C1-145

Oritavancin: Comparative in vitro Activity against Hospital-Acquired Enterococci from Multicenter Surveillance – The ORION Study

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ABSTRACT

Background: Oritavancin (ORI) is a semi-synthetic bactericidal lipoglycopeptide with multiple modes of action, possessing superior pharmacodynamic properties compared to vancomycin. The ORI Susceptibility Profile Initiative (ORION) study is designed to determine ORI activity against a variety of gram-positive pathogens. This analysis focuses on the in vitro activity of ORI and comparators against common clinical enterococci and resistant phenotypes.
Methods: 647 clinical isolates of *E. faecalis* (350) and *E. faecium* (297) were collected from 29 labs in the US and Korea in late 2007/early 2008. MICs were determined using broth microdilution following CLSI guidelines and interpretive criteria (M7-A7 and M100-S18).
Results: ORI MIC_{90} (µg/mL) and %S compared to vancomycin (VAN), daptomycin (DAP) and linezolid (LIN) are summarized below:

	ORI		VAN		DAP		LIN	
	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
E. faecalis (350)	0.12	nd	4	95.1	2	100	2	95.7
E. faecalis, VRE (15)	0.25	nd	>128	0	2	100	2	100
E. faecium (297)	0.12	nd	>128	38.4	4	98.3	4	86.9
E. faecium, VRE (183)	0.12	nd	>128	0	4	97.8	4	84.2
E. faecalis/E. faecium (647)	0.12	nd	>128	58.1	4	99.2	2	91.7
All VREs (198)	0.25	nd	>128	0	4	98.0	4	85.4
Linezolid Non-Sus (54)	0.25	nd	>128	46.3	4	100	8	0

nd= breakpoints not defined.

Conclusions: ORI had the lowest MICs against all enterococci compared to VAN, DAP and LIN without regard to resistant phenotypes. ORI MIC_{90} values were 8- to 16-fold lower than either DAP or LIN and >512-fold lower than VAN *against E. faecalis* and *E. faecium*. ORI demonstrates potent in vitro activity against these common gram-positive pathogens.

INTRODUCTION

Oritavancin is a semisynthetic lipoglycopeptide antibiotic with rapid bactericidal activity against not only vancomycin-susceptible but also vancomycin–intermediate and –resistant gram-positive bacteria. Like vancomycin, oritavancin's primary mode of action is through inhibition of cell wall synthesis. However, unlike vancomycin and teicoplanin, oritavancin exerts additional activity through cooperative interactions derived from dimerization, membrane anchoring, disruption of membrane potential and partial inhibition of RNA synthesis [1, 2]. These additional modes of killing are thought to be responsible for the increased activity of oritavancin against such important drug resistant pathogens such as vancomycin-intermediate and –resistant *S. aureus* (VISA and VRSA) and vancomycin-resistant enterococci (VRE).

The purpose of this study is to document the in vitro activity of oritavancin and comparable antimicrobials in a surveillance of hospital-acquired *E. faecalis* and *E. faecium* clinical pathogens, including vancomycin-resistant and linezolid non-susceptible isolates, from a multicenter population within the United States and Korea.

METHODS

Fresh clinical isolates were derived from blood or skin and skin structure defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between December 2007 and August 2008 from 29 investigative sites from the United States (20) and Korea (9). Isolates were identified to the species level and tested at each site by the participating laboratory.

Organism transport, confirmation of organism identification, storage and development, and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.

Antimicrobial Susceptibility Testing: Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method using custom Sensititre® panels (TREK Diagnostics Systems, Cleveland, OH) [3]. MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute where available [4].

Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299, and *S. aureus* ATCC 29213.

RESULTS

Table 1. The in vitro activity of oritavancin and comparators against 647 isolates of *E. faecalis, E. faecium*, and vancomycin-resistant phenotypes from Korea and the United States.

Organism	Drug	MIC mcg/ml Range	MIC_{50}	MIC_{90}	%Sus*	%Res
Enterococcus spp [*E. faecium* and *E. faecalis* combined] (647)	Oritavancin	≤0.001 - 0.5	0.03	0.12	na	na
	Ampicillin	≤0.25 - >128	2	>128	56.6	43.4
	Daptomycin	≤0.03 - >8	2	4	99.2	0.8
	Levofloxacin	≤0.03 - >4	>4	>4	36	62.2
	Linezolid	≤0.12 - >32	2	2	91.7	0.5
	Teicoplanin	≤0.03 - >32	0.5	>32	69.9	28.4
	Tetracycline	≤0.12 - >64	32	64	38.3	60.6
	Vancomycin	0.25 - >128	2	>128	69.1	30.6
All VREs ** (198)	Oritavancin	≤0.001 - 0.5	0.06	0.25	na	na
	Ampicillin	0.5 - >128	>128	>128	6.1	93.9
	Daptomycin	0.12 - >8	2	4	98	2
	Levofloxacin	0.5 - >4	>4	>4	0.5	99
	Linezolid	≤0.12 - >32	2	4	85.4	1.5
	Teicoplanin	0.25 - >32	>32	>32	4.5	91.9
	Tetracycline	≤0.12 - >64	16	64	46.5	52
	Vancomycin	16 - >128	>128	>128	0	100
E. faecalis (350)	Oritavancin	0.004 - 0.5	0.03	0.12	na	na
	Ampicillin	≤0.25 - >128	1	2	98.6	1.4
	Daptomycin	≤0.03 - 4	1	2	100	0
	Levofloxacin	0.25 - >4	2	>4	62.3	36.3
	Linezolid	0.25 - 4	2	2	95.7	0
	Teicoplanin	≤0.03 - >32	0.25	0.5	94.6	3.7
	Tetracycline	0.25 - >64	32	64	24	74.9
	Vancomycin	0.25 - >128	2	4	95.1	4.3
E. faecalis, VRE (15)	Oritavancin	0.008 - 0.5	0.25	0.25	na	na
	Ampicillin	0.5 - 128	2	128	80	20
	Daptomycin	0.5 - 2	1	2	100	0
	Levofloxacin	0.5 - >4	>4	>4	6.7	93.3
	Linezolid	0.5 - 2	1	2	100	0
	Teicoplanin	8 - >32	>32	>32	13.3	73.3
	Tetracycline	0.25 - 64	32	64	33.3	66.7
	Vancomycin	16 - >128	>128	>128	0	100
E. faecium (297)	Oritavancin	≤0.001 - 0.5	0.015	0.12	na	na
	Ampicillin	≤0.25 - >128	>128	>128	7.4	92.6
	Daptomycin	0.12 - >8	2	4	98.3	1.7
	Levofloxacin	≤0.03 - >4	>4	>4	4.7	92.9
	Linezolid	≤0.12 - >32	2	4	86.9	1
	Quinu/Dalfo	≤0.12 - 32	1	4	75.1	11.8
	Teicoplanin	≤0.03 - >32	32	>32	40.7	57.6
	Tetracycline	≤0.12 - >64	2	>64	55.2	43.8
	Vancomycin	0.5 - >128	>128	>128	38.4	61.6
E. faecium, VRE (183)	Oritavancin	≤0.001 - 0.5	0.06	0.12	na	na
	Ampicillin	16 - >128	>128	>128	0	100
	Daptomycin	0.12 - >8	2	4	97.8	2.2
	Levofloxacin	4 - >4	>4	>4	0	99.4
	Linezolid	≤0.12 - >32	2	4	84.2	1.6
	Quinu/Dalfo	≤0.12 - 32	1	2	78.7	8.2
	Teicoplanin	0.25 - >32	>32	>32	3.8	93.4

*Drug susceptibilities are defined in CLSI document M100-S18 (2008), where available; na=susceptibility breakpoints are not defined.
** VRE = vancomycin-resistant enterococci.

Table 2. The in vitro activity of oritavancin and comparators against 647 isolates of *E. faecalis, E. faecium*, and vancomycin-resistant phenotypes from Korea and the United States categorized by country.

Organism	Drug	Korea MIC (mcg/ml) MIC_{50}	Korea MIC_{90}	Korea %Sus*	United States MIC (mcg/ml) MIC_{50}	United States MIC_{90}	United States %Sus*
Enterococcus spp Korea (251) US (396) [*E. faecium* and *E. faecalis* combined]	Oritavancin	0.015	0.06	na	0.03	0.25	na
	Ampicillin	8	>128	53.4	2	>128	58.6
	Daptomycin	2	4	99.6	2	4	99
	Levofloxacin	>4	>4	35.9	>4	>4	36
	Linezolid	2	2	94.8	2	4	89.6
	Quinu/Dalfo	8	16	39	8	16	32.5
	Teicoplanin	0.5	32	83.7	0.5	>32	61.1
	Tetracycline	32	>64	44.6	32	64	34.3
	Vancomycin	1	>128	82.9	2	>128	60.4
All VREs** Korea (42) US (156)	Oritavancin	0.015	0.06	na	0.06	0.25	na
	Ampicillin	>128	>128	2.4	>128	>128	7.1
	Daptomycin	2	4	97.6	2	4	98.1
	Levofloxacin	>4	>4	0	>4	>4	0.6
	Linezolid	2	2	92.9	2	4	83.3
	Quinu/Dalfo	1	2	88.1	1	8	69.9
	Teicoplanin	>32	>32	4.8	>32	>32	4.5
	Tetracycline	0.5	64	69	32	>64	40.4
	Vancomycin	>128	>128	0	>128	>128	0
E. faecalis Korea (130) US (220)	Oritavancin	0.03	0.12	na	0.03	0.25	na
	Ampicillin	1	4	96.9	1	2	99.5
	Daptomycin	1	2	100	1	2	100
	Levofloxacin	1	>4	65.4	2	>4	60.5
	Linezolid	2	2	96.2	2	2	95.5
	Quinu/Dalfo	16	32	2.3	16	32	0
	Teicoplanin	0.25	0.5	96.9	0.25	0.5	93.2
	Tetracycline	64	>64	19.2	32	64	26.8
	Vancomycin	2	4	96.2	2	4	94.5
E. faecalis, VRE Korea (4) US (11)	Oritavancin	0.015	0.25	na	0.25	0.25	na
	Ampicillin	128	128	25	2	2	100
	Daptomycin	1	2	100	1	1	100
	Levofloxacin	>4	>4	0	>4	>4	9.1
	Linezolid	2	2	100	1	2	100
	Quinu/Dalfo	1	8	50	8	16	0
	Teicoplanin	16	>32	25	>32	>32	9.1
	Tetracycline	32	64	25	32	32	36.4
	Vancomycin	128	>128	0	>128	>128	0
E. faecium Korea (121) US (176)	Oritavancin	0.008	0.03	na	0.06	0.12	na
	Ampicillin	128	>128	6.6	>128	>128	8
	Daptomycin	2	4	99.2	2	4	97.7
	Levofloxacin	>4	>4	4.1	>4	>4	5.2
	Linezolid	2	2	93.4	2	4	82.4
	Quinu/Dalfo	1	4	78.5	1	4	72.7
	Teicoplanin	0.5	>32	69.4	>32	>32	21
	Tetracycline	0.5	64	71.9	32	>64	43.8
	Vancomycin	1	>128	68.6	>128	>128	17.6
E. faecium, VRE Korea (38)	Oritavancin	0.015	0.06	na	0.06	0.25	na
	Ampicillin	>128	>128	0	>128	>128	0

* Drug susceptibilities are defined in CLSI document M100-S18 (2008), where available; na=susceptibility breakpoints are not defined. Susceptibilities, MIC_{50} and MIC_{90} values may not be reliable for n <10.
** VRE = vancomycin-resistant enterococci.

Table 3. Summary of the in vitro activity of oritavancin against various drug resistant phenotypes of *E. faecalis* and *E. faecium* from Korea and the United States.

Phenotypes [a]	N	MIC (mcg/ml) Range	MIC_{50}	MIC_{90}
HL Aminoglycoside Resistant [c]	88	≤0.001 - 0.25	0.03	0.12
Ampicillin Resistant	280	≤0.001 - 0.5	0.015	0.12
Daptomycin Resistant	5 [b]	0.03 - 0.5	--	--
Levofloxacin Resistant	402	≤0.001 - 0.5	0.03	0.12
Linezolid Non-Susceptible	54	0.004 - 0.25	0.06	0.25
Quinu/Dalfo Resistant	35	0.004 - 0.25	0.008	0.25
Teicoplanin Resistant	184	0.002 - 0.5	0.06	0.25
Tetracycline Resistant	394	≤0.001 - 0.5	0.03	0.12
Vancomycin Resistant	198	≤0.001 - 0.5	0.06	0.25

[a] Phenotypes determined by respective resistant breakpoint as defined in CLSI document M100-S18 (2008).
[b] MIC_{50} and MIC_{90} values not calculated for n < 10
[c] High Level aminoglycoside resistant – gentamicin >500 mcg/ml and streptomycin >1000 mcg/ml.

CONCLUSIONS

- ORI demonstrated potent in vitro activity against recent hospital-acquired *E. faecalis* and *E. faecium* from a diverse population of centers in Korea and the United States. ORI median MIC values of 0.03 mcg/ml against all enterococci were at least 64-fold lower than all study drugs except teicoplanin. ORI MIC_{90} values of 0.12 mcg/ml were the lowest of all study drugs and 16- to 32-fold lower than linezolid and daptomycin, respectively, and more than 64-fold lower than levofloxacin, teicoplanin, and vancomycin.
- ORI was equally potent against various drug resistant isolates with MIC_{90} values of 0.12 mcg/ml against high level aminoglycoside-, ampicillin-, levofloxacin- and tetracycline-resistant strains. All linezolid-, quinupristin/dalfopristin-, teicoplanin-, and vancomycin-resistant groups had oritavancin MIC_{90} values of 0.25 mcg/ml. The highest ORI value observed against any isolate was 0.5 mcg/ml.
- Regional variations in ORI MIC values were observed with 2- to 4-fold higher MICs in the United States compared to the isolates collected from the laboratories in Korea.
- The treatment of hospital-acquired vancomycin-resistant enterococci can be problematic. The in vitro activity of ORI in this study suggests it may be a viable and promising adjuvant to physicians' armamentarium against drug-resistant *E. faecalis* and *E. faecium*.

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ACKNOWLEDGEMENTS

This study was sponsored by a grant from Targanta Therapeutics. We gratefully acknowledge the contributions of all investigators, laboratory personnel and the current members of the ORION Surveillance Study group.