Prolonged Use of Oritavancin for Vancomycin-Resistant *Enterococcus faecium* Prosthetic Valve Endocarditis

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Oritavancin is a novel lipoglycopeptide with activity against Gram-positive organisms including streptococci, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *S aureus* (VRSA), and vancomycin-resistant enterococci (VRE) [1–3]. The US Food and Drug Administration approved oritavancin as a single intravenous dose of 1200 mg for the treatment of acute bacterial skin and skin structure infections on the basis of 2 clinical trials demonstrating noninferiority compared with vancomycin [4, 5].

There are limited options for treatment of serious VRE infections. Monotherapy with daptomycin or tigecycline or linezolid may be sufficient in some cases, but combination therapy is often indicated for severe or complicated infections such as endocarditis. Several antibiotic combinations have been used in isolated case reports with some efficacy, including the following: high-dose ampicillin with an aminoglycoside [6], ampicillin with ceftriaxone or imipenem [7, 8], high-dose daptomycin with ampicillin and gentamicin [9] or with gentamicin and rifampin [10], daptomycin with tigecycline [11, 12], quinupristin-dalfopristin with high-dose ampicillin [13] or doxycycline and rifampin [14], and linezolid with tigecycline [15]. The limited efficacy, limited susceptibility, and extensive toxicities with many of these agents and combinations present barriers to effective treatment. Additional treatment options for VRE endocarditis would be valuable. Although oritavancin has been shown to have in vitro activity against some isolates of VRE, clinical data are lacking. We describe the first use of a prolonged course of oritavancin in the treatment of a serious VRE infection, prosthetic valve endocarditis.

Keywords. **endocarditis; enterococci; oritavancin; vancomycin-resistant; VRE.**

CASE REPORT

A 73-year-old male with a bioprosthetic aortic valve placed 4 years previously, renal artery stenosis with stent placement, chronic kidney disease (creatinine clearance estimated at 22 mL/min), and spinal fusion at L5-S1 with hardware placement 1 year previously, presented with several months of malaise and weight loss. Blood cultures grew *Enterococcus faecium*, which was resistant to vancomycin but susceptible to daptomycin (Table 1). Treatment with intravenous daptomycin 8 mg/kg every other day was initiated. His bacteremia initially cleared but recurred after 48 hours. Tigecycline was added, and bacteremia resolved. Magnetic resonance imaging of the spine revealed slight displacement of the spinal hardware concerning for possible hardware loosening, although there were no definite findings of infection; surgical intervention was not pursued. Transthoracic and transesophageal echocardiograms showed no evidence of valvular vegetations. The patient continued parenteral antibiotic therapy with daptomycin and tigecycline. Eight weeks after initiation of intravenous antibiotic therapy, the patient was readmitted with *Pseudomonas aeruginosa* bacteremia and central venous catheter infection. The central venous catheter was removed, tigecycline and daptomycin were discontinued, and treatment with oral linezolid was initiated, which was discontinued 2 weeks later, the patient having completed a 10-week total antibiotic course.

Approximately 5 months after his initial presentation, the patient again presented with malaise and back pain. Blood cultures again grew vancomycin-resistant enterococci (VRE) (Table 1). Treatment with daptomycin and tigecycline was initiated, and blood cultures cleared after 3 days of bacteremia. However, VRE bacteremia recurred with a stuttering course, and susceptibility testing demonstrated daptomycin resistance (Table 1). Daptomycin was discontinued, therapy with linezolid and tigecycline was initiated, and subsequent blood cultures were negative. Transesophageal echocardiography again showed no evidence of cardiac valvular vegetation. Positron emission

Table 1. Susceptibility Testing of *Enterococcus faecium* Isolates

Antibiotic	Initial Presentation	First Recurrence (5 mo Later)	Second Recurrence (8 mo Later)
Ampicillin	KBD 6 mm (R)	KBD 6 mm (R) MIC > 256 µg/mL (R)	KBD 6 mm (R) MIC 256 µg/mL (R)
Vancomycin	KBD 6 mm (R)	KBD 6 mm (R)	KBD 6 mm (R)
Gentamicin	KBD 26 mm (Syn)	KBD 26 mm (Syn)	KBD 28 mm (Syn)
Streptomycin	KBD 21 mm (Syn)	KBD 22 mm (Syn)	KBD 26 mm (Syn)
Tetracycline	KBD 6 mm (R)	KBD 6 mm (R)	KBD 6 mm (R)
Doxycycline	–	KBD 12 mm	–
Telavancin	–	Initial: MIC > 32 µg/mL Repeat: MIC 0.19 µg/mL	Initial: MIC 32 µg/mL
Linezolid	KBD 30 mm (S)	KBD 31 mm (S)	KBD 35 mm (R) MIC 0.75 µg/mL (S)
Daptomycin	MIC 4 µg/mL (S)	Initial: MIC 4 µg/mL (S) Repeat: MIC 6 µg/mL (R)	Initial: MIC 4 µg/mL (S)
Quinupristin/dalfopristin	–	MIC 1.5 µg/mL (I)	–
Tigecycline	MIC 0.25 µg/mL	Initial: MIC 0.19 µg/mL Repeat: MIC 0.25 µg/mL	MIC 0.094 µg/mL
Oritavancin	–	MIC 0.5 µg/mL	MIC 0.5 µg/mL

Abbreviations: KBD, Kirby Bauer disk diffusion test; MIC, minimal inhibitory concentration; R, resistant; S, sensitive; Syn, synergy likely.

tomography-computed tomography showed slightly increased fludeoxyglucose uptake around the spinal hardware at L5-S1. Operative exploration of the spinal hardware was undertaken, and no evidence of spinal hardware infection was discovered. The patient continued outpatient therapy with oral linezolid and intravenous tigecycline, but this treatment was poorly tolerated with anorexia, nausea, thrombocytopenia, hyperlactatemia, and altered mental status. Although blood cultures remained negative, alternative antibiotic treatment was pursued. In vitro susceptibility testing of the VRE isolate, performed by JMI Laboratories (North Liberty, IA) by broth microdilution (CLSI M7-A09), showed an oritavancin minimal inhibitory concentration (MIC) of 0.5 µg/mL. At that time, oritavancin had not yet received US Food and Drug Administration (FDA) approval, so permission was obtained from the FDA and the institutional review board to initiate compassionate use of oritavancin for treatment of recurrent VRE bacteremia.

Oritavancin was initiated at a dose of 1200 mg every other day for 3 doses, and subsequently once weekly for 6 weeks. Linezolid and tigecycline were discontinued. The patient's appetite and strength improved, nausea and altered mental status resolved, and platelet count and lactate returned to normal. He was discharged home, returning weekly for intravenous oritavancin infusions in the outpatient infusion center. Complete blood count, blood urea nitrogen, creatinine, serum electrolytes, liver function tests (LFTs), blood cultures, serum oritavancin level (Table 2), and electrocardiogram were monitored weekly while on therapy. Blood cultures remained negative while on oritavancin, and he had no reported adverse effects from his infusions. An elevated activated partial thromboplastin time was noted, which was felt to be due to oritavancin interference

with reagents in the testing kit and not clinically significant, as is currently noted in the US Prescribing Information [16]. He completed 7 weeks of treatment with oritavancin, following the 4 weeks of linezolid and tigecycline for the most recent episode of VRE bacteremia, and weekly blood cultures were negative throughout the antibiotic course.

Eight days after completion of the final dose of oritavancin, the patient was seen in follow-up and was feeling well. Blood cultures were collected and again grew VRE, with similar susceptibility test results (Table 1). He was admitted to the hospital and oritavancin was reinitiated at a dose of 1200 mg twice weekly, without additional loading doses given the proximity to the previous course and the now twice weekly dosing. The addition of gentamicin was attempted, but creatinine rose steadily with this, so gentamicin was discontinued after 4 days of treatment. Blood cultures initially cleared but subsequently were intermittently positive over the following 2 weeks. Transesophageal echocardiogram now showed worsening of aortic incompetence and mitral valve regurgitation, but without valvular vegetations. The patient underwent cardiac surgery for aortic and mitral valve replacements. Linezolid and tigecycline were restarted perioperatively. The excised prosthetic aortic valve grew VRE in culture, and the excised native mitral valve had evidence of healing endocarditis with cocci present on hematoxylin and eosin staining, although culture was negative.

Postoperatively, the patient developed worsening anorexia, nausea, and rising lactate (2.2 mmol/L). Linezolid and tigecycline were discontinued on the 10th postoperative day, and oritavancin was continued at 1200 mg twice weekly. Again his symptoms improved. Blood cultures remained negative. He continued twice weekly infusions of oritavancin for 10 weeks postoperatively. In

Table 2. Oritavancin Pharmacokinetic Data

Parameter	Values/Estimates for This Patient
Trough levels[a] – this patient	Mean (range)
Once weekly dosing	4.83 µg/mL (3.78–7.61)
Twice weekly dosing	8.57 µg/mL (6.82–12.85)
Peak levels[a] – this patient	Mean (range)
Once weekly dosing	124.19 µg/mL (114.79–133.58)
Twice weekly dosing	90.39 µg/mL (67.02–113.91)
Posttreatment drug levels[a] – this patient	
1 wk after completion of treatment	12.00 µg/mL
7 mo after completion of treatment	0.77 µg/mL
C_{max}[b]	
After 1st dose	114.79 µg/mL
Average	100.00 µg/mL
Highest	133.58 µg/mL
Population mean from literature[c]	138 µg/mL
Population max from literature[c]	319 µg/mL
AUC[b]	
0–48 h: this patient	2845 µg h/mL
0–48 h: population mean from literature[c]	1390 µg h/mL
0–48 h: population max from literature[c]	5370 µg h/mL
0–168 h: this patient	11 537 µg h/mL
T1/2 alpha[b]	
This patient	9.10 h
Population mean from literature[c]	2.29 h
Population max from literature[c]	6.97 h

Abbreviations: AUC, area under the curve; max, maximum.

[a] Levels are reported of total plasma drug. The drug is 85% protein-bound, so free drug levels would be only 15% of the reported concentrations.

[b] Formulas derived from References 16 and 17.

[c] Population values from literature quoted from Reference 18.

routine follow-up examination at 10 weeks postoperatively, he noted some anorexia and nausea, and LFTs revealed some new mild abnormalities: alanine aminotransferase 84 U/L (upper limit of normal = 50), aspartate aminotransferase 77 U/L (upper limit of normal = 50), alkaline phosphatase 333. Bilirubin was normal. In the absence of any other clear etiology for these new laboratory abnormalities, a concern for causal relationship with oritavancin was raised, and oritavancin was discontinued. Anorexia and nausea gradually improved. He did not have any other related adverse events during the oritavancin course. Liver function tests remained mildly abnormal for many months but resolved to normal at 11 months after completion of oritavancin therapy. Plasma oritavancin levels also remained detectable through 7 months after completion of oritavancin therapy. In clinical follow up, the patient has done well through 22 months after completion of oritavancin treatment. Blood cultures obtained 17 months after completion of oritavancin, in the setting of biliary disease, were negative.

DISCUSSION

The options for treatment of resistant Gram-positive infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE have significantly improved over the years with the advent of the oxazolidinone linezolid, the glycylcycline tigecyline, and the lipopeptide daptomycin. Nonetheless, resistance to all of these agents is well described, and intolerance or toxicities may limit their use. Oritavancin was initially developed because of its activity against both MRSA and VRE, but there has been no clinical data to support its use in VRE infections to date. This case demonstrates the tolerability of oritavancin at a high dose over a prolonged treatment course, and it provides preliminary evidence of clinical efficacy.

In this case, most other antibiotic options were not viable. The *E faecium* isolate had ampicillin MIC > 256 µg/mL, making β-lactams unlikely to be effective, even in combination therapy. Daptomycin therapy was unlikely to be effective given the rising MIC; recent data suggest that even VRE isolates with an MIC of 4 µg/mL may be difficult to treat effectively with daptomycin [17, 18]. The MIC for quinupristin-dalfopristin was intermediate. The patient was unable to tolerate linezolid or tigecycline due to severe side effects. Nephrotoxicity developed quickly with gentamicin therapy and was especially concerning given his underlying chronic kidney disease. Oritavancin presented a unique opportunity for this patient as a drug that might be efficacious and also expected to be well tolerated. The once, or later twice, weekly infusions via peripheral intravenous catheter were also favorable compared with the daily infusions by central venous catheter, which had been complicated by catheter-associated bloodstream infection earlier in his course.

In this case, the dosing regimen of oritavancin was determined by balancing safety with the goal of frontloading oritavancin exposure for the highest possible levels to treat a severe infection. Because oritavancin exerts concentration-dependent bactericidal activity and a long post-antibiotic effect [19, 20], the loading period over the first week was designed to impart the highest exposure safely over the initial portion of treatment. Although data suggests that the optimal MIC threshold for *E faecium* susceptibility to oritavancin is 0.25 µg/mL [1], the pharmacy team determined that at the loading dose schedule would maintain oritavancin plasma levels above 6–10 mL (total drug; 0.9–1.5 mg/L as free drug assuming 85% plasma protein binding) for the first 7 days of dosing, yielding early bacterial killing given the oritavancin MIC of 0.5 µg/mL for the VRE isolate in this case. Oritavancin is not renally cleared, nor is it associated with nephrotoxicity, so the dose was not adjusted for the patient's chronic kidney disease. A once-weekly dose frequency during the sustained dosing

phase was anticipated to provide lasting coverage against Gram-positive pathogens during the entire dosing interval. Oritavancin exhibits a long post-antibiotic effect with bacterial inhibition even after plasma concentration has fallen below MIC. When bacteremia recurred shortly after completion of the first course of oritavancin, the dose was increased to twice weekly for the subsequent course with the hope of more effective bacterial killing at higher concentration and hope for sustained response. However, with both the once-weekly and twice-weekly dosing regimens, the trough levels of oritavancin remained low prior to each dose, which was reassuring for drug safety. In reviewing the available peak and trough levels, we were able to calculate some pharmacokinetic parameters of oritavancin as observed in this case [21, 22] (Table 2), which were similar to those reported in the literature from prior clinical trials with oritavancin [23]. Oritavancin is distributed into the tissues, stored, and then slowly eliminated by macrophages, so a prolonged posttreatment, detectable, plasma drug level was anticipated. Still, it is remarkable that the drug level 1 week after completion of the 10-week course were significantly higher than any earlier trough levels. This is likely due in part to the 3-compartment pharmacokinetics this drug exhibits, and there is likely a saturation effect from tissue accumulation [23, 24]. Furthermore, the detectable oritavancin levels at 7 months posttreatment highlight the prolonged effects of this drug, which was fortunately well tolerated by this patient.

Efficacy of oritavancin is difficult to confirm in this case given the requirement for surgery and other antibiotics on several occasions over the course of illness. Nonetheless, the negative blood cultures throughout the initial course of oritavancin and the persistently negative blood cultures postoperatively support a potential clinical efficacy of oritavancin for treatment of VRE bacteremia. The recurrence of bacteremia immediately after completion of the initial oritavancin course and then intermittent bacteremia despite ongoing oritavancin are concerning for antibiotic failure, but this most likely represented ongoing unresolved source of infection, highlighting the importance of surgical management for this type of infection.

CONCLUSIONS

Despite this patient's age, multiple comorbid conditions, and active infection and complications, he tolerated oritavancin with no adverse events for the first 7 weeks of treatment. After 12 additional weeks of treatment, the patient developed mild nausea and LFT abnormalities, both of which slowly resolved over the following 11 months despite detectable bloodstream levels throughout this period. Although the optimal dosing regimen of oritavancin for serious VRE infections will require further investigation, this report provides valuable and encouraging information for the potential future use of oritavancin in serious infections due to enterococci.

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