

Continued Dosing of Oritavancin for Complicated Gram-Positive Infections

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Several retrospective and cohort analyses have suggested that continued dosing of oritavancin is both safe and efficacious for complicated Gram-positive infections, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.

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Oritavancin is a lipoglycopeptide antibiotic. The US Food and Drug Administration (FDA) approved oritavancin in 2014 for adults with acute bacterial skin and skin structure infections (ABSSSI).¹ The antibiotic is currently FDA approved for infections caused by Gram-positive organisms, including methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (MRSA, MSSA), a variety of *Streptococcus* species, and vancomycin-susceptible *Enterococcus faecalis* (VSE). Oritavancin demonstrates concentration-dependent bactericidal activity and has a half-life of 245 hours. This half-life allows for treatment of ABSSSI with a single 1,200 mg IV dose, which has been shown to be noninferior to vancomycin dosed twice daily for 7 to 10 days.¹⁻³

PROPOSAL FOR EXPANDED USES

Although the approved indication for oritavancin is narrow, *in vitro* studies have shown that oritavancin also has activity against vancomycin-resistant enterococci (VRE), and rabbit studies have demonstrated its excellent bone penetration.^{4,5} These findings have raised the question of whether oritavancin can be safely and effectively used for infections such as endocarditis, osteomyelitis, and bacteremia, which are often caused by invasive Gram-positive organisms. These types of invasive infections, particularly when MRSA is implicated, generally require IV antibiotic therapy for several weeks, often with vancomycin.⁶

To avoid long hospital stays solely for antibiotic administration, health care practitioners will often use outpatient parenteral antimicrobial therapy (OPAT). However, using OPAT presents many challenges due to the need for frequent dosing, the risk of peripheral or

central-line infections, and therapeutic drug monitoring when using vancomycin; additionally, administration and line care oftentimes require caregiver support, which may not be present for all patients.⁷ Concerns also have been raised regarding the use of OPAT in patients with a history of IV drug use due to the potential increased risk of line infections or line abuse. Few studies have explored OPAT in this population, and the Infectious Diseases Society of America OPAT guidelines recommend that the decision to use OPAT should be made on a case-by-case basis.⁷ Thus, patients who are deemed inappropriate for OPAT oftentimes remain hospitalized or reside briefly in nursing facilities solely for antibiotic administration.

Oritavancin's long half-life and potent activity against Gram-positive organisms has led to increased interest in off-label use of infrequent dosing intervals, such as weekly, to treat complicated and invasive infections. Weekly rather than daily dosing would allow for less burdensome antibiotic administration regimens and shorter hospital stays especially for patients who are not candidates for OPAT.

Efficacy of Continued Dosing

This proposed weekly dosing pattern, referred to as continued dosing or a multiple-dose regimen, has gained traction in the literature. To date, no randomized controlled trials have been conducted to assess oritavancin's efficacy in off-label indications or continued dosing, but several case reports and retrospective cohort analyses show promising outcomes.⁸⁻¹⁶ In an analysis of data from the Clinical and Historic Registry and Orbactiv Medical Evaluation (CHROME) patient registry, 32 patients received multiple doses of oritavancin for

complicated Gram-positive infections with a 93.8% overall clinical success rate, including success rates of 90.9% (10/11) for general bone and joint infections and 87.5% (7/8) for patients diagnosed specifically with osteomyelitis.⁸

Patients received between 2 and 10 doses of 1,200 mg IV given every 6 to 14 days. Johnson and colleagues report using oritavancin 1,200 mg IV every other day for 3 doses followed by 1,200 mg IV once weekly for a patient with daptomycin- and vancomycin-resistant *Enterococcus* endocarditis, resulting in negative blood cultures while on therapy.⁹ However, source control via valve replacement and post-operative oritavancin 1,200 mg IV twice weekly for 10 weeks was required to fully clear the infection.

Schulz and colleagues published a retrospective cohort analysis of 17 patients who received multiple doses of oritavancin for complicated bacterial infections, including osteomyelitis, pneumonia, and bacteremia.¹⁰ They reported 100% of patients were either successfully cured or had demonstrable improvements in their infections by using a 1,200 mg IV loading dose followed by 800 mg IV if the second dose was given within 7 days or 1,200 mg IV if the second dose was given more than 10 days later. Patients received between 2 and 18 total doses, with 6 out of 17 (35%) receiving only 2 doses. One patient who received 18 doses was an outlier, as her treatment goal was palliative suppression due to an infected endovascular graft that could not be removed.

In a published case series, 1 of 10 patients receiving oritavancin for invasive Gram-positive infections received multiple doses of oritavancin for an MSSA deep tissue infection.¹¹ The 3 total doses (strength not reported) were separated by 19 days and 14 days and resulted in cure. Several case reports and a retrospective chart review study specifically show the effectiveness of oritavancin for osteomyelitis caused by MSSA, MRSA, and VRE.¹²⁻¹⁶ However, dosing strategies varied widely after the initial 1,200 mg IV loading dose.

Drug Interactions, Safety, and Tolerability

Oritavancin has minimal drug-drug interactions, the most notable being with an-

ticoagulants.¹ Use of IV heparin within 120 hours of oritavancin administration can falsely elevate activated partial thromboplastin time (aPTT) levels; therefore, heparin should not be monitored with aPTT during this period. Oritavancin also can artificially prolong international normalized ratio (INR) values for up to 12 hours, and dose adjustments based on INRs during this window are not recommended. Of note, factor Xa laboratory monitoring is unaffected by oritavancin, as it does not depend on phospholipid reagents as do aPTT and INR measurements.

Oritavancin has been shown to be well tolerated when dosed according to both the package insert and continued dosing strategies. The most common adverse effects (AEs) ($\geq 3\%$), occurring at similar rates to vancomycin, are nausea, vomiting, diarrhea, headache, and limb and subcutaneous abscesses.¹ Infusion reactions also have been reported, although they are usually reversible on slowing or stopping the infusion. It is worth noting that the use of oritavancin for osteomyelitis is not recommended in the product labeling, as an increased rate of osteomyelitis was observed in the oritavancin vs IV vancomycin groups for the treatment of patients with acute bacterial skin and skin structure infection (SOLO) trials (0.6% in oritavancin group vs 0.1% in vancomycin group, statistical significance not reported).¹⁷ However, it was postulated that these osteomyelitis cases were likely present, yet not recognized, at baseline and were not the result of administering oritavancin. This conclusion is further corroborated by previously presented research demonstrating successful cure of osteomyelitis with continued dosing strategies.¹²⁻¹⁶

Many patients receiving multiple doses of oritavancin did not experience AEs or laboratory abnormalities.^{13,15} Four of 17 patients (24%) in one retrospective review experienced AEs, including infusion reactions, anemia, and leukopenia; all were reversible on discontinuation of oritavancin, and contributions of other antibiotics in some cases could not be ruled out.¹⁰ One patient experienced taste disturbance for several hours after each infusion, and a second had documented hearing loss after 3 doses of oritavancin in a 33-day period,

though she had received 6 weeks of IV vancomycin prior to oritavancin.^{11,12} A patient treated for daptomycin- and vancomycin-resistant *Enterococcus faecium* prosthetic valve endocarditis experienced nausea, anorexia, and minor liver function test (LFT) abnormalities after cumulative oritavancin exposure over 18 weeks.⁹ On discontinuation of the drug, nausea and anorexia improved, and LFTs normalized 11 months later. Overall, AEs reported with continued dosing of oritavancin have been minimal and largely reversible, mimicking the AEs in the product labeling for traditional dosing. This suggests that using a continued dosing strategy may not result in worse or more frequent AEs, though randomized controlled trials are needed to fully ascertain these preliminary findings.

CONCLUSIONS

The literature supporting the use of oritavancin beyond single-dose administration for ABSSSI is growing. Continued dosing regimens have been well tolerated and have resulted in clinical cure for many patients with barriers to first-line treatment and complicated or invasive infections. While randomized controlled trials are needed to concretely demonstrate the efficacy and safety of continued dosing of oritavancin, it may fill an important treatment niche in this era of growing antibiotic resistance and increasing complexity of patient cases.

Author disclosures

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