

# Experience with expanded use of oritavancin in a tertiary hospital: indications, tolerability and outcomes

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**Background:** Oritavancin is a lipoglycopeptide antibacterial agent used to treat infections caused by Gram-positive organisms. It is FDA-approved for the treatment of acute bacterial skin and soft tissue infections (ABSSIs) but is increasingly being used off-label to treat invasive bacterial infections such as osteomyelitis, prosthetic joint infection and infective endocarditis.

**Objectives:** This study describes the clinical outcomes and adverse reactions related to oritavancin.

**Patients and methods:** This was a retrospective study conducted over a 5 year period at a tertiary care medical centre. Ninety-five adult patients were included in this study and were followed for 1 year after the last dose of oritavancin.

**Results:** The most common indication for oritavancin at our institution was osteomyelitis, followed by ABSSI. Other indications were vertebral infection, hardware-associated infection, bacteraemia and infective endocarditis. Fourteen percent (13/95) of patients developed an adverse reaction to oritavancin during the study period. Cure with no recurrence up to 1 year after the last dose of oritavancin was achieved in 74% (53/71) of patients, and the treatment failure rate was 19% (14/71 patients).

**Conclusions:** Oritavancin is an effective agent that can be used to treat invasive Gram-positive bacterial infections other than ABSSI. Adverse events requiring drug discontinuation were common.

## Introduction

Vancomycin has traditionally been the drug of choice for infections caused by MRSA, *Corynebacterium* and other Gram-positive organisms when allergies preclude use of  $\beta$ -lactams.<sup>1</sup> Monitoring of vancomycin levels and ensuring adequate dosing can be challenging in the outpatient setting. In addition, the need for a long-term IV catheter for drug administration provides additional challenges as well as safety concerns. For example, patients may require admission to a short-term rehabilitation (STR) facility for drug administration due to lack of insurance coverage or inability to self-administer and/or for safety concerns such as in those who have a history of injection drug use. Thus, the potential for a once-a-week dosing schedule has made oritavancin an attractive option

for long-term use for indications beyond acute bacterial skin and soft tissue infections (ABSSIs).

Oritavancin is a lipoglycopeptide antimicrobial with a long half-life that is active against Gram-positive organisms. It is bactericidal and is approved for use in ABSSIs. Single-dose oritavancin has been shown to be non-inferior to vancomycin in treating ABSSI.<sup>2,3</sup> Because of its *in vitro* bactericidal activity and ability to sterilize biofilm, it is increasingly being used off-label for treatment of complicated infections including osteomyelitis, prosthetic joint infection (PJI), bacteraemia and even infective endocarditis.<sup>4,5</sup> The long half-life allows for less frequent dosing intervals (e.g. once a week), avoiding the need for long-term IV catheters.<sup>6</sup> For these off-label indications, data are lacking regarding clinical outcomes, adverse

reactions associated with long-term use of oritavancin and appropriate dosing intervals.

The aims of the study were to review all the indications for oritavancin use, clinical outcomes and adverse events over a 5 year period at our institution. We were particularly interested in studying adverse effects of oritavancin use when multiple doses were administered.

## Patients and methods

This was a retrospective study of adult patients ( $\geq 18$  years of age) who received at least one outpatient dose of oritavancin at Yale New Haven Hospital from January 2016 through December 2020. Eligible subjects were adults ( $\geq 18$  years of age). Subjects were identified in collaboration with the Yale Center for Clinical Investigation Joint Data Analytics Team (JDAT).

We retrospectively reviewed the medical records of eligible patients and abstracted the following data: patient demographics, underlying medical conditions, laboratory and microbiology results, results of imaging studies, and details of surgical and antimicrobial therapy. Outcomes included cure (defined as no recurrence at 1 year), treatment failure (worsening infection requiring readmission or change in antibiotics or recurrence within 1 year), lost to follow-up, and other outcomes (those who did not fall into cure, failure or lost to follow-up). In addition, we were particularly interested in the adverse drug events patients developed in response to oritavancin infusion. All patients who had requested to opt out of research were automatically excluded during the JDAT search. The project was approved by the Yale School of Medicine Institutional Review Board.

## Results

A total of 104 charts were reviewed, of which 95 were included (59 male and 36 female patients); 8 were excluded after chart review as they never received oritavancin although it was ordered, and 1 patient was excluded as the chart could not be located despite being included in the JDAT-generated list. Patient characteristics are listed in Table 1. Median age of male patients was 55 years, and median age of female patients was 57.5 years. Most of our patients (73%) were Caucasian, and 22% were African American. There was some overlap in racial/ethnic data for Hispanic patients. Not all comorbidities are listed.

The most common indication for prescribing oritavancin at our institution during the study period was osteomyelitis (OM) (20%), and skin and soft tissue infection (SSTI) (20%). There were 10.5% with vertebral infection, 10.5% with bacteraemia, 7.3% with infective endocarditis and 7.3% with hardware-associated infections (other than PJI and hardware-associated vertebral infections). Over the 5 year period, 5.2% with PJI were treated with oritavancin. Less common infections and further details are listed in Table 2. Due to overlap between three patients with bacteraemia and vertebral OM the total number of patients appears to be over 95 but it was not possible to list these patients under one category.

Cure with no recurrence up to 1 year was achieved in 74% (53/71) of patients. The treatment failure rate was 19% (14/71 patients). Four patients were lost to follow-up. If we further exclude the four lost to follow-up, the treatment success rate increases to 79% (53/67). Of the other 24 patients, 11 could not complete treatment with oritavancin due to adverse reactions and oritavancin had to be stopped. Thirteen of the 24 other outcomes are listed in Table 3.

**Table 1.** Demographics and clinical characteristics

Baseline characteristics	Number	Percentage
Total charts reviewed	104	n/a
Excluded	9	n/a
Total included in the study	95	n/a
Gender		
Number of male patients	59	62.1
Number of female patients	36	37.9
Median age, y (n = 95)		
Male	55 (range 28–80 y)	
Female	57.5 (range 18–91 y)	
Race		
White or Caucasian	70	73.7
African American	21	22.1
Other/race not listed	4	4.2
Comorbidities		
Diabetes mellitus	35	36.8
People living with HIV infection	0	0
Solid organ transplant	1	1.1
Injection drug use/polysubstance use (prior or active)		
Yes	25	26.3
No	67	70.5
Not asked/missing	3	3.2

## Oritavancin adverse reactions

During the study period, 13 out of 95 (13.7%) developed adverse reactions to oritavancin with most (85%) occurring during the infusion, which led to stopping of the infusion (Table 4). One patient experienced a reaction (localized rash) a day after completing their third dose of oritavancin with prior doses having been given 2 weeks apart without issue, whereas another developed phlebitis shortly after completing the last infusion.

## Infusion reactions

In this cohort, more males (7) developed an infusion reaction than females (4); 9 out of 11 (81.8%) of those who developed an infusion reaction were under 65 years of age.

During the infusion, 4% of patients experienced back pain including back numbness, 4% had itching, 4% had chills or shaking, 3% had chest pain, 3% experienced nausea, 2% had vomiting and 2% had light-headedness or dizziness. Multiple patients had more than one type of reaction to the infusion.

Ten out of 11 (90.9%) of the infusion reactions that led to stopping the medication occurred after the second dose. The dose administered at the time of the infusion reaction was 1200 mg, given 2 weeks after the first infusion in 91% of cases. Only one person had an infusion reaction after the third infusion using a weekly dosing strategy starting at 1200 mg the first week followed by 800 mg doses thereafter. The majority of patients (9/11; 81.8%) received diphenhydramine 25–50 mg IV or orally as routine premedication prior to the infusion. The premedication with diphenhydramine was instituted as part of our administration protocol as the practice had started seeing infusion reactions shortly after starting to do oritavancin infusions.

**Table 2.** Indications and pathogens

Indications	Number of patients	Percentage	Notes
Diabetic foot infection without osteomyelitis	4	4.2	1 <i>Coryne</i> sp., 1 MSSA/GBS, 1 GBS/aerobic GP, 1 CoNS
Diabetic foot infection with osteomyelitis	8	8.4	3 polymicrobial (MSSA/GBS/ <i>C. striatum</i> /CoNS/mixed GP), 1 MRSA, 2 MSSA, 1 MSSA/ <i>C. striatum</i> , 1 MSSA/mixed GP
Osteomyelitis	19	20	2 MSSA, 2 CoNS, 2 no culture data, 1 MSSA/ <i>C. striatum</i> , 1 MSSA/GBS, 11 polymicrobial
Vertebral osteomyelitis (with and without hardware)	10	10.5	
Vertebral infection without HW	5	5.2	1 MRSA, 1 MSSA, 2 no culture data, 1 <i>C. striatum</i>
Vertebral osteomyelitis with HW	5	5.2	1 CoNS (MRSE), 2 MRSA, 1 VRE, 1 no culture data
HW-associated infection (other than PJI and HW-associated vertebral infection)	7	7.3	2 CoNS, 1 MRSA, 1 MSSA, 1 CoNS/ <i>Coryne</i> sp., 1 culture negative, 1 no culture data
Prosthetic joint infection	5	5.2	2 CoNS, 1 <i>Corynebacterium striatum</i> , 1 <i>E. faecalis</i> and <i>Coryne</i> sp., 1 <i>Cutibacterium acnes</i>
Skin and soft tissue infection	19	20	7 no culture data, 3 MRSA, 1 GBS, 1 MSSA, 1 MRSA/GBS, 1 <i>C. striatum</i> /mixed, 3 polymicrobial, 1 MRSA/CoNS, 1 <i>Cutibacterium acnes</i>
Bacteraemia	10	10.5	3 MRSA, 6 MSSA (2/6 had polymicrobial with MSSA), 1 GBS
Infective endocarditis (total)	7	7.3	
Native valve endocarditis	4	4.2	3 MSSA (1/3 also with CoNS), 1 MRSA
Prosthetic valve endocarditis	3	3.1	1 <i>E. faecalis</i> (susceptible to vancomycin and ampicillin), 1 MSSA, 1 <i>Coryne</i> sp.
Other infections (MRSA LVAD drive line infection, postoperative finger infection due to MRSE and MSSA, recurrent abdominal wall abscess due to CoNS and mixed Gram-positive organisms, MSSA, abdominal mesh abscess, MRSA penile implant infection, MSSA deep-brain stimulator generator infection, MSSA wound dehiscence at hip arthroplasty site, breast abscess with culture positive for <i>Actinomyces</i> )	8	8.4	1 MSSA/CoNS, 1 MRSA, 1 CoNS/mixed GP, 4 MSSA, 1 <i>Actinomyces</i>
Total	95 <sup>a</sup>		

CoNS, coagulase-negative *Staphylococcus*; *E. faecalis*, *Enterococcus faecalis*; *Coryne* sp., *Corynebacterium* species; GBS, group B  $\beta$ -haemolytic *Streptococcus*; GP, Gram-positive organisms; HW, hardware; LVAD, left ventricular assist device; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PJI, prosthetic joint infection; VRE, vancomycin resistant *Enterococcus*.  
<sup>a</sup>Due to overlap of infection when the numbers are added, the total (97) is higher than the actual total number of patients (95) because some patients are included under two indications as described in the text.

**Table 3.** Overall outcomes (total  $n=71$ )

Outcome	Number	Percentage
No recurrence/cure up to 1 y	53	74
Treatment failure	14	19
Lost to follow-up	4	0.05
Other (the 24 other outcomes excluded from outcome analysis are listed below)	24	N/A
Adverse reactions leading to discontinuation of oritavancin	11	11.6
Treatment success of initial cellulitis followed by recurrent cellulitis	1	1.0
Received multiple courses due to persistent symptoms	1	1.0
Lack of transport for infusions, missed infusions, moved out of state	3	3.0
Received one dose post routine antibiotics as a brief suppression dose	1	1.0
Received oritavancin as a bridge to IV cefazolin while awaiting a tunnelled central venous catheter	1	1.0
Required oral antibiotics after oritavancin	4	4.2
No clear outcome as the course was complicated by injection drug use and readmission	1	1.0
Multiple readmissions due to skin and soft tissue infection in opposite lower extremity	1	1.0

**Table 4.** Adverse reactions

Age	Sex	Diagnosis	Oritavancin doses	Premedication	Reaction during infusion	Management
83	F	Thoracic abscess	1200 mg (2nd dose)	DPH 50 mg PO	Chest and back pain, dyspnoea, dry heaves, chills itching	Admitted Given IV DPH 25 mg
30	M	Endocarditis	1200 mg (2nd dose)	DPH 25 mg PO	Numbness in back radiating to legs, nausea, light-headedness, tachycardia	IV fluid, DPH 50 mg, ondansetron 4 mg, famotidine 20 mg Infusion stopped, discharged home
56	F	PJI	1200 mg (1st dose)	None	Itching, hives, throat swelling	DPH 25 mg IV Infusion stopped
62	M	Foot hardware infection	1200 mg (2nd dose)	None	Dizziness, nausea, light-headed, itching, hives	DPH 25 mg IV, ondansetron 4 mg Infusion stopped
60	F	PJI	1200 mg (3rd dose)	DPH 50 mg, ondansetron 4 mg	Rash—did not occur during the infusion	Topical steroids after biopsy by dermatology for persistent rash
58	F	Vertebral OM	1200 mg (2nd dose)	DPH 50 mg PO	Back and chest pain	DPH 25 mg IV Infusion stopped, discharged home
57	M	Foot infection	1200 mg (2nd dose)	DPH 50 mg PO	Shaking chills, nausea	IV hydrocortisone 100 mg, famotidine 20 mg, ondansetron 4 mg, DPH 25 mg Infusion stopped
71	M	OM frontal bone	1200 mg (1st dose)	DPH 25 mg IV	Facial flushing/redness (2nd dose—leg cramping/spasm, involuntary movements)	DPH 50 mg PO, 25 mg IV DPH Sent to ED, observation
46	F	PJI	3 (1200 mg then 800 mg × 2)	DPH 50 mg PO	Shaking, felt cold, vomited, back pain	Infusion stopped Hydrocortisone 100 mg, DPH 50 mg IV, famotidine 20 mg, ondansetron 4 mg
51	M	Foot OM	2 (1200 mg)	DPH 50 mg PO	Shaking, vomiting, headache, elevated BP	DPH 50 mg, ondansetron 4 mg ER
45	M	Elbow hardware infection	2 (1200 mg)	DPH 50 mg PO	R arm, chest wall pain	50 mg DPH, ondansetron 4 mg Infusion stopped Admitted
60	M	OM toe	2 (1200 mg)	DPH 50 mg PO, acetaminophen 650 mg	Itching	25 mg DPH IV
61	M	Lumbar skin soft tissue infection with hardware	2 (1200, 800 mg)	DPH 50 mg	Phlebitis	

DPH, diphenhydramine; ED, emergency department; ER, emergency room; F, female; M, male; OM, osteomyelitis; PJI, prosthetic joint infection; PO, per os (orally); R, right.

Treatment for the infusion reaction varied and included IV diphenhydramine, IV ondansetron, IV hydrocortisone, IV fluids and IV famotidine. Four patients required evaluation at the emergency department and/or admission for observation. One patient developed facial flushing with first infusion but did not require the medication to be stopped. This patient did have another reaction on their second dose that required discontinuation of the medication and observation in the emergency department.

Of the 13 who developed reactions during or after the infusion, 1 person developed an acute kidney injury, 1 had elevated ALT/AST 16 days after the infusion (which could have been caused by other

antibiotic use), 1 developed mild leucopenia, and 1 developed hyperglycaemia in the setting of known diabetes.

Four patients included in the study had an allergy reported to vancomycin, which is a glycopeptide antibiotic, but they had no reaction to oritavancin infusion.

## Discussion

In this small, single-centre, retrospective study, oritavancin was an effective antimicrobial agent for treatment of complicated Gram-positive infections, with 74% of patients having cure with no evidence of recurrence at 1 year. Choosing this agent allowed

patients to leave the hospital, while avoiding admission to skilled nursing facilities. Reasons for selecting oritavancin included the necessity to avoid placement of a peripherally inserted central catheter (PICC) in certain populations (patient history of injection drug use/patient refusal for short-term rehabilitation stay for antibiotic infusions), acute or chronic kidney injury requiring close monitoring of vancomycin levels, Medicare not paying for home antibiotics, patient preference not to have a PICC line and ease of regimen. Other indications included allergies to other antibiotics (cephalosporins, penicillin), failure to respond to oral antibiotics, need for chronic suppression with lack of options for oral agents, and concern for non-adherence.

Advantages of oritavancin included ability to avoid STR and need for an indwelling IV catheter, thereby avoiding IV-line related adverse outcomes such as bloodstream infection, and deep vein thrombosis. The use of oritavancin is also beneficial since we can prevent the need for prolonged hospitalizations for IV antibiotic administration in certain patient populations (i.e. patients with a history of injection drug use). There is no dose adjustment per creatinine clearance (acute kidney insufficiency or end-stage renal disease/haemodialysis). This removes the extra work related to close monitoring of creatinine clearance and dose adjustment needed with use of vancomycin.

Our study cohort showed a success rate of 74%, which is somewhat lower than that reported by other investigators.<sup>7</sup> A recent systematic review showed a cure rate of 85% with oritavancin. Over 25% of patients had injection drug use and 17% had MRSA, which has been shown by others to be a predictor of success.<sup>7</sup> In the systematic review only 1.1% were lost to follow-up.

In our study 11.6% had an adverse reaction leading to discontinuation of oritavancin. Another study reported an adverse effect rate of 6.6%.<sup>8</sup> In a randomized, double-blind trial using a single dose of oritavancin (SOLO I), nausea, vomiting, headache and diarrhoea were reported as the most common side effects and had a 7.4% rate of adverse reactions.<sup>3</sup> Glycopeptide antibiotics can cause nephrotoxicity.<sup>9</sup> However, only one person in our study had acute kidney insufficiency, which is similar to that reported by others.<sup>7</sup>

Since no set dosing guidelines were available when oritavancin was used initially at our institution, we used the recommended dose of 1200 mg every 2 weeks. Dosing recommendations changed since initiation of the study, which explains why every patient received 1200 mg as the initial dose, but subsequent dosing was with either 1200 or 800 mg. This decision was based on the institutional dosing protocol used at the time of treatment. Oritavancin was supplied as 400 mg vials. Of note, during the study period every infusion was given over a 3 h period as the short-infusion oritavancin was not available. The number of doses is determined based on the infection and is generally one to two doses for SSTI. All patients were expected to complete 4 to 6 weeks of total antibiotics for treatment of osteomyelitis and 6 weeks for treatment of vertebral OM, hardware-associated infection, PJI and endocarditis. Similar dosing for osteomyelitis with 1200 mg followed by 800 mg weekly has been used in other centres.<sup>10</sup>

Studies suggest that two doses of dalbavancin administered a week apart can be equivalent to 6 weeks of antibiotics.<sup>11</sup> A pharmacokinetic study showed that the drug concentration remained above MIC for >4.6 weeks when oritavancin was dosed 1200 mg followed by 800 mg a week later.<sup>12</sup> The study also showed that

the total and unbound free drug concentration was much higher with two doses compared with one dose at Day 29. Further pharmacokinetic and pharmacodynamic studies are needed to understand the optimal multiple dosing regimens. It is possible that multiple doses can result in a rise in total and unbound free drug, thereby increasing overall exposure and possible adverse drug reactions. We did not have access to therapeutic drug monitoring and were therefore unable to measure oritavancin levels in this study. It may be that reducing the number of infusions and the dose of subsequent oritavancin doses may reduce the risk of adverse reactions. Further data are required to explore this hypothesis.

Limitations of our study included the small sample size (95 patients) from only a single institution. Oritavancin MIC is not checked at our institute and this was assumed to be susceptible if the aetiological agent was susceptible to vancomycin. Prior investigators have found that vancomycin susceptibility was an accurate surrogate for oritavancin susceptibility.<sup>13</sup> Because there is often no specific test to confirm 'cure', we used clinical outcomes and inflammatory markers to determine response to therapy. Our study cohort had a treatment failure rate of 19%. Of note, failure could be due to other factors such as patient non-compliance with recommendations such as early weight bearing after surgery for diabetic foot infection, ongoing tobacco use, poor control of diabetes mellitus, and underlying vasculopathy rather than failure of the oritavancin itself.

In this small, single-centre study, we found that oritavancin can be used successfully to treat infections other than ABSSI. More data are needed to assess whether a 1200 mg initial dose, followed by 800 mg for subsequent doses would be associated with a lower incidence of toxicity and whether the newer formulation of oritavancin, designed for more rapid infusion, will have a different rate of infusion reactions. Further study is also needed for long-term follow-up of patients with PJI, vertebral osteomyelitis and bacterial endocarditis.

## Conclusion

Oritavancin may have an important role for treatment of infections other than ABSSI. More studies are needed to determine optimal dosing and duration. Adverse reactions to oritavancin are common and prescribers should be aware of this and consider premedication. The authors hope that these results will provide additional options for providers who are treating invasive Gram-positive infections.

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## Transparency declarations

The authors do not have any disclosures at the time of submitting this manuscript.

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