E-1582

Activity of Oritavancin Tested against Vancomycin-Resistant Enterococci Recovered from Bacteremic Patients in USA and European Hospitals (2008 – 2009)

Contact info:
Rodrigo Mendes, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317 USA
Tel: 319-665-3370 ext 218
Email: rodrigo-mendes@jmilabs.com

R.E. MENDES, R.N. JONES, H.S. SADER

JMI Laboratories, North Liberty, IA

Abstract

Background: The activity of oritavancin and comparators (nine) was evaluated against recent vancomycin-resistant enterococci (VRE) causing bloodstream infections (BSI).

Methods: 2,407 enterococci (1,432 *E. faecalis*; 939 *E. faecium*, 26 *E. gallinarum* and 10 *E. casseliflavus*) were collected from 29 sites in the USA and 29 sites among 14 European countries, including Turkey and Israel. Identification was performed by Vitek 2. Isolates were tested for susceptibility by CLSI methods (M07-A8 and M100-S20-U). Oritavancin activity was evaluated against VanA- and VanB-resistance type and *vanC*-harboring enterococci.

Results: Oritavancin showed equivalent activity against vancomycin-susceptible and VanB-type *E. faecalis*. Oritavancin MIC values against VanA-type *E. faecalis* were higher (16-fold) compared to susceptible strains, yet inhibiting all *E. faecalis* at ≤0.5 μg/mL, except for one isolate (MIC, 1 μg/mL). Ampicillin ($MIC_{50/90}$, ≤1/2 μg/mL; 100% susceptible), daptomycin ($MIC_{50/90}$, 1/2 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; 100% susceptible) showed coverage against vancomycin-resistant *E. faecalis*. Oritavancin was ≥2-fold more active against vancomycin-susceptible *E. faecium* (MIC_{50}, ≤0.008 μg/mL) than vancomycin-susceptible *E. faecalis* (MIC_{50}, 0.015 μg/mL). Similar oritavancin MIC results were noted against vancomycin-susceptible and VanB-type *E. faecium*, while oritavancin was 4-fold less active against VanA-type *E. faecium*. Daptomycin ($MIC_{50/90}$, 2/2 μg/mL; ≥99.8% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; ≥97.6% susceptible) were active against VanA- and VanB-type *E. faecium*. VanC strains were very susceptible to oritavancin ($MIC_{50/90}$, ≤0.008/0.015 μg/mL), ampicillin (94.4% susceptible), daptomycin (100% susceptible) and linezolid (100% susceptible).

Conclusions: Oritavancin demonstrated activity greater than comparators when tested against VRE causing BSI. Oritavancin activity was reduced against VanA-type strains compared to susceptible and VanB-type strains but inhibited all VRE at ≤1 μg/mL.

Introduction

Enterococcus spp. are part of the normal human microbial flora and the lack of a virulence factor armamentarium makes these organisms less successful pathogens when compared to other Gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pyogenes*. The majority of invasive enterococcal infections are caused by *Enterococcus faecalis*, and the remainders are mostly caused by *E. faecium*. During the past decades, *Enterococcus* species have emerged as important nosocomial pathogens, with a greater concern directed towards *E. faecium*, which is often resistant to commonly used antimicrobial agents, such as penicillins, aminoglycosides and glycopeptides.

Introduction-continued

E. faecalis and *E. faecium* may acquire various types of glycopeptides resistance determinants via *van*-associated genetic elements (*vanA/B/D/E/G/L*), of which *vanA* and *vanB* are the most prevalent in clinically relevant species. Although vancomycin-resistant enterococci (VRE) are seldom encountered in serious clinical infections, they occasionally cause invasive infections, notably in immunocompromised hosts. Some of these infections, particularly those caused by *E. faecium*, are often difficult to treat since only few antimicrobial treatment options are available.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide in late stage of clinical development for treatment of severe infections caused by numerous Gram-positive organisms, including multidrug-resistant (MDR) enterococci, staphylococci and streptococci. This study describes the activity of oritavancin and comparator agents tested against enterococcal clinical isolates causing bloodstream infections in United States (USA) and European hospitals.

Methods

Bacterial strain collection. A total of 2,407 enterococci (1,432 *E. faecalis*; 939 *E. faecium*, 26 *E. gallinarum* and 10 *E. casseliflavus*) were collected from 29 medical institutions in the USA and 29 centers among 14 European countries, including Turkey and Israel. Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) following established protocols as part of the SENTRY Antimicrobial Surveillance Program. Bacterial species identification was performed by using an automated system (Vitek®2; bioMérieux, Hazelwood, Missouri, USA) or conventional biochemical algorithms, as required.

Antimicrobial susceptibility testing. Isolates were tested for susceptibility by the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) recommendations. Susceptibility testing was performed by using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains: *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213. Interpretation of comparator (nine) MIC results was in accordance with published CLSI (M100-S20-U) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2010) criteria. Enterococcal isolates were clustered according to glycopeptide resistance. The VanA phenotype was characterized by non-susceptibility to vancomycin and teicoplanin, while isolates with a VanB phenotype were those non-susceptible to vancomycin, but susceptible to teicoplanin, according to CLSI criteria. In addition, strains harboring the intrinsic *vanC* gene (*E. gallinarum* and *E. casseliflavus*) were grouped based on species identification.

Results-1

- Oritavancin tested against vancomycin-susceptible *E. faecium* (MIC_{50}, ≤0.008 μg/mL) was ≥two-fold more active than against vancomycin-susceptible *E. faecalis* (MIC_{50}, 0.015 μg/mL; Table 1). In addition, the oritavancin $MIC_{50/90}$ values when tested against VRE of the VanB-type were comparable to those obtained against their susceptible counterpart strains.
- Although vancomycin-susceptible *E. faecalis* displayed oritavancin $MIC_{50/90}$ results 16-fold lower than VanA-type strains, all these VRE were inhibited by an oritavancin MIC of ≤0.5 μg/mL, except for one strain (MIC, 1 μg/mL; Table 1). Similarly, VanA-type *E. faecium* also exhibited higher oritavancin MIC results when compared to vancomycin-susceptible isolates, but oritavancin still demonstrated low $MIC_{50/90}$ results (0.03/0.12 μg/mL).
- Glycopeptides (≥99.5% susceptible), daptomycin (≥99.3% susceptible) and linezolid (≥99.8% susceptible) were active against vancomycin-susceptible *E. faecalis* and *E. faecium*. In addition, ampicillin (100.0% susceptible by CLSI) showed complete coverage against vancomycin-susceptible *E. faecalis* as well (Table 2).
- The MIC_{90} result obtained for oritavancin ($MIC_{50/90}$, 0.25/0.5 μg/mL) when tested against VanA-type *E. faecalis* was four-fold lower than those of ampicillin ($MIC_{50/90}$, ≤1/2 μg/mL; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible; Table 2).
- Only daptomycin ($MIC_{50/90}$, 2/2 μg/mL; 99.8% susceptible), linezolid ($MIC_{50/90}$, 1/2 μg/mL; 97.6% susceptible by CLSI) and quinupristin/dalfopristin ($MIC_{50/90}$, 1/1 μg/mL; 96.0% susceptible) had acceptable coverage (≥90.0% susceptible) against VanA-type *E. faecium*. Furthermore, oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL) was 32- to 64-fold more active than the comparator drugs described above (Table 2).
- Oritavancin ($MIC_{50/90}$, 0.015/0.03 μg/mL) was generally 64-fold more active than ampicillin ($MIC_{50/90}$, ≤1/2 μg/mL; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible) tested against VanB-type *E. faecalis* (Table 2). Moreover, oritavancin ($MIC_{50/90}$, ≤0.008/≤0.008 μg/mL) was at least 128-fold more active than daptomycin ($MIC_{50/90}$, 2/2 μg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; 100.0% susceptible) against VanB-type *E. faecium.*
- The *vanC*-carrying enterococcal isolates were very susceptible to oritavancin ($MIC_{50/90}$, ≤0.008/0.015 μg/mL) and comparator agents tested, such as ampicillin ($MIC_{50/90}$, ≤1/4 μg/mL), teicoplanin ($MIC_{50/90}$, ≤2/≤2 μg/mL), daptomycin ($MIC_{50/90}$, 1/2 μg/mL) and linezolid ($MIC_{50/90}$, 1/2 μg/mL; Table 2).

Results-2

Table 1. MIC frequency distribution for oritavancin tested against enterococcal clinical isolates from USA and European hospitals (2008 – 2009).

	MIC (μg/mL)		Number (cumulative %) inhibited at MIC (μg/mL)						
Resistance pattern[a] (no. tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
E. faecalis VAN-S[a] (1,378)	0.015	0.03	446(32.4)	**608(76.5)**[b]	272(96.2)	48(99.7)	3(99.9)	1(100.0)	–
E. faecalis VanA (37)	0.25	0.5	1(2.7)	2(8.1)	1(10.8)	2(16.2)	2(21.6)	**18(70.3)**	10(97.3)
E. faecalis VanB (17)	0.015	0.03	6(35.3)	**9(88.2)**	1(94.1)	1(100.0)	–	–	–
E. faecium VAN-S[a] (412)	≤0.008	≤0.008	**403(97.8)**	7(99.5)	2(100.0)	–	–	–	–
E. faecium VanA (505)	0.03	0.12	58(11.5)	54(22.2)	**172(56.2)**	167(89.3)	48(98.8)	4(99.6)	2(100.0)
E. faecium VanB (22)	≤0.008	≤0.008	**21(95.5)**	1(100.0)	–	–	–	–	–
VanC (36)[c]	≤0.008	0.015	**31(86.1)**	4(97.2)	1(100.0)	–	–	–	–

a. VAN-S = vancomycin-susceptible.
b. Modal MIC values are in bold.
c. Includes *E. casseliflavus* (10 isolates) and *E. gallinarum* (26 isolates).

Table 2. Antimicrobial activity of oritavancin and comparator antimicrobial agents tested against enterococcal clinical isolates from USA and European hospitals (2008 – 2009).

Resistance (phenotype/genotype) Organism (no. tested)/ Antimicrobial agent	MIC (μg/mL)			Susceptibility category[a] % Susceptible / % Resistant	
	50%	90%	Range	CLSI	EUCAST
Vancomycin-susceptible					
E. faecalis (1,378)					
Oritavancin	0.015	0.03	≤0.008 – 0.25	–[b] / –	– / –
Ampicillin	≤1	2	≤1 – 8	100.0 / 0.0	99.8 / 0.0
Vancomycin	1	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	99.9 / 0.1
Erythromycin	>2	>2	≤0.25 – >2	7.2 / 61.3	– / –
Tetracycline	>8	>8	≤2 – >8	24.7 / 75.0	– / –
Levofloxacin	1	>4	≤0.5 – >4	67.6 / 31.9	– / –
Daptomycin	1	2	0.12 – 4	100.0 / –	– / –
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	0.9 / 95.6	0.9 / 95.6
E. faecium (412)					
Oritavancin	≤0.008	≤0.008	≤0.008 – 0.03	– / –	– / –
Ampicillin	>16	>16	≤1 – >16	14.1 / 85.9	13.8 / 85.9
Vancomycin	1	1	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	99.5 / 0.5
Erythromycin	>2	>2	≤0.25 – >2	7.3 / 85.2	– / –
Tetracycline	≤2	>8	≤2 – >8	60.7 / 38.8	– / –
Levofloxacin	>4	>4	≤0.5 – >4	16.3 / 77.7	– / –
Daptomycin	2	4	0.12 – >8	99.3 / –	– / –
Linezolid	1	2	1 – >8	99.8 / 0.2	99.8 / 0.2
Quinupristin/dalfopristin	1	>2	≤0.25 – >2	71.1 / 19.2	71.1 / 19.2
Vancomycin-resistant (VanA)					
E. faecalis (37)					
Oritavancin	0.25	0.5	≤0.008 – 1	– / –	– / –
Ampicillin	≤1	2	≤1 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>16	>16	16 – >16	0.0 / 97.3	0.0 / 100.0
Erythromycin	>2	>2	>2	0.0 / 100.0	– / –
Tetracycline	>8	>8	≤2 – >8	8.1 / 91.9	– / –
Levofloxacin	>4	>4	1 – >4	5.4 / 94.6	– / –
Daptomycin	1	2	≤0.06 – 2	100.0 / –	– / –
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	2 – >2	0.0 / 97.3	0.0 / 97.3
E. faecium (505)					
Oritavancin	0.03	0.12	≤0.008 – 0.5	– / –	– / –
Ampicillin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Vancomycin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Teicoplanin	>16	>16	16 – >16	0.0 / 95.4	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	2.4 / 95.6	– / –
Tetracycline	≤2	>8	≤2 – >8	51.3 / 47.7	– / –
Levofloxacin	>4	>4	2 – >4	0.2 / 99.6	– / –
Daptomycin	2	2	≤0.06 – 8	99.8 / –	– / –
Linezolid	1	2	0.5 – >8	97.6 / 2.2	97.8 / 2.2
Quinupristin/dalfopristin	1	1	≤0.25 – >2	96.0 / 1.8	96.0 / 1.8
Resistance (phenotype/genotype) Organism (no. tested)/ Antimicrobial agent	MIC (μg/mL)			Susceptibility category[a] % Susceptible / % Resistant	
	50%	90%	Range	CLSI	EUCAST
Vancomycin-resistant (VanB)					
E. faecalis (17)					
Oritavancin	0.015	0.03	≤0.008 – 0.06	– / –	– / –
Ampicillin	≤1	2	≤1 – 4	100.0 / 0.0	100.0 / 0.0
Vancomycin	>16	>16	8 – >16	0.0 / 88.2	0.0 / 100.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	0.5 – >2	5.9 / 88.2	– / –
Tetracycline	>8	>8	≤2 – >8	29.4 / 70.6	– / –
Levofloxacin	>4	>4	>4	0.0 / 100.0	– / –
Daptomycin	1	2	≤0.06 – 2	100.0 / –	– / –
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	>2	>2	>2	0.0 / 100.0	0.0 / 100.0
E. faecium (11)					
Oritavancin	≤0.008	≤0.008	≤0.008	– / –	– / –
Ampicillin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Vancomycin	>16	>16	8 – >16	0.0 / 72.7	0.0 / 100.0
Teicoplanin	≤2	4	≤2 – 8	100.0 / 0.0	81.8 / 18.2
Erythromycin	>2	>2	2 – >2	0.0 / 90.9	– / –
Tetracycline	≤2	>8	≤2 – >8	54.5 / 45.5	– / –
Levofloxacin	>4	>4	>4	0.0 / 100.0	– / –
Daptomycin	2	2	0.5 – 4	100.0 / –	– / –
Linezolid	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	0.5	>2	0.5 – >2	81.8 / 18.2	81.8 / 18.2
Vancomycin-resistant (VanC)[c]					
Oritavancin	≤0.008	0.015	≤0.008 – 0.03	– / –	– / –
Ampicillin	≤1	4	≤1 – >16	94.4 / 5.6	94.4 / 5.6
Vancomycin	4	8	0.5 – >16	77.8 / 2.8	77.8 / 22.2
Teicoplanin	≤2	≤2	≤2 – >16	97.2 / 2.8	97.2 / 2.8
Erythromycin	1	>2	≤0.25 – >2	44.4 / 30.6	– / –
Tetracycline	≤2	>8	≤2 – >8	63.9 / 36.1	– / –
Levofloxacin	2	>4	≤0.5 – >4	80.6 / 11.1	– / –
Daptomycin	1	2	≤0.06 – 4	100.0 / –	– / –
Linezolid	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	2	>2	0.5 – >2	2.8 / 50.0	2.8 / 50.0

MIC, minimum inhibitory concentration.
a. Criteria for susceptibility as published by the CLSI (M100-S20-U; Update June 2010) and EUCAST (2010).
b. –, no breakpoint available.
c. Includes *E. casseliflavus* (10 isolates) and *E. gallinarum* (26 isolates).

Conclusions

- Oritavancin demonstrated pronounced activity when tested against this collection of *E. faecalis* and *E. faecium* clinical isolates, demonstrating greater potency (four- to 128-fold) than the active comparator antimicrobial agents, particularly when tested against VRE.
- Although the MIC values for oritavancin were higher when tested against VanA-type enterococci compared to susceptible isolates, this agent inhibited all VRE at achievable clinical concentrations (≤1 μg/mL).
- These *in vitro* data observed from the analysis of oritavancin activity tested against contemporary enterococcal clinical isolates may reflect important therapeutic advantages, where options are relatively limited.

References

Clinical and Laboratory Standards Institute (2009). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically–Eighth Edition: Approved Standard M07-A8*. Wayne, PA, USA.

Clinical and Laboratory Standards Institute (2010). *Performance standards for antimicrobial susceptibility testing: Twentieth Information Supplement M100-S20-U (June 2010 update)*. Wayne, PA, USA.

European Committee on Antimicrobial Susceptibility Testing (2010). Breakpoint tables for interpretation of MICs and zone diameters. Version 1.1, April 2010. Available at: http://www.eucast.org/clinical_breakpoints.

Hegstad K, Mikalsen T, Coque TM, Werner G, Sundsfjord A (2010). Mobile genetic elements and their contribution to the emergence of antimicrobial resistant *Enterococcus faecalis* and *Enterococcus faecium*. *Clin Microbiol Infect* 16: 541-554.

McBride SJ, Upton A, Roberts SA (2010). Clinical characteristics and outcomes of patients with vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium* bacteraemia--a five-year retrospective review. *Eur J Clin Microbiol Infect Dis* 29: 107-114.

Sava IG, Heikens E, Huebner J (2010). Pathogenesis and immunity in enterococcal infections. *Clin Microbiol Infect* 16: 533-540.