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Treatment of chronic osteomyelitis with multidose oritavancin: A case series and literature review ☆

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ABSTRACT

Osteomyelitis remains difficult to treat, typically requiring a prolonged course of intravenous (i.v.) antibiotics. The optimal route and duration of antibiotics remains ill-defined due to limited prospective clinical trials. Oritavancin is a long-acting, semisynthetic lipoglycopeptide antibiotic with rapid concentration-dependent bactericidal activity against many Gram-positive organisms. Favourable pharmacokinetics makes oritavancin an appealing alternative to currently available antibiotics requiring daily infusion to decrease the risk of vascular access complications associated with outpatient antimicrobial therapy. The purpose of this study was to report the outcomes of nine patients with chronic osteomyelitis receiving multidose oritavancin. Using electronic medical records, patients aged ≥18 years treated with i.v. oritavancin between September 2015 and April 2018 at Downtown Dublin Wound Center, a hospital-owned outpatient wound care clinic and infusion centre affiliated with Meadows Regional Health System in Dublin, GA, were identified. Of 12 cases reviewed, 9 patients received at least two doses of i.v. oritavancin for the treatment of chronic osteomyelitis. All nine patients experienced clinical cure at 6-month follow-up after the last dose of oritavancin. Multidose oritavancin was found to be a safe and efficacious option for chronic osteomyelitis when treatment options are limited by patient complexities or barriers in their ability to access healthcare services.

1. Introduction

Osteomyelitis occurs when micro-organisms gain access to bone through contiguous dissemination, haematogenous seeding or direct inoculation, leading to inflammatory changes and bone necrosis, hallmarks of the disease [1,2]. Compared with acute osteomyelitis, chronic osteomyelitis is characterised by sinus tract and sequestrum development with vague symptoms. Although it was among the first infectious processes recorded, chronic osteomyelitis remains one of the most difficult to diagnose, relying on a combination of clinical suspicion as well as laboratory, radiographic and microbiological findings. Furthermore, the paucity of prospective clinical trials forces clinicians to rely on animal models, case reports and series, and retrospective studies to guide treatment.

Surgical treatment with debridement of necrotic bone accompanying identification of the infectious aetiology via surgical sampling or needle aspiration allows the optimisation of therapy [1,2]. *Staphylococcus aureus*, in particular methicillin-resistant *S. aureus* (MRSA), is among the most common micro-organisms causing osteomyelitis owing to its multitude of virulence factors enhancing pathogenesis and biofilm formation while impairing the host immune response [1–3]. In addition, *S. aureus* may internalise in osteoblasts, likely contributing to its persistence [4]. Limited bone and intraosteoblastic penetration coupled with increasing rates of antimicrobial resistance, in particular methicillin resistance, further complicates the treatment of osteomyelitis [4–6]. Co-morbidities impairing peripheral blood flow, including diabetes mellitus, may make osteomyelitis in these patients even more difficult to treat [6,7].

The optimal route and duration of antibiotics in osteomyelitis caused by *S. aureus*, especially MRSA, remains unknown but usually requires a prolonged treatment course of intravenous (i.v.) antibiotics [5]. Vancomycin remains the most commonly used agent for MRSA osteomyelitis despite high treatment failure and recurrence rates [5]. Alternative regimens for MRSA osteomyelitis include daptomycin, ceftaroline, linezolid and telavancin, but these are plagued by adverse events (AEs) that may develop with extended use [8]. Oritavancin, a long-acting, semisynthetic lipoglycopeptide antibiotic with rapid concentration-dependent bactericidal activity

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against many common Gram-positive organisms, including MRSA, has emerged as a viable i.v. treatment option for osteomyelitis [9–12]. Oritavancin, with its long terminal half-life and excellent safety profile, could potentially replace available i.v. antibiotics currently requiring one or more daily infusions, possibly leading to a decrease in common complications associated with outpatient antimicrobial therapy [13]. However, limited data are available supporting the use of oritavancin for osteomyelitis [9,11,12]. The purpose of this case series was to report our experience with oritavancin in treating patients with chronic osteomyelitis.

2. Methods

This was a retrospective chart review of patients treated with oritavancin at Downtown Dublin Wound Center, a hospital-owned outpatient wound care clinic and infusion centre affiliated with Meadows Regional Health System in Dublin, GA. This research was carried out in accordance with the Declaration of Helsinki. Eligible patients included adults aged ≥18 years who received at least two doses of i.v. oritavancin for the treatment of chronic osteomyelitis between September 2015 and April 2018 at Downtown Dublin Wound Center. Oritavancin was dosed at 1200 mg i.v. infused over 3 h as the initial dose and as each subsequent dose for all patients. Patients receiving oritavancin for indications other than chronic osteomyelitis were excluded. Chronic osteomyelitis was defined as osteomyelitis lasting ≥3 months as per the Waldvogel classification system [14] and was confirmed by imaging studies, including radiography, magnetic resonance imaging (MRI) and/or nuclear medicine bone scan findings [1]. Pertinent data were extracted from the electronic medical record (EMR) and included past medical history, co-morbid conditions, prior and concomitant antibiotic exposure, type and anatomical location of osteomyelitis, and oritavancin therapy characteristics, including dose, time between doses and AEs.

Microbiological data, including pathogen and susceptibility profile, were also collected. The number of oritavancin doses was at the sole discretion of the treating physician and was dependent upon patient co-morbidities, clinical status of the patient, anatomical location of osteomyelitis, and patient availability for follow-up care. Clinical outcomes were determined by the treating clinician. Patients were followed-up at 6 months after the last dose of oritavancin and were evaluated for clinical cure. Clinical cure was defined as complete wound epithelial closure and continued resolution of signs and symptoms of infection, which included cessation of fever, normalisation of leukocytosis, and reduction in size of the lesion compared with baseline without the need for additional Gram-positive antibiotics, surgical debridement or amputation. Aside from routine haematology and chemistry tests, no inflammatory biomarkers, such as erythrocyte sedimentation rate or C-reactive protein, were obtained during the follow-up period. Failure was defined as inadequate resolution or progressive worsening of signs and symptoms of the infection and the need for continued or alternative Gram-positive therapy, or if the patient was lost to follow-up. Safety was assessed by evaluation of all recorded AEs regardless of proximity to administration of oritavancin throughout the 6-month follow-up period. Data were assessed using descriptive statistics.

3. Results

Of the 12 patients receiving oritavancin for the treatment of osteomyelitis during the study period, 3 were excluded due to receipt of only one dose of oritavancin. Of note, all three of these patients were deemed to have achieved clinical cure at the 6-month follow-up visit. Thus, nine patients met the study criteria and were included in the analysis (Table 1). The median patient age was 65

Table 1
Patients receiving oritavancin for the treatment of chronic osteomyelitis.

Patient	Age (years)	Sex	Race	Medical history	Site of osteomyelitis	Antibiotics received prior to oritavancin	Organism	Concomitant antibiotic therapy	Oritavancin dosing[a]	6-month follow-up
1	65	M	C	CAD, DM, HTN	Right great toe	None	MRSA	Doxycycline × 3 months	D1, D13	Clinical cure
2	31	M	AA	DM, HTN, morbid obesity	Left distal first metatarsal	Clindamycin × 1 week	MRSA	None	D1, D52, D90	Clinical cure
3	47	M	C	HTN, lymphoedema, morbid obesity	Right distal first metatarsal	Clindamycin × 1 week, then doxycycline × 3 months	MRSA	None	D1, D72	Clinical cure
4	66	F	C	COPD, HTN, RA	Left patella	AMC and levofloxacin for unknown duration	NG	None	D1, D34	Clinical cure
5	37	M	C	Paraplegia	Right lateral malleolus	None	N/A	None	D1, D14, D44, D148	Clinical cure
6	89	F	C	AF, CHF, HTN, right BKA	Left lateral malleolus	None	MRSA	None	D1, D36, D73, D147	Clinical cure
7	86	M	C	AF, CAD, HTN, PVD	Left fifth toe	None	N/A	None	D1, D28,	Clinical cure
8	62	M	C	COPD, DM	Right calcaneus	None	MRSA	None	D1, D14, D28, D70, D84, D113	Clinical cure
9	79	F	C	Asthma, CHF, DM, PVD	Right fifth metatarsal	None	NG	None	D1, D27	Clinical cure

C, Caucasian; AA, African–American; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; AF, atrial fibrillation; CHF, congestive heart failure; BKA, below-knee amputation; PVD, peripheral vascular disease; AMC, amoxicillin/clavulanic acid; MRSA, methicillin-resistant *Staphylococcus aureus*; NG, no growth; N/A, culture results not available.

[a] Oritavancin was dosed at intravenous infused over 3 h as the initial dose and as each subsequent dose for all patients.

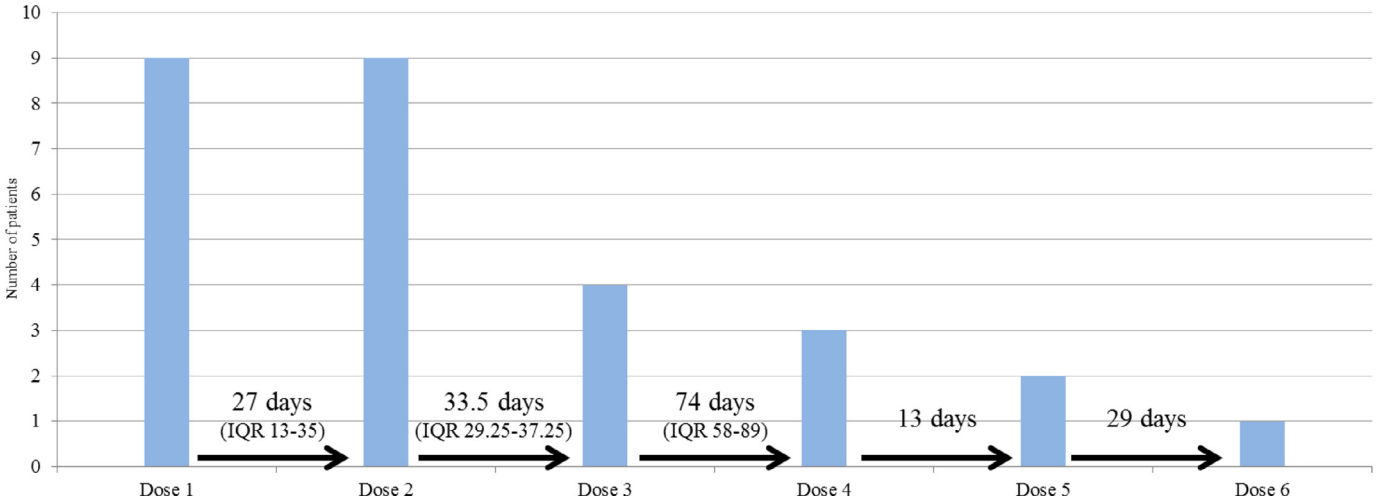

Fig. 1. Comparison of the median [interquartile range (IQR)] time between oritavancin doses.

years [interquartile range (IQR) 47–79 years], 67% (6/9) were male and the majority were Caucasian (89%; 8/9). The most common co-morbidities were hypertension (67%; 6/9) and diabetes mellitus (44%; 4/9). Study patients were generally obese with an average body mass index (BMI) of 36.4 kg/m^2. Osteomyelitis was confirmed in two patients with positive nuclear medicine bone scans, whilst the remaining cases were confirmed by MRI. All patients had chronic osteomyelitis of the lower extremity, of which the most common sites of infection were the metatarsal (33%; 3/9), toe (22%; 2/9) and malleolus (22%; 2/9). Only three (33%) of the nine patients had documentation in the EMR of receiving antibiotic therapy prior to administration of oritavancin at the wound clinic. All patients received local wound care, whereas only one patient underwent surgical debridement. The most common pathogen was MRSA, which was isolated in 5 patients (56%).

Overall, clinical cure was achieved in all nine patients (100%). Patient 5 had residual osteomyelitis in his right lateral malleolus confirmed by MRI on Day 144 of oritavancin therapy. Following notification of this result, an additional dose of oritavancin was administered on Day 148. Clinical cure was noted at the 6-month follow-up. The median number of oritavancin doses was 2 (IQR 2–4); 44% (4/9) received more than two doses, of which 1 patient received three total doses, 2 patients received four total doses and 1 patient received six total doses. Compared with the median time between dose 1 and dose 2, the time between dose 2 and dose 3 was 6.5 days longer (27 days vs. 33.5 days); and compared with the median time between dose 2 and dose 3, the time between dose 3 and dose 4 was 40.5 days longer (33.5 days vs. 74 days) (Fig. 1). The time between doses 4 and 5 was 13 days, whilst the time between doses 5 and 6 was 29 days. Concomitant antibiotics were only administered in one patient who received 3 months of doxycycline (Patient 1). All patients were included in the safety analysis. Oritavancin was well tolerated with no treatment-emergent AEs reported. In addition, no laboratory abnormalities were observed in the chemistry panels and complete blood counts obtained during the study period. No patient required hospitalisation, and all patients finished therapy completely as outpatients.

4. Discussion

Here we report the outcomes of nine patients with lower extremity osteomyelitis treated with at least two doses of oritavancin. Despite the small number of patients included and the retrospective nature of data collection, this represents the largest case series of patients receiving multidose oritavancin for the treatment of chronic osteomyelitis, the majority of which were caused by MRSA. There was a paucity of oritavancin efficacy data in the treatment of osteomyelitis at the time the first patient (Patient 1) in the series was treated. Therefore, the treating clinician elected to concomitantly prescribe oral doxycycline as adjuvant antimicrobial therapy. Since that time, recent reports have described using oritavancin in two patients with vertebral osteomyelitis [11,12], one of which was due to MRSA [12] while the other was not cultured [11], one patient with methicillin-susceptible *S. aureus* (MSSA) lower extremity osteomyelitis [9], one patient with decubitus ulcers and osteomyelitis caused by mixed skin flora [11], one patient with a history of i.v. drug abuse with culture-negative osteomyelitis and septic arthritis [11] and one patient with osteomyelitis caused by MSSA and *Klebsiella oxytoca* [11] (Table 2).

S. aureus, especially MRSA, is responsible for the majority of cases of osteomyelitis, which may persist or recur in up to 40% of patients and frequently leads to irreversible damage [15]. The pathogenicity of *S. aureus* is due to its ability to colonise, form biofilms, internalise within, and even destroy bone through the production of proteins and toxins. Osteomyelitis typically requires surgical management in concert with antibiotic therapy active against the infecting pathogen [2]. Selecting the optimal antibiotic therapy and route requires an understanding of the extent and rate of bone penetration, particularly in diseased bone, as well as conditions limiting peripheral circulation depending on patient-specific co-morbidities [6]. Preliminary data from the OVIVA trial presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2017 suggest highly bioavailable agents may be acceptable, however use of oral antibiotics remains controversial [16,17]. Until more data are available on the exact role of oral antibiotics, vancomycin remains the most frequently selected antibiotic for the treatment of chronic osteomyelitis [5]. However, use of vancomycin is associated with increased rates of failure and recurrence, perhaps due to poor penetration into bone and biofilms. In in vitro models, oritavancin demonstrated higher bone concentrations compared with dalbavancin, teicoplanin, linezolid and vancomycin [18]. Oritavancin displays potent in vitro activity against actively-growing Gram-positive organisms, including MSSA and MRSA. Notably, oritavancin kills *S. aureus* cells in stationary phase and within biofilms owing to its unique triple mechanism of action [10,19]. Although susceptibility testing for oritavancin was not readily available during the study period, previous in vitro data validated the use of vancomycin susceptibility against *S. aureus* as a surrogate for

Table 2
Previous reports of patients with osteomyelitis treated with oritavancin.

Reference	Age (years)	Sex	Past medical/social history	Indication	Dosing regimen	Outcome
Schulz et al. [11]	56	M	–	Probable vertebral osteomyelitis with discitis (not cultured)	1200 mg × 1, then 800 mg once weekly × 2 weeks	Clinical success
Ruggero et al. [12]	46	M	AIDS, chronic HBV, HTN, PTSD, tobacco and cocaine abuse, non-compliance	MRSA-associated vertebral osteomyelitis	1200 mg every 2 weeks × 4 doses, then 1200 mg 1 month later	Clinical success
Delaportas et al. [9]	49	F	Allergies to penicillins, cephalosporins, erythromycin	MSSA-associated right tibial osteomyelitis secondary to retained intramedullary nail	1200 mg once weekly × 6 weeks	Clinical success
Schulz et al. [11]	62	F	Autologous HSCT secondary to multiple myeloma	Decubitus ulcers and osteomyelitis with mixed skin flora	1200 mg × 1, then 800 mg once weekly × 4 weeks (concomitant with ertapenem)	Improvement noted but oritavancin discontinued due to anaemia and leukopenia. Ertapenem continued × 4 weeks
Schulz et al. [11]	31	F	IVDA, non-compliance	Osteomyelitis and septic arthritis with abscess	1200 mg × 1, then 800 mg once weekly × 7 weeks	Clinical success
Schulz et al. [11]	76	F	Anaphylaxis to β-lactam antibiotics	MSSA and *Klebsiella pneumoniae*-associated osteomyelitis	1200 mg twice per week	Improvement with oritavancin, then transitioned to doxycycline × 10 days

AIDS, acquired immunodeficiency syndrome; HBV, hepatitis B virus; HTN, hypertension; PTSD, post-traumatic stress disorder; HSCT, haematopoietic stem cell transplant; IVDA, intravenous drug abuse; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

oritavancin susceptibility with a predictive probability of 98.8% at a minimum inhibitory concentration (MIC) of ≤0.12 mg/L [20].

Use of vancomycin frequently requires one or more daily infusions, based on renal function, to achieve trough concentrations of 15–20 mg/L required for osteomyelitis [21,22]. However, evidence is lacking to support an association between vancomycin trough concentrations and clinical efficacy. Significant correlations between nephrotoxicity and supratherapeutic trough concentrations and doses ≥4 g/day have been reported. Dosing vancomycin appropriately in obese patients remains challenging as empirical dosing recommendations routinely lead to underdosing in patients with a BMI ≥ 30 kg/m^2 [23]. Whilst daptomycin, telavancin, ceftaroline and linezolid may serve as effective alternatives for osteomyelitis, each has limitations that may preclude their use [8]. Despite once-daily administration requirements, treatment with daptomycin may lead to elevated creatinine phosphokinase, myopathies or eosinophilic pneumonia, whereas higher rates of nephrotoxicity have been observed with telavancin compared with vancomycin. Prolonged use of ceftaroline or linezolid, beyond 14 days, is associated with the development of neutropenia and thrombocytopenia, respectively [8,24].

No clinical trial data are available for the use of oritavancin in osteomyelitis. However, pharmacokinetics and bone concentrations in rabbits administered 20 mg/kg oritavancin [human equivalent dose of 1200 mg based on 24-h area under the concentration–time curve (AUC_{0-24})] have been investigated [18]. Oritavancin was found to rapidly distribute to bone where concentrations remained above the *S. aureus* MIC_{90} until the end of the study period (7 days). Although the active fraction of oritavancin in bone remains unknown, bone penetration in this animal model, defined as the tissue-to-serum AUC_{0-168} ratio into bone matrix and bone marrow, was 1.7 and 3.1, respectively. These data provided the impetus for intermittent oritavancin dosing in patients with osteomyelitis. However, the majority of patients in the current series were successfully treated with at least two doses of oritavancin administered a median of 33.5 days (IQR 29.25–37.25 days) apart. Patient complexities and barriers in returning to the wound care clinic, coupled with medical non-compliance and insurance benefits verification, limited precision scheduling of oritavancin.

Compared with vancomycin for the treatment of acute bacterial skin and skin-structure infections in the SOLO 1 and SOLO 2 clinical trials, oritavancin displayed similar rates of AEs, including drug-related, severe and those leading to study drug discontinuation [25,26]. The most common AEs reported were nausea, vomiting, diarrhoea and headache. In the pooled SOLO data, osteomyelitis occurred in a greater percentage of patients receiving oritavancin (0.6%; 6/976) than those receiving vancomycin (0.1%; 1/983). The median time to osteomyelitis onset was 4.6 days in the oritavancin-treated patients compared with 2.6 days in vancomycin-treated patients, prompting the US Food and Drug Administration (FDA) to require the addition of a warning related to osteomyelitis in the package insert [25]. Notably, these events occurred within 9 days following administration of oritavancin, suggesting that osteomyelitis was pre-existing at study enrolment. Oritavancin was well tolerated and no treatment-emergent AEs were reported in the current study. Furthermore, epithelial closure was documented in all nine patients achieving clinical cure and remained re-epithelialised without the need for additional antibiotics, debridement or amputation through the 6-month follow up period (Fig. 2).

This study is limited by its retrospective design and small sample size from a single centre, which may limit its generalisability. Although many of the patients may have received prior antibiotic therapy, reporting of prior antibiotic therapy was limited by documentation in the EMR and patient recall. Prior or concomitant use of antibiotics with oritavancin hinders our ability to

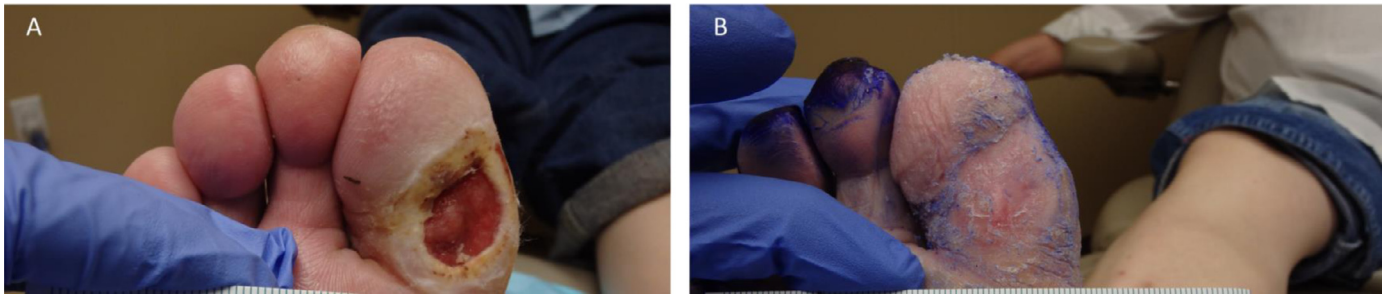

Fig. 2. Chronic osteomyelitis of the right great toe (A) at baseline and (B) with re-epithelialisation of the wound at 6-month follow-up.

conclude that the high rate of clinical success was due to oritavancin alone. In addition, inconsistencies in time between oritavancin doses prohibit our ability to identify the optimal dosing frequency. In this study, the patient with calcaneal osteomyelitis received six doses of oritavancin, and the two patients with lateral malleolus osteomyelitis each received four doses. Osteomyelitis of the calcaneus and lateral malleolus are complex infections characterised by frequent recurrence and delayed healing, often requiring prolonged treatment durations [27–29]. Notably, none of the patients included in this case series had post-traumatic or hardware-associated osteomyelitis. However, to our knowledge, this is the first reported case series evaluating the use of oritavancin for the treatment of chronic osteomyelitis.

5. Conclusion

Osteomyelitis remains a formidable foe in an era of increasing incidence of MRSA, with limited guidance for treatment optimisation. The success observed in the nine patients described here suggests that multidose oritavancin may prove advantageous for chronic osteomyelitis. Oritavancin was chosen due to its convenience as a single i.v. infusion, negating the need for indwelling i.v. access and frequent administration at an infusion centre or through home health services. Clinicians should consider multidose oritavancin for patients with chronic osteomyelitis as a safe and efficacious option when limited by patient complexities or barriers in their ability to access healthcare services. Further research is needed to define the optimal dose and frequency of oritavancin for the treatment of chronic osteomyelitis.

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Competing interests

None declared.

Ethical approval

This research was carried out in accordance with the Declaration of Helsinki.

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