Oritavancin Susceptibility Testing in Vancomycin-Resistant Daptomycin non-Susceptible *Enterococcus Faecium*

Poster
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REVISED ABSTRACT

Background: Vancomycin-resistant enterococcus (VRE) is the most common gram-positive bacteria isolated from febrile, neutropenic patients and those with pre-engraftment bacteremia after allogenic stem cell transplant. Treatment of invasive infections due to this organism is challenging; no drugs have received FDA approval for treatment of VRE bacteremia. Daptomycin is commonly used to treat VRE infections but non -susceptibility to this drug is a growing problem. Oritavancin, a synthetic lipoglycopeptide, has shown *in vitro* activity against VRE. The goal of this study is to test *in vitro* susceptibilities of oritavancin against VRE blood isolates with a daptomycin MIC of ≥ 4 mcg/mL.
Methods: Fifty VRE blood isolates from patients who developed bacteremia at MSKCC between 2009-2013 were included in the study. Testing by broth microdilution was simultaneously performed for the following drugs: vancomycin, range: ≤0.25 to≥16 mcg/mL; linezolid, range: ≤0.5 to ≥8 mcg/mL; daptomycin, range: ≤0.12 to ≥ 4 mcg/mL; teicoplanin, range: ≤0.12 to ≥16 mcg/mL; oritavancin, range: ≤0.004 to ≥ 4 mcg/mL; high-level gentamicin, ≥/≤500 mcg/mL; high-level streptomycin, ≤500 to ≥1,000 mcg/mL; and penicillin, range: ≤0.12 to ≥8 mcg/mL. Testing was performed in duplicate according to CLSI M07-A10 and CLSI M100-S26 standards for broth microdilution method and interpretation.
Results: Eighteen (36%) isolates had daptomycin MIC of > 4 mcg/mL. Median oritavancin MIC was 0.25 mcg/mL (range: 0.06-0.5). Median linezolid MIC was 4 mcg/mL (range 1->8). All 50 (100%) isolates had vancomycin and teicoplanin MIC >16 mcg/mL & penicillin MIC > 8 mcg/mL; 31(62%) had high-level gentamicin MIC >500 mcg/mL; and 30 (60%) had high-level streptomycin MIC >1,000 mcg/mL.
Conclusions: For VRE isolates with daptomycin MIC ≥ 4, oritavancin median MIC was 0.25 mcg/mL. Oritavancin may have a role in management of serious VRE infections with limited treatment options. Further data are needed to evaluate oritavancin utility in clinical practice.

INTRODUCTION

Vancomycin-resistant enterococcus (VRE) is an important pathogen and a major therapeutic challenge in immunocompromised hosts, particularly those receiving hematopoietic stem cell transplant (HSCT).

VRE is now the most common gram-positive organism isolated from febrile, neutropenic patients and those with pre-engraftment bacteremia after allogenic HSCT [1-3]. VRE bacteremias in transplant recipients have been associated with mortality rates of 9-22% [4,5].

Few drugs have been approved for treatment of VRE. In addition to lack of comparative efficacy, their use has been limited by unfavorable side effects (e.g., linezolid and myelotoxicity with prolonged use).

Daptomycin has been used "off label" for the treatment or salvage therapy for VRE infections including bacteremias. However, emergence of non-susceptible isolates has been reported[6-9]. Mechanisms for daptomycin resistance have not been fully explained, although several genetic pathways have been described[7]. In a 2011 report by Kamboj et al., daptomycin-resistant VRE bacteremia at Memorial Sloan Kettering Cancer Center (MSKCC) increased from 3.4% in 2007 to 15.2% in 2009 [6]. Among 78 patients with VRE bacteremia at MSKCC between Jan. 1, 2012 - Dec. 31, 2013, 53(68%) had an initial isolate with daptomycin MIC ≥ 4 mcg/mL.

Oritavancin is a novel synthetic lipoglycopeptide that has been FDA-approved for the treatment of adult patients with acute bacterial skin and skin structure infections caused by susceptible isolates of the following gram-positive bacteria:

- *Staphylococcus aureus* (including methicillin-susceptible and methicillin–resistant isolates),
- *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group , and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

INTRODUCTION (cont)

Oritavancin has shown *in vitro* activity against VRE , including *Enterococcus faecium* [10].

The study objective is to test *in vitro* susceptibilities of vancomycin-resistant *Enterococcus faecium* with a daptomycin MIC of ≥ 4 mcg/mL.

MATERIALS AND METHODS

Strain collection: 50 archived bacterial isolates of vancomycin-resistant *Enterococcus faecium* with daptomycin MIC ≥4 mcg/mL were identified. Isolates were collected from oncology patients with sustained bloodstream infections (BSI) (defined as ≥ 48 hours of bacteremia) between 2009-2013 at MSKCC.

Susceptibility testing: Simultaneous testing was performed using validated broth microdilution method according to CLSI M07-A10.[11] Panels, 100-µl frozen 96-well panels, were produced by The Medicines Company (Saint-Laurent, Quebec, Canada). Panels contained a range of doubling dilutions and a growth control well (Figure 1). Quality control for each batch of panels was performed and interpreted according to CLSI M07-A10 and CLSI M100-S26 guidelines and standards prior to shipping and upon receipt at MSKCC. Each panel was with a single isolate tested in duplicate Susceptibility testing was simultaneously performed for vancomycin, range: ≤0.25 to≥16 mcg/mL; linezolid, range: ≤0.5 to ≥8 mcg/mL; daptomycin, range: ≤0.12 to ≥ 4 mcg/mL; teicoplanin, range: ≤0.12 to ≥16 mcg/mL; oritavancin, range: ≤0.004 to ≥ 4 mcg/mL; high-level gentamicin, ≥/≤500 mcg/mL; high-level streptomycin, ≤500 to ≥1,000 mcg/mL; and penicillin, range: ≤0.12 to ≥8 mcg/mL.

When duplicate results were discordant within the doubling dilution, the higher MIC was reported.

Figure 1. Panel design for susceptibility testing by broth microdilution

	1	2	3	4	5	6	7	8	9	10	11	12
A	Dapto >4 / 4	4	0.5	Linezolid >8 / 8	Teicoplanin >16 / 16	Pen >8 / 8	Dapto >4 / 4	4	0.5	Linezolid >8 / 8	Teicoplanin >16 / 16	Pen >8 / 8
B	2	2	0.25	4	8	4	2	2	0.25	4	8	4
C	1	1	0.12	2	4	2	1	1	0.12	2	4	2
D	0.5	0.5	0.06	1	2	1	0.5	0.5	0.06	1	2	1
E	0.25	≤0.25	0.03	≤0.5	1	0.5	0.25	≤0.25	0.03	≤0.5	1	0.5
F	≤0.12	Orita >4 / 4	0.015	Genta (HL) >500 / ≤500	0.5	0.25	≤0.12	Orita >4 / 4	0.015	Genta (HL) >500 / ≤500	0.5	0.25
G	Vanco >16 / 16	2	0.008	Strep (HL) >1000 /1000	0.25	≤0.12	Vanco >16 / 16	2	0.008	Strep (HL) >1000 /1000	0.25	≤0.12
H	8	1	≤0.004	≤500	≤0.12	Control	8	1	≤0.004	≤500	≤0.12	Control

RESULTS

- Fifty-eight isolates of vancomycin-resistant *Enterococcus faecium* with daptomycin MIC ≥ 4 were identified.
- Eight isolates were not viable during the sub-culturing process and were excluded.

RESULTS (cont)

- Fifty isolates representing 21 unique patients were analyzed.
- Oritavancin exhibited activity against VRE with median MIC 0.25 mcg/mL (range: 0.06-0.5 mcg/mL) (Figure 2).
- Five (10%) of 50 isolates had discordant oritavancin MIC within 1 dilution difference.
- All 50 (100%) isolates had vancomycin and teicoplanin MICs > 16 mcg/mL and were resistant to penicillin and gentamicin.
- The median linezolid MIC was 4 mcg/mL (range: 1->8 mcg/mL).
- Thirty (60%) isolates were resistant to streptomycin (MIC >1,000 mcg/mL)
- 18 (36%) of isolates had daptomycin MIC > 4 mcg/mL

Figure 2. MIC Distribution of Oritavancin

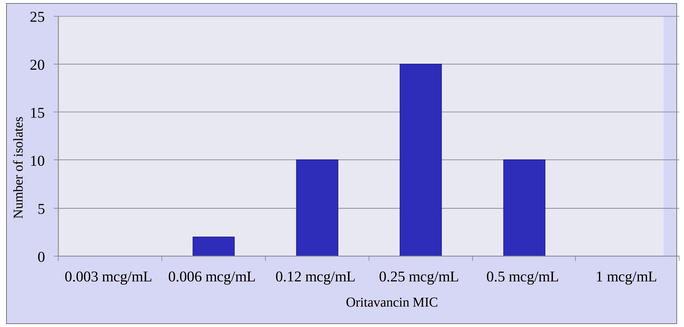

Table 1. Oritavancin MIC (mcg/mL) distributions and frequency (%) against Linezolid MIC (mcg/ml) and Daptomycin MIC(mcg/mL)

		Oritavancin MIC (mcg/mL)					
Drug	Isolate Count	0.003	0.006	0.12	0.25	0.5	1
Linezolid MIC ≤2mcg/mL	18	0	1(7)	4(22)	7(39)	6(33)	0
Linezolid MIC= 4mcg/mL	19	0	1(5)	4(21)	8(42)	7(37)	0
Linezolid MIC=8mcg/mL	10	0	0	2(20)	3(30)	5(50)	0
Linezolid MIC=>8mcg/mL	3	0	0	1(33)	1(33)	1(33)	0
Daptomycin MIC = 4mcg/mL	32	0	2(7)	8(25)	11(34)	11(34)	0
Daptomycin MIC >4mcg/mL	18	0	0	2(11)	8(44)	8(44)	0

CONCLUSIONS

- For VRE isolates with high MIC to daptomycin, the oritavancin median MIC was 0.25 mcg/mL.
- Oritavancin may have a role in management of serious VRE infections with limited treatment options.
- The findings of this investigation support the value of further studies on the role of oritavancin in treating vancomycin-resistant *Enterococcus faecium* infections with high daptomycin MIC.

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