

Unmet Needs and Prospects for Oritavancin in the Management of Vancomycin-Resistant Enterococcal Infections

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The treatment of infections caused by vancomycin-resistant enterococci (VRE) has become an important clinical challenge and compromises the care of critically ill patients. A striking increase in the frequency of nosocomial isolation of multidrug-resistant *Enterococcus faecium* has dramatically reduced the therapeutic alternatives because the majority of *E. faecium* isolates are resistant to ampicillin and vancomycin. Only 2 agents have US Food and Drug Administration approval for the treatment of VRE (*E. faecium*) infections, namely, linezolid and quinupristin/dalfopristin (Q/D). However, the use of these compounds in severe VRE infections is hampered by the lack of in vivo bactericidal activity, reports of therapeutic failures with monotherapy, a requirement for central venous access for administration (Q/D), and adverse-effect profile. The lipopeptide antimicrobial daptomycin has in vitro bactericidal activity against VRE; however, clinical use of this compound for VRE has not been well studied, and the reports of resistance emerging during therapy at the approved doses are worrisome. Tigecycline has in vitro bacteriostatic activity against VRE, but its clinical use for serious enterococcal infections is unclear due to low serum levels and static effect. Thus, current reliable therapies for VRE appear to be limited, and clinical data that use the above compounds are certainly scant. Oritavancin is an investigational semisynthetic glycopeptide with potent in vitro activity against VRE (both VanA and VanB phenotypes). Although review of the available preclinical data indicates that this compound used as a single agent is likely to have important limitations for the treatment of a severe VRE infection (ie, endocarditis), combination of oritavancin with other agents such as aminoglycosides may offer promise and deserves further investigation, as does use of oritavancin for less serious infections as monotherapy for vancomycin-susceptible and multidrug-resistant enterococci.

In September 1899, a 37-year-old German man with a history of rheumatic fever (11 years prior to his hospital visit) was admitted to The Johns Hopkins University Hospital complaining of fever for 2 months accompanied by severe frontal headaches, weakness, and an unintentional 26-pound weight loss. Physical

examination revealed a diastolic murmur, and a Gram-positive organism was recovered from his blood cultures, which was designated *Micrococcus zymogenes* (known today as *Enterococcus faecalis*); the patient died from his infective endocarditis, with complications of cardiac failure, 18 days after admission [1]. More than 100 years later, a 70-year-old American in San Francisco, California, was diagnosed with vancomycin-resistant *Enterococcus faecium* aortic valve infective endocarditis; the patient remained in the hospital for 35 days and died of the infection despite the administration of various antimicrobial agents with activity against vancomycin-resistant enterococci (VRE) (including linezolid, daptomycin, daptomycin plus gentamicin/doxycycline, and

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quinupristin/dalfopristin). The patient remained bacteremic through the entire hospitalization, and clinicians were ultimately unable to sterilize the patient's blood [2].

The above-cited cases illustrate the dramatic fact that the development of multidrug resistance in enterococci poses enormous challenges for clinicians treating patients in the 21st century and “resets the clock” back to the times when antimicrobial agents were not available to treat these infections. Although several agents have been approved by the US Food and Drug Administration (FDA) over the past 10–15 years for the treatment of infections caused by resistant Gram-positive organisms (ie, linezolid, quinupristin/dalfopristin [Q/D], tigecycline, daptomycin, telavancin, and ceftaroline), the majority were developed for the treatment of methicillin-resistant *Staphylococcus aureus* infections; only linezolid and Q/D are FDA approved for VRE infections (with important limitations; see below). Thus, there is an important vacuum in the therapeutic arsenal against VRE infections, and new agents are needed to fill this gap in infectious disease clinical practice. Here, we will discuss this need and whether oritavancin, a novel glycopeptide, has the potential to fill this gap in treatment.

TREATING MULTIDRUG-RESISTANT ENTEROCOCCI: RUNNING OUT OF OPTIONS

Enterococci are best known today as multidrug-resistant, healthcare-associated, opportunistic causes of infections and are ranked as the second most common bacteria recovered from nosocomial infections in the United States after staphylococci [3]. The SENTRY Antimicrobial Surveillance Program has monitored the susceptibility patterns of enterococci from bacteremias since 1997 (the largest collection of bloodstream enterococcal isolates in the United States). In the last 10 years, the prevalence of vancomycin resistance among 7424 bloodstream enterococcal clinical isolates was 27.8%. However, the rate of vancomycin resistance among *E. faecium* escalated from 57.1% in 2000 to 80.7% of all bloodstream *E. faecium* infections in 2010, a trend that resembles that of methicillin resistance in *S. aureus* (Table 1). The data correlate with the striking increase in the frequency of isolation of *E. faecium* in US hospitals [3]; in fact, *E. faecium* is now isolated at a rate approaching that of *E. faecalis* (1 *E. faecium* per every 1.8 *E. faecalis*; Table 1).

Rates of vancomycin resistance are much lower in *E. faecalis* (average of 4% over the 10-year period), although the prevalence of the VanA phenotype (resistance to vancomycin and teicoplanin) in *E. faecalis* increased from 42.5% to 77.4% between 2000 and 2010 (Table 1). Table 2 shows the comparative antimicrobial activity of vancomycin and other agents tested against a recent collection of *E. faecium* and *E. faecalis* bloodstream isolates recovered from US hospitals (2010 subset of isolates from Table 1). The data indicate that both ampicillin and vancomycin are compromised for the treatment of *E. faecium* infections in

Table 1. Trends in Vancomycin-Resistant Enterococcal Bacteremia Rates in the SENTRY Antimicrobial Surveillance Program Hospitals (US, 2000–2010)—Quantitating Vancomycin Resistance Patterns

Surveillance Year	Vancomycin Nonsusceptible Rate (% VanA) ^a	
	<i>E. faecium</i>	<i>E. faecalis</i>
No. tested	2614	4810
2000	57.1 (84.2)	4.0 (42.5)
2001	60.0 (88.2)	1.4 (35.7)
2002	70.7 (86.4)	2.9 (55.2)
2003	70.5 (88.5)	4.6 (34.8)
2004	68.6 (94.9)	2.6 (50.0)
2005	70.5 (95.6)	4.3 (51.2)
2006	69.7 (99.0)	4.8 (87.5)
2007	71.6 (97.6)	3.9 (89.7)
2008	75.3 (97.9)	6.5 (75.4)
2009	76.3 (97.6)	3.2 (65.6)
2010	80.7 (97.0)	5.3 (77.4)
All years	71.7 (94.8)	4.0 (65.0)

Abbreviations: CLSI, Clinical Laboratory and Standards Institute; *E. faecalis*, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*; MIC, minimum inhibitory concentration.

^a MIC values interpreted by CLSI M100-S21 breakpoint criteria [20]. The VanA phenotype was characterized by nonsusceptibility to vancomycin (MIC, ≥ 8 $\mu\text{g/mL}$) and teicoplanin (MIC, ≥ 16 $\mu\text{g/mL}$), according to CLSI criteria [20]. A total of 401 other *Enterococcus* species were tested (data not shown) for a total of 7823 US enterococcemias.

the United States with resistance rates of 94.6% and 80.2%, respectively. Conversely, all *E. faecalis* isolates tested were susceptible to ampicillin, and only a small percentage exhibited resistance to vancomycin ($\sim 5\%$).

It has been recognized since the early 1950s that the treatment of enterococcal infective endocarditis differs substantially from that of streptococcal and staphylococcal endocarditis. Indeed, endovascular infection is the most serious presentation of enterococcal disease and is one in which antimicrobial therapy is essential for successful outcomes. In various series, dating from the 1920s, enterococci are responsible for 5%–20% of the cases of infective endocarditis [5] and today are the second most common cause of hospital-associated infective endocarditis [6, 7]. Currently, enterococci are also important causes of catheter-associated bloodstream infections and urinary tract infections and are frequently isolated from skin and skin structure infections in the United States [3].

The challenges in the treatment of severe enterococcal infections were illustrated by the observation that, although monotherapy with penicillin was appropriate to treat streptococcal infective endocarditis, the same strategy yielded poor outcomes in the treatment of enterococcal infective endocarditis. It was later recognized that the combination of penicillin and an aminoglycoside was needed for optimal cure rates [8] but added

Table 2. Antimicrobial Activity of 10 Selected Agents Tested Against 884 *E. faecium* and *E. faecalis* Bloodstream Infection Isolates From Patients in US Medical Centers (2010)

Species (No. Tested)	Antimicrobial Agent ^a	MIC (μg/mL)			CLSI Category (%) ^a	
		50%	90%	Range	Susceptible	Resistant
<i>Enterococcus faecium</i> (368)	Ampicillin	>8	>8	≤1 to >8	5.4	94.6
	Vancomycin	>16	>16	0.25 to >16	19.3	80.2
	Teicoplanin	>8	>8	≤1 to >8	21.7	ND
	Oritavancin	0.03	0.06	≤0.008–0.5
	Daptomycin	2	2	0.12–8	99.7	...
	Erythromycin	>4	>4	≤0.25 to >4	3.3	83.2
	Levofloxacin	>4	>4	≤0.5 to >4	4.6	94.0
	Linezolid	1	1	0.5–8	98.6	0.5
	Q/D	≤0.5	≤0.5	≤0.5–4	94.3	0.8
	Tetracycline	>8	>8	≤0.25 to >8	28.3	71.5
<i>Enterococcus faecalis</i> (516)	Ampicillin	≤1	2	≤1–4	100.0	0.0
	Vancomycin	1	2	0.5 to >16	94.8	5.0
	Teicoplanin	≤1	≤1	≤1 to >8	95.9	ND
	Oritavancin	0.015	0.06	≤0.008–1
	Daptomycin	1	1	0.12–4	100.0	...
	Erythromycin	>4	>4	≤0.25 to >4	9.5	57.4
	Levofloxacin	1	>4	≤0.5 to >4	64.3	35.1
	Linezolid	1	1	0.25 to >8	99.8	0.2
	Q/D	>4	>4	≤0.5 to >4	0.8	95.7
	Tetracycline	>8	>8	≤0.25 to >8	23.1	76.7

Abbreviations: CLSI, Clinical Laboratory and Standards Institute; MIC, minimum inhibitory concentration; ND, not determined (no criteria have been established); Q/D, quinupristin/dalfopristin.

^a MIC results for antimicrobial agents were obtained by using validated dry-form broth microdilution panels (TREK Diagnostics; Cleveland, Ohio). Accuracy of the MIC values was assured by concurrent testing of CLSI-recommended quality control strains: *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213 [20]. MIC quality control results for antimicrobial agents tested were within published ranges found in the CLSI M100-S21 document [20]. Interpretation of MIC values was in accordance with published CLSI criteria, when available [20].

toxicities inherent to the aminoglycoside component of the regimen [9]. The synergism between a cell wall–active agent (eg, penicillin, ampicillin, or vancomycin) and an aminoglycoside (eg, gentamicin and streptomycin) was clearly demonstrated in vitro, and this regimen became the standard of care for severe enterococcal infections [10]. However, emergence of high-level resistance to all aminoglycosides was recognized in the early 1980s [11] and, by the mid-1990s, started to rise worldwide, precluding the ability of these compounds to achieve synergistic bactericidal therapy against some isolates. The combination of ampicillin and ceftriaxone also appears to be synergistic and has been used in the treatment of isolates exhibiting high-level resistance to gentamicin and streptomycin [12].

Among the cell wall synthesis inhibitors, the aminopenicillins (ampicillin, amoxicillin) are the most active antienterococcal compounds. However, increased rates of resistance to ampicillin have become a major problem in the treatment of enterococcal infections. Ampicillin resistance in enterococci has distinct patterns in *E. faecalis* versus *E. faecium*, the 2 most common species isolated from enterococcal infections (Tables 1 and 2). Ampicillin resistance in *E. faecalis* is uncommon; the mechanism

is largely unknown, although β-lactamase production has been described on rare occasions. On the other hand, the majority of contemporary *E. faecium* isolates are highly resistant to ampicillin (minimum inhibitory concentration [MIC], >64 μg/mL), reflecting the low affinity for the β-lactam of penicillin-binding protein 5 (PBP5), a cell wall synthesis enzyme of *E. faecium* whose amino acid sequence differs from that of ampicillin-susceptible *E. faecium*. PBP5 may also be overexpressed in resistant isolates and can assume the synthesis of the cell wall in the presence of penicillins, which inhibit the other cell wall synthesis enzymes [13]. The fact that ampicillin is no longer useful for the treatment of *E. faecium* infections (Table 2) appears to be a relatively recent phenomenon. Indeed, a few decades ago, *E. faecium* infections were rare and due to ampicillin-susceptible strains as observed in community fecal isolates. In fact, *E. faecium* preparations are still sold “over the counter” as probiotics for humans and animals and for the treatment of diarrhea (a “tame” *E. faecium*). However, in the last few decades, *E. faecium* has managed to rise as an important nosocomial pathogen. Population genetics studies of this microorganism have demonstrated that the “untaming” of *E. faecium* is likely due to the presence in certain genetic lineages

with greater virulence, resistances, and/or colonization determinants; thus, these lineages have more propensity to cause disease and disseminate in the hospital environment [14]. Indeed, it is within these lineages of ampicillin-resistant *E. faecium* in US hospitals that the genes responsible for vancomycin resistance have disseminated.

Among the newer agents with activity against ampicillin-resistant and vancomycin-resistant enterococci, linezolid and Q/D have FDA approvals for VRE infections. Linezolid is bacteriostatic, and its use in severe infections caused by VRE (such as infective endocarditis and other endovascular infections) is limited by the frequent occurrence of clinical failures and recurrences [15]. Moreover, the toxicity profile of linezolid limits its use for infections that require prolonged therapy (eg, infective endocarditis, bone infections). Q/D was the first compound approved by the FDA for the treatment of VRE (*E. faecium*) infections. However, Q/D is now infrequently used in clinical practice due to its metabolic interactions, adverse-effect profile, need for central vein administration, and issues with efficacy, and because it is not active against *E. faecalis* [15, 16].

Apart from linezolid and Q/D, 2 other agents are available with in vitro activity against VRE (tigecycline and daptomycin), but neither has achieved regulatory approval for treating infections caused by VRE. Tigecycline is bacteriostatic against enterococci and the off-label use of tigecycline as monotherapy in severe bloodstream infections has been discouraged due to the lack of a bactericidal activity against enterococci and low blood levels achieved at standard doses [17]. Similarly, the use of daptomycin against VRE has been problematic due to the emergence of resistance during therapy [4, 18, 19]. Moreover, the Clinical Laboratory and Standards Institute breakpoint [20] for enterococci is 4-fold higher than for *S. aureus* (≤ 4 vs ≤ 1 $\mu\text{g/mL}$, respectively), which has led some to suggest the use of higher doses of daptomycin (8–12 mg/kg for the treatment of VRE infections, instead of the approved dose of 4–6 mg/kg for other organisms), although clinical data to support this suggestion are still lacking. Additionally, although the new cephalosporins, such as ceftaroline and ceftobiprole, have activity against some *E. faecalis*, they lack useful activity against most *E. faecium*. Therefore, clinicians are often left with no reliable options for the treatment of VRE infections.

RATIONALE FOR THE POTENTIAL USE OF ORITAVANCIN AGAINST VRE

Mechanism of Action

Oritavancin is a semisynthetic derivative of vancomycin characterized by an epi-vancosamine and *p*-chlorophenylbenzyl substituents [21]. Studies using solid-state nuclear magnetic resonance to detect alterations in peptidoglycan precursors and

cell wall structure suggest that vancomycin and oritavancin have different modes of action, which may explain the increased in vitro activity of the latter against VRE. Oritavancin appears to adopt a unique conformation when bound to peptidoglycan precursors with a primary binding site similar to that of vancomycin (D-alanine-D-alanine [D-Ala]) and a secondary site formed by the triangulation of a D-aspartate (or asparagine) bridge, an L-lysine residue, and a penultimate D-Ala of peptidoglycan precursors [21]. Thus, unlike vancomycin, which has marked reduced affinity to D-lactate-ending peptidoglycan precursors, oritavancin primarily inhibits the transpeptidase reaction of vancomycin-resistant *E. faecium* by sterically interfering with the ability of the D-aspartate of 1 peptidoglycan stem to form a cross-link with the penultimate D-Ala of an adjacent stem [21]. Similarly, oritavancin is strongly dimerized and can anchor to the cytoplasmic membrane by its alkyl side chain. Interactions derived from dimerization and membrane anchoring may contribute to the higher binding to D-Ala or D-lactate-ending precursors [22]. Additionally, it has been shown that, unlike vancomycin, oritavancin is capable of disrupting the cell membrane of VRE causing increased membrane depolarization, which leads to bacterial cell death. This cell membrane effect appears to be mediated by the 4'-chlorobiphenylmethyl side chain [23].

In Vitro Studies

Several studies have shown that oritavancin has good in vitro activity against enterococci that exhibit both VanA and VanB phenotypes (high-level resistance to glycopeptides), although the MIC results for VRE are higher (~ 4 - to 8-fold) than those for vancomycin-susceptible enterococci (VSE). Moreover, the MIC method may vary among studies, because it was identified only in the past few years that the addition of the nonionic emulsifier polysorbate-80 was required for accurate determination of oritavancin MIC values [24].

The SENTRY program found that among 884 clinical isolates of *E. faecalis* and *E. faecium* recovered from bloodstream infections (2010), the oritavancin MIC range was between <0.008 and 1 $\mu\text{g/mL}$, MIC₉₀ 0.06 $\mu\text{g/mL}$ (Table 2). Oritavancin has been shown to exhibit in vitro bactericidal activity for both VRE and VSE in time-kill experiments; however, an increased concentration of oritavancin relative to MIC was required for bactericidal activity in VRE [25]. In a subsequent study, oritavancin was bactericidal at a concentration of 8 and 30 $\mu\text{g/mL}$ against *E. faecalis* exhibiting the VanB and VanA phenotype, respectively [26]. The bactericidal activity against the VanA-type *E. faecalis* was markedly reduced in the presence of 90% serum, with a 100-fold reduction in killing at 24 hours compared with broth [26, 27]. Oritavancin showed concentration-dependent killing at 10 hours against VRE (both *E. faecalis* and *E. faecium* harboring the *vanA* and *vanB* gene clusters) at the predicted free peak concentration (fC_{max}) derived from administering a human dose

of 800 mg (16 µg/mL). Of note, the compound was bactericidal at a lower concentration 4 µg/mL (which represents the fC_{max} of a human 200-mg dose) against VSE [28]. The combination of oritavancin and gentamicin (4 µg/mL) has been shown to have in vitro synergistic bactericidal activity against VRE (both VanA and VanB phenotypes) [29], although a concentration of oritavancin higher than that used for VSE was required to achieve the synergistic effect (8 vs 2 µg/mL, respectively).

The protein binding of oritavancin in rat serum has been found to be high, which suggests a reduction of bactericidal activity in the presence of serum proteins [26]. Similarly, oritavancin is approximately 85% protein bound in human serum [30]. When the effect of human serum albumin on oritavancin in vitro activity against enterococci was evaluated by MIC and time-kill methods [27], oritavancin MICs increased 2- to 8-fold in the presence of 4% human serum albumin, which suggests that the presence of physiological concentrations of albumin are likely to affect the in vivo antimicrobial activity [27].

In Vivo Studies

The in vivo activity of oritavancin was tested in a rabbit model of endocarditis (40 mg/kg initial dose followed by 20 mg/kg twice daily intramuscularly for 5 days) using *E. faecalis* JH2-2 and its transconjugants harboring either the *vanA* or *vanB* gene clusters [26]. Oritavancin was the only glycopeptide that showed a significant decrease in colony-forming unit (CFU) from vegetations (reduction of 2.1–2.8 log₁₀ CFU/g vegetation) when used against JH2-2 exhibiting the VanA or VanB phenotypes compared with controls, although it did not sterilize the vegetations. Using radioactive-labeled oritavancin, it was found that the drug was distributed without a gradient of concentration between the core and the periphery of rabbit vegetations [26], although the diffusion of the drug was somewhat heterogeneous (a 1:8 ratio between the highest and the lowest concentrations) [26]. Using the same experimental model of rabbit endocarditis but a different oritavancin dosing regimen (20 mg/kg intravenously via the ear vein, daily), Lefort et al found that oritavancin monotherapy did not significantly decrease the CFU/g of vegetations compared with controls [29], although pharmacokinetic and pharmacodynamic parameters indicated that the dosing scheme may not have been optimal for the therapeutic assay. Mutants with decreased susceptibility to oritavancin were selected in vivo from a VanA–*E. faecalis* strain at frequencies of 10^{−7}; the mutants were stable after 3 subcultures on drug-free agar and exhibited MIC values that were 4- to 8-fold higher than the parent strain [29]. It is not known whether VanA–*E. faecium*, which tends to have lower MICs than VanA–*E. faecalis* [31], will also show the same phenomenon. Additionally, it is important to note that selection of in vivo mutants is not exclusive to oritavancin; for example, VRE mutants with decreased susceptibility to daptomycin have also been isolated in an in vitro model of simulated endocarditis

vegetations [32]. Of interest, the addition of gentamicin to the same oritavancin dose scheme in rabbit endocarditis resulted in a significant decrease in bacterial counts from vegetations for the VanA–*E. faecalis* strain and prevented the emergence of mutants with decreased susceptibility to oritavancin [29].

Thus, we conclude from the available in vivo data that monotherapy with oritavancin in experimental rabbit endocarditis caused by VRE, although able to reduce CFU at a 1-dose regimen, may have limitations at other doses (as is true for agents such as daptomycin at approved doses). However, combination with an aminoglycoside (if the organism lacks high-level resistance to aminoglycosides) or possibly another in vitro active agent may offer better potential in the treatment of serious VRE infections.

Resistance

High-level resistance to vancomycin in enterococci and staphylococci is due to a dual mechanism that involves the replacement of D-Ala-D-Ala–ending peptidoglycan precursors for D-Ala-D-lactate–ending peptides and the concomitant destruction of the former “vancomycin-susceptible” precursors ending in D-Ala [33]. Unlike vancomycin, acquisition of the *vanA* or *vanB* gene clusters by enterococcal isolates of *E. faecalis* or *E. faecium* appears to affect only modestly the in vitro susceptibility to oritavancin, although several lines of evidence [33] suggest that increased MIC results may emerge during therapy, as was seen with in vitro–generated derivatives, due to the following mechanisms: (1) complete elimination of precursors ending in D-alanine by increased expression of the resistance genes or inactivation of the D-Ala-D-Ala host ligase, (2) expression of the *vanZ* gene (whose function is unknown), and (3) mutation in the VanS_B sensor gene of the *vanB* cluster causing cross-resistance to teicoplanin [33]. Thus, there is the possibility that enterococci, at least *E. faecalis*, carrying the *vanA* or *vanB* gene cluster might develop decreased oritavancin susceptibility during monotherapy for serious deep-seated infections such as endocarditis.

CONCLUSIONS

There is a clear need for a reliable antimicrobial therapy against VRE, and oritavancin may become an option for these infections. The potent in vitro activity of oritavancin against VRE suggests that this antibiotic may have potential for use in infections caused by these microorganisms. However, the paucity of animal models for the most recalcitrant enterococcal species (*E. faecium*) and the possible ability to select mutants with decreased susceptibility during therapy raises questions about the usefulness of oritavancin as monotherapy for successful eradication of the organisms in serious deep-seated infections. Nonetheless, the in vitro data and limited in vivo experiments suggest that oritavancin plus aminoglycosides warrants further study for the treatment of severe VRE infections. Additional in vivo data for multidrug-resistant *E. faecium*, perhaps using other compounds

as part of a combination regimen that includes oritavancin, would be of value to explore the potential for clinical use of this compound against VRE endocarditis. The role of this antibiotic for urinary tract infections, nonendocarditis bacteremia, and skin and soft tissue infections caused by VRE is also unknown at present and should be explored further.

Notes

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