycin	≤0.25	≤0.25	90.5 / 9.2
Tetracycline	≤2	>8	53.4 / 43.9
Penicillin	≤0.015	0.06	100.0 / -

a. Criteria as published by the CLSI [2008].

CONCLUSIONS

- Among tested agents, oritavancin displayed the greatest potency against recent staphylococcal, enterococcal and streptococcal isolates, inhibiting all strains at ≤ 0.5, ≤ 1 and ≤ 0.25 µg/ml, respectively.
- Oxacillin resistance in staphylococci and penicillin resistance in *S. pneumoniae* had negligible effect on the activity of oritavancin.
- Although oritavancin activity was decreased (eight- to sixteen-fold) among vancomycin-resistant enterococci compared with susceptible strains, no MIC value exceeded 1 µg/ml.
- Bactericidal activity combined with enhanced potency are key attributes of oritavancin; rapidly emerging resistances as seen with other Gram-positive-targeted therapies, however, necessitate continued international surveillance.

REFERENCES

Arhin FF, Sarmiento I, Belley A, McKay GA, Draghi DC, Grover P, Sahm DF, Parr TR, Jr., Moeck G (2008). Antimicrob Agents Chemother 52: 1597-1603.

Arhin FF, Tomfohrde K, Draghi DC, Aranza M, Parr TR, Jr., Sahm DF, Moeck G (2008). Diagn Microbiol Infect Dis. 2008 Jul 7. [Epub ahead of print]

Belley A, Neesham-Grenon E, Arhin FF, McKay GA, Parr TR, Jr., Moeck G (2008). Antimicrob Agents Chemother. 2008 Jul 21. [Epub ahead of print]

Clinical and Laboratory Standards Institute. (2006). M7-A7, Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute. (2008). M100-S18, 18th informational supplement. Wayne, PA: CLSI.

Crandon J, Nicolau DP (2008). Future Microbiol 3: 251-263.

Kim SJ, Cegelski L, Stueber D, Singh M, Dietrich E, Tanaka KS, Parr TR, Jr., Far AR, Schaefer J (2008). J Mol Biol 377: 281-293.

Van Bambeke F (2006). Curr Opin Investig Drugs 7: 740-749.