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Comparative *In Vitro* Potency of Oritavancin, Teicoplanin, and Vancomycin against Glycopeptide-Susceptible and -Resistant Gram-Positive Organisms

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Abstract

Background: Oritavancin (ORI), a novel class of glycopeptide (GLY) that is rapidly bactericidal against gram-positive (GP) pathogens, is currently in post-Phase III clinical development. With the emergence of GLY resistance among enterococci and staphylococci, knowledge regarding the level of activity of any new compound in development against such phenotypes is important. This analysis was done to establish the potency (on a µg/ml basis) of ORI relative to that of other currently available GLY (teicoplanin [TEI] and vancomycin [VAN]).

Methods: ORI, TEI, and VAN MIC data generated by testing US and European enterococcal isolates (*E. faecalis* [EF] and *E. faecium* [EM]) and the MI VRSA (VRSA1) and PA VRSA (VRSA2) were analyzed according to relative potency ratios that were calculated based on modal MIC VAN/modal MIC ORI, modal MIC VAN/modal MIC TEI, MIC_{90} VAN/ MIC_{90} ORI, and MIC_{90}VAN/ MIC_{90}TEI, for both VAN-susceptible (VAN-S) and VAN nonsusceptible (VAN-NS) EF and EM.

Results:

	In vitro Potency Ratios		
Organism/ Phenotype	VAN mode/ ORI mode	VAN mode/ TEI mode	VAN MIC_{90}/ ORI MIC_{90}	VAN MIC_{90}/ TEI MIC_{90}
EF VAN-S	1	4	1	8
EF VAN-NS	256	4	256	2
EM VAN-S	2	2	2	2
EM VAN-NS	512	8	256	4

For all VAN-NS strains, the VAN modal MIC and MIC_{90} was >256 µg/ml; therefore, the ratios displayed are greater than or equal to the value displayed. Similar to the profiles shown for enterococci, the VAN/ORI MIC ratios for VRSA1 and VRSA2 were >128 and 32, respectively.

Conclusions: These ratios demonstrate that among VAN-S enterococci, ORI, VAN, and TEI have comparable potency, but against VAN-NS enterococci only ORI maintains a high level of activity. This same pattern occurred with the 2 VRSA strains studied. The level of activity that ORI maintained against GLY-resistant GP pathogens is an important attribute for an agent that will be used in clinical settings where antimicrobial resistance is common.

Background

Oritavancin, a novel class of glycopeptide that is rapidly bactericidal against gram-positive pathogens, is currently in post-Phase III clinical development. With the emergence of glycopeptide resistance among enterococci and staphylococci, knowledge regarding the level of activity of any new compound in development against such phenotypes is important. The current study was undertaken to determine the *in vitro* potency of oritavancin relative to that of other currently available glycopeptides, ie, teicoplanin and vancomycin.

Methods

E. faecalis (n=941) and *E. faecium* (n=644) were collected from 49 hospital laboratories in the US and 39 hospital laboratories across 14 countries in Europe. Additionally, 2 vancomycin-resistant *S. aureus* (VRSA1, MI; VRSA2, PA) were included in the study. Isolates were tested by broth microdilution according to CLSI methodology against oritavancin, teicoplanin, and vancomycin. Results were analyzed according to relative potency ratios that were calculated by comparison of vancomycin to oritavancin and to teicoplanin, based on or modal MICs and MIC_{90} by vancomycin-susceptible and -resistant phenotypes for *Enterococcus* spp. and based on MICs for VRSA isolates.

Results

			µg/ml			Vancomycin MIC_{90}/ Comparator agent MIC_{90}	Vancomycin MIC mode/ Comparator agent MIC mode
Organism	Phenoype	Agent	MIC_{90}	Modal MIC	Comparator Agent	Times more potent than vancomycin	
E. faecalis	VAN-S (n=870)	Vancomycin	2	1			
		Oritavancin	2	1	Oritavancin	1	1
		Teicoplanin	0.25	0.25	Teicoplanin	8	4
	VAN-NS (n=71)	Vancomycin[a]	>256	>256			
		Oritavancin	2	2	Oritavancin	≥256	≥256
		Teicoplanin[b]	>128	128	Teicoplanin	≥2	≥4
E. faecium	VAN-S (n=329)	Vancomycin	2	1			
		Oritavancin	1	0.5	Oritavancin	2	2
		Teicoplanin	1	0.5	Teicoplanin	2	2
	VAN-NS (n=315)	Vancomycin[a]	>256	>256			
		Oritavancin	2	1	Oritavancin	≥256	≥512
		Teicoplanin	128	64	Teicoplanin	≥4	≥8

[a]MIC values >256 µg/ml were determined to at least be 512 µg/ml when determining potency ratios

[b]MIC values >128 µg/ml were determined to at least be 256 µg/ml when determining potency ratios

Table 1.
Activity of Oritavancin, Vancomycin, and Teicoplanin against *Enterococcus* spp

Among vancomycin-susceptible *E. faecalis* and *E. faecium*, the modal MIC and MIC_{90}s were within one doubling dilution for oritavancin and vancomycin (Table 1).

The oritavancin modal MIC and MIC_{90}s remained similar (within one doubling dilution; ranging from 0.5 to 2 µg/ml) among the vancomycin-resistant population compared with the vancomycin-susceptible population for both *E. faecalis* and *E. faecium* (Table 1).

The teicoplanin modal MIC and MIC_{90}s were 128 to 512 times higher among the vancomycin nonsusceptible population compared with the vancomycin-susceptible population for *E. faecalis* and *E. faecium* (Table 1).

Oritavancin was of the same potency or twice as potent as vancomycin among vancomycin-susceptible enterococci and ≥256 times more potent than vancomycin among vancomycin nonsusceptible enterococci (Table 1).

Table 2.
Activity of Oritavancin and Teicoplanin Compared with Vancomycin against Vancomycin-Resistant *S. aureus*

Strain	Vancomycin MIC (µg/ml)	Oritavancin MIC (µg/ml)	Ratio of Vancomycin MIC/ Oritavancin MIC	Teicoplanin MIC (µg/ml)	Ratio of Vancomycin MIC/ Teicoplanin MIC
VRSA 1 MI	>256[a]	4	≥128	32	≥16
VRSA 2 PA	64	2	32	8	8

[a]MIC values >256 µg/ml were determined to at least be 512 µg/ml when determining potency ratios

Oritavancin showed the lowest MICs (2 and 4 µg/ml) among the VRSA isolates compared with vancomycin (>256 and 64 µg/ml) and teicoplanin (32 and 8 µg/ml; Table 2).

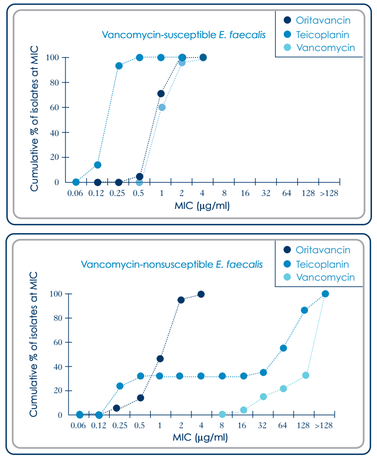

Figure 1.
Glycopeptide Activity among *E. faecalis*

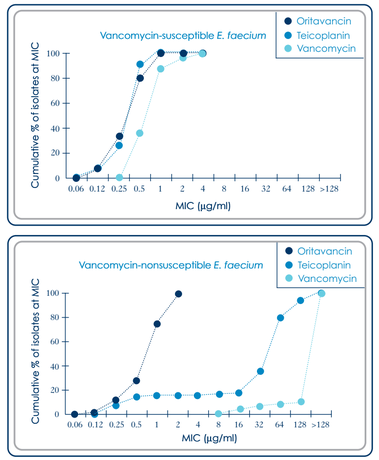

Figure 2.
Glycopeptide Activity among *E. faecium*

Based on MIC values, all glycopeptides tested displayed similar activity among vancomycin-susceptible populations; however, oritavancin displayed exceptional activity against vancomycin nonsusceptible population against enterococci (Figures 1 and 2).

Conclusions

Among vancomycin-susceptible enterococci, oritavancin, teicoplanin, and vancomycin have comparable potency; however, against vancomycin nonsusceptible enterococci, only oritavancin maintains a high level of activity.

Oritavancin retained the lowest MICs among the glycopeptides tested for both VRSA strains studied.

The level of activity that oritavancin maintained against glycopeptide nonsusceptible Gram-positive bacteria is an important attribute for an agent that will be used in clinical settings where antimicrobial resistance is common.

Acknowledgements

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Targanta Therapeutics