



Clinical Studies

Dalbavancin for the management of gram-positive osteomyelitis: Effectiveness and potential utility☆



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ABSTRACT

Dalbavancin is approved by the US Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections. It has promising pharmacokinetic/pharmacodynamic profiles in treating bone infections and safety data after multiple weekly dosing. The primary objective of this study is to describe the effectiveness and tolerability of dalbavancin in the treatment of osteomyelitis in adults. This study is a multicenter retrospective review, designed to identify patients with osteomyelitis who were treated with dalbavancin. Thirty-six patients with confirmed diagnosis of osteomyelitis who received dalbavancin were identified. Thirty-one patients met inclusion criteria for evaluation of clinical success at the end of the antibiotic course and 3 months after the completion of therapy. Twenty-eight (90%) patients achieved clinical success and there were no adverse events noted. Dalbavancin appears to be safe and effective in the treatment of osteomyelitis. More studies are needed to validate these findings.

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1. Introduction

Osteomyelitis is an inflammatory process characterized by a progressive destruction of the bone due to infecting pathogenic microbial organisms and considered one of the most challenging to treat infectious diseases (Lew and Waldvogel, 2004). In adults, *Staphylococcus aureus* (*S. aureus*) is the most commonly isolated organism in osteomyelitis, while incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased in the past several decades (Hatzenbuehler and Pulling, 2011; Lew and Waldvogel, 2004; Zimmerli, 2010).

Six weeks of parenteral antimicrobial therapy is the standard pharmacological approach for the treatment of osteomyelitis caused by gram-positive organisms (Spellberg and Lipsky, 2012; Zimmerli, 2010).

Removal of necrotic bone through surgical debridement, particularly in chronic osteomyelitis, is necessary to achieve the clinical cure (Hatzenbuehler and Pulling, 2011; Lew and Waldvogel, 2004; Liu et al., 2011; Spellberg and Lipsky, 2012; Zimmerli, 2010). Intravenous vancomycin has been the standard antimicrobial agent for the treatment of osteomyelitis caused by MRSA and daptomycin is an alternative option (Berbari et al., 2015; Liu et al., 2011; Spellberg and Lipsky, 2012; Zimmerli, 2010). Nafcillin, oxacillin and cefazolin are the primary treatment options for the management of osteomyelitis caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) (Berbari et al., 2015; Hatzenbuehler and Pulling, 2011; Zimmerli, 2010). However, drug allergy, intolerance, elevated minimum inhibitory concentrations (MICs), antimicrobial resistance, infection relapse, and persistence of the infection leading to clinical or microbiological failure, all can limit treatment options. Further, central-line placement for long-term daily antibiotic administration in outpatient settings is not always feasible due to intravenous drug abuse (IVDA) status or central intravenous access complications such as venous thrombosis and central line-associated infections, which may result in increased duration and cost of hospital stay.

Dalbavancin is a lipoglycopeptide, indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following gram-positive microorganisms: *S. aureus* (both MSSA and MRSA), *Streptococcus pyogenes*, *Streptococcus*

☆ No conflict.

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agalactiae, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group and vancomycin-susceptible *Enterococcus faecalis* (Dalvance, 2014). The recommended dose for this indication is 1500 mg administered as a single dose or 1000 mg followed by 500 mg 1 week later, given as intravenous infusion over 30 minutes (Dalvance, 2014). Dalbavancin demonstrated potent activity against several gram-positive microorganisms in an antimicrobial surveillance program, high bone penetration in animal and phase I clinical trials, long half-life allowing once weekly dosing, and favorable safety profile when administered weekly for up to 8 weeks (Dunne et al., 2015; Jones et al., 2013; Solon et al., 2007). The pharmacokinetic/pharmacodynamic profiles and safety data after multiple weekly dosing are promising that dalbavancin may play a fundamental role in the treatment of osteomyelitis. Given the need for long-term antibiotic therapy in osteomyelitis and the once weekly dosing administration interval of dalbavancin, cost-saving opportunities exist through shortening the duration of hospitalization or even more, by preventing hospital admission. We report, to the best of our knowledge, the first descriptive study on the use of dalbavancin in the treatment of osteomyelitis. The primary objective is to describe the effectiveness and tolerability of dalbavancin infusion in the treatment of osteomyelitis. The impact of dalbavancin on the duration of hospitalization and the projected cost-savings are also highlighted.

2. Methods

2.1. Study design, participating sites, and patient eligibility

This study was a multicenter retrospective review, designed to identify cases of osteomyelitis that were treated, at least in part, with dalbavancin from January 1, 2015 to January 31, 2018 at three different sites: Hendrick Medical Center in Abilene, Texas; Deaconess Hospital in Spokane, Washington; and The University of North Carolina at Chapel Hill. The study was approved by the institutional review boards at the participating centers. Patients ≥ 18 years of age with confirmed osteomyelitis due to gram-positive pathogens who were treated with at least one dose of dalbavancin were included in this study. Patients were also included if dalbavancin was used later in the disease course to complete the course of therapy. Clinical, laboratory, and microbiological findings were used to aid in the diagnosis of osteomyelitis which was confirmed by imaging studies (Table 1). Patients were excluded if lost to follow-up or if the available data were insufficient to evaluate the clinical outcome. Patients were evaluated at the start of therapy, while being treated, at the end of therapy, and for at least 3 months after the completion of the antibiotic course.

2.2. Data collection

For this descriptive study, several variables were collected which include: age, gender, ethnicity, comorbid conditions, type of osteomyelitis (acute or chronic), site of infection, source of infection, etiologic pathogen, specimen source for culture, presence of bacteremia, type of imaging study used for diagnosis, pertinent laboratory data at diagnosis and end of therapy, reason dalbavancin was used, number of disease episodes, initial therapies used and durations, setting (inpatient or outpatient), dosages and durations of dalbavancin therapy, concomitant antibiotics, clinical outcome at the end of therapy and at follow-up visit, adverse events, long term suppressive therapy, and surgical intervention.

2.3. Study outcomes, definitions, and evaluation

The primary efficacy outcome is the clinical success at the end of treatment which is defined as the resolution of signs and symptoms attributable to the infection per assessment by treating clinicians, and no requirement for repeat surgical intervention or alteration of dalbavancin therapy. Secondary efficacy outcome is the continuous absence of clinical

Table 1
Demographics and clinical characteristics.

Variable	No./% (n = 31)
Demographic data	
Age, mean (SD)	50 (14)
Male gender	23 (74)
Caucasian	23 (74)
Hispanic	8 (26)
African American	0 (0)
Comorbidities	
Diabetes	10 (32)
IVDU	10 (32)
Current smoker	8 (26)
Previous osteomyelitis at same site	5 (16)
Hepatitis/cirrhosis	4 (13)
Orthopedic hardware	4 (13)
Alcoholism	3 (10)
Hypertension	2 (6)
Peripheral neuropathy	2 (6)
Chronic renal disease	1 (3)
Current immunosuppressive therapy	1 (3)
Coronary artery disease	0 (0)
Peripheral arterial disease	0 (0)
Active malignancy	0 (0)
Source of infection	
Contiguous	18 (58)
Hematogenous	10 (32)
Unknown	3 (10)
Site of infection	
Vertebrae	14 (45)
Foot	9 (29)
Other sites ^a	8 (26)
Duration of illness^b	
Acute	26 (84)
Chronic	5 (16)
Pertinent laboratory data at diagnosis (Median)	
WBC (cells/mm ³), Median (IQR)	18 (9.3)
CRP (mg/dl), Median (IQR)	12 (9.8)
ESR (mm/h), Median (IQR)	90 (28)
Concomitant bacteremia	10 (32)
Causative pathogen	
MRSA	15 (48)
MSSA	12 (39)
Mixed gram-positive	2 (6)
Other ^c	4 (13)
Site of positive culture	
Bone tissue/fluid/abscess	18 (58)
Blood	10 (32)
Wound	10 (32)
Diagnostic image	
MRI	24 (77)
CT scan	11 (35)
X-ray	1 (3)
Gallium scan	1 (3)

CRP = C-reactive protein; CT scan = computed tomography scan; ESR = erythrocyte sedimentation rate; IQR = interquartile range; IVDU = intravenous drug user; MRI = magnetic resonance image; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; SD = standard deviation; WBC = white blood cell count.

^a This includes: medial clavicle, ischial tuberosity, left elbow, right knee, left ischial, right wrist, left ankle, bellow knee amputation stump, left thumb distal phalanx and left thumb middle phalanx.

^b Acute osteomyelitis developed within days to weeks after disease onset while chronic osteomyelitis developed within months.

^c This includes: *Staphylococcus saccharolyticus*, culture negative, and unknown pathogen.

manifestations attributable to the infection at 3 months after the completion of therapy and lack for the need of additional antibiotic, debridement, or surgical intervention during this time frame. Improvement of laboratory values was evaluated by treating clinicians in the context of clinical status of the patients. Safety outcome includes the absence of adverse events attributable to dalbavancin with specific focus on alanine aminotransferase, renal function, hematologic abnormalities, nausea, vomiting, headache, diarrhea, rash, and pruritus. To be reported in this study as

dalbavancin-related, adverse events had to be clearly documented in medical records as attributable to dalbavancin at the discretion of the treating clinicians. For the impact of dalbavancin on the duration of hospitalization due to osteomyelitis treatment, the decrease in the length of hospital stay (LOS) was calculated by subtracting the actual LOS from the estimated total LOS. We define actual LOS as the duration between the first day of the appropriate antibiotic therapy and the day of hospital discharge. Estimated total LOS is 42 days from starting the appropriate antibiotic therapy unless otherwise specified by treating clinicians. Projected cost saving was calculated by subtracting the actual cost of the administered dalbavancin therapy from what would have been spent administering equal duration with standard of care therapy in inpatient setting.

3. Results

Thirty-six patients with confirmed diagnosis of osteomyelitis who were treated with dalbavancin were identified; however, only 31 patients were eligible for inclusion. Three patients were excluded due to loss to follow-up while two were excluded due to insufficient data available in the medical record. Demographics, comorbidities, anatomical site of infection, diagnostic data, and other baseline characteristics are listed in Table 1.

Dalbavancin regimens including the dose, dosing interval, and treatment duration varied across patients (Table 2). Dalbavancin was initiated in an inpatient setting for 26 (84%) patients. In addition, 26 (84%) patients received antimicrobial therapy prior to receipt of dalbavancin. The median duration of antibiotic therapy prior to dalbavancin was 20 days and ranged from 2 to 55 days. Number of dalbavancin doses varied from a single dose to 14 doses (Median = 3; IQR = 3) based on the rate of improvement, the duration of therapy remaining at the initiation of dalbavancin, success of initial therapy prior to dalbavancin, anatomical site of infection, and ability to achieve adequate source control. Dalbavancin doses ranged from 500 to 1500 mg per dose. Oral long-term suppressive therapy after the dalbavancin course of treatment was given to 3 (10%) patients. The most common indications for dalbavancin were to reduce length of hospital stay while obviating the need for peripherally-inserted central catheter (PICC) line placement due to concerns for PICC-related complications or IVDA status, treatment failure to primary antimicrobial agents, and due to lower cost for patients who are under- or uninsured who have limited funding for post-hospital care. Antibiotics used and durations prior to dalbavancin, concomitant antibiotics, and performed surgical procedures are listed in Table 2.

There was no adverse event noted or required treatment discontinuation during dalbavancin therapy in any of the regimens. The primary efficacy outcome was achieved in 28 (90%) patients and all these patients subsequently attained the secondary efficacy outcome. At the end of therapy, median (IQR) for WBC (cells/mm³), CRP (mg/dl), and ESR (mm/h) were 6.6 (5), 1.3 (1.7), and 29 (27), respectively. Dalbavancin prevented the admission of 5 patients who received the entire course of therapy in outpatient setting. The remaining 26 patients were hospitalized and received the first dose of dalbavancin at discharge and continued subsequent weekly doses, if needed, in the outpatient setting. Considering 26 hospitalized patients, the mean reduction in LOS was 28 ± 10 days per patient with a total reduction of 735 days. Patient specific data and treatment outcomes are listed in Table 2.

4. Discussion

In this multicenter study, for 31 patients with osteomyelitis treated, at least in part, with dalbavancin, the long-acting lipoglycopeptide appeared to be effective and well tolerated. It should be noted, however, that different treatment regimens were used. Various anatomical sites of infection are reported in this study with vertebral osteomyelitis being the most common. While the failure rates of patients treated with other antibiotics for vertebral osteomyelitis have been previously reported between 10% to 30%, all patients with vertebral osteomyelitis in this study achieved

clinical success (Berbari et al., 2015). In contrast, the three patients who failed to achieve clinical success at end of therapy had foot infections and eventually required amputation. Comorbidities that might have been associated with treatment failure included poorly controlled diabetes mellitus, IVDA status, hepatitis, and chronic osteomyelitis.

Given its long half-life and weekly dosing administration interval, dalbavancin can provide cost-saving opportunities through a decrease in LOS, particularly, in patients where central-line placement for long-term daily antibiotic administration in outpatient settings is not feasible or should be avoided, and in patients who are under- or uninsured with limited funding for extended care facility, home health care, and medical equipment. For the treatment of osteomyelitis, the inpatient care including broad-spectrum parenteral antibiotics, laboratory tests, and basic nursing care costs approximately \$1200 per day (2015 US dollars) (Odom et al., 2016). Dalbavancin costs \$1841.64 per 500 mg vial (Dalbavancin, n.d.). In this study, total LOS for 26 hospitalized patients can be decreased by 735 days with a total cost reduction of \$882,000 while 126 vials of dalbavancin 500 mg were used with a total cost of \$232,046. Therefore, the estimated total cost-savings for 26 patients are \$649,954. Noteworthy, the average cost per inpatient day is higher in all the three states; therefore, the total cost-saving might have been underestimated (Kaiser State Health, n.d.). On the other hand, with the assumption that all patients should be hospitalized for the entire estimated LOS, cost savings could have been overestimated. However, this is applicable to patients who need to be hospitalized for longer periods than necessary due to being under- or uninsured with limited funding for post-hospital care as well as when central-line placement is not feasible or should be avoided for long-term antibiotic administration in outpatient settings. These represent the condition for most of our patients in this study.

Very limited therapeutic options are currently available for the treatment of osteomyelitis caused by *S. aureus*, the most common causative pathogen in this infection. Intravenous penicillinase-resistant penicillins and first-generation cephalosporins are the standards of care for the treatment of osteomyelitis caused by MSSA whereas intravenous vancomycin and alternatively, daptomycin are the primary agents for the management of osteomyelitis caused by MRSA (Berbari et al., 2015; Hatzenbuehler and Pulling, 2011; Liu et al., 2011; Spellberg and Lipsky, 2012; Zimmerli, 2010). Linezolid can achieve adequate bone concentration which exceeds the MICs of most gram-positive cocci with successful clinical outcomes reported in case reports and case series (Falagas et al., 2007). However, it is a bacteriostatic and the adverse effects such as bone marrow suppression, peripheral neuropathy, and optic neuritis are worrisome with prolonged duration of treatment which may limit its role in this infection. Ceftaroline and tigecycline have a spectrum of activity to cover *S. aureus*, both MSSA and MRSA; however, the clinical data for the safety and effectiveness of prolonged courses of these agents to treat osteomyelitis are limited (Griffin et al., 2013; Lalikian et al., 2017). Unfortunately, several factors may further limit the treatment options which include drug allergy, intolerance, elevated MICs, antimicrobial resistance, infection relapse, and persistence of the infection leading to clinical or microbiological failure.

Dalbavancin has several advantages to be considered in the management of osteomyelitis caused by *S. aureus*. In an antimicrobial surveillance program, dalbavancin MIC₉₀ against *S. aureus* was 0.06 µg/ml compared with 0.5 µg/ml for daptomycin and 1 µg/ml for vancomycin. Therefore, dalbavancin has 8 and 16-fold more potent activity against *S. aureus* compared to daptomycin and vancomycin, respectively (Jones et al., 2013). Additionally, in a phase I dalbavancin bone penetration study, the mean non-infected cortical bone to plasma area under the curve penetration ratio was 13.1% which is higher than the mean ratio of vancomycin previously reported at 7% (Dunne et al., 2015; Graziani et al., 1988). The bone concentration after a single 1000 mg dose of dalbavancin was 6.3 µg/g which remained high at 4.1 µg/g after 14 days (Dunne et al., 2015). Moreover, it has long terminal half-life of 14.4 days which provides more convenient (weekly) dosing administration, optimizes medication

Table 2
Patient specific data and treatment outcomes for 31 patients on dalbavancin therapy.

Patient (n = 31)	Organism	Site of infection	Surgical procedure	Initial therapy preceding dalbavancin	Subsequent dalbavancin regimen	Concomitant antibiotics	Primary outcome reached	Secondary outcome reached	AE	LOS (d)
1	MSSA	Right 4th MTP OM with abscess	R MTP 4th toe I and D	None	1500 mg weekly × 2	None	Yes	Yes	None	41
2	MRSA	Left BKA stump	None	None	1500 mg weekly × 2	None	Yes	Yes	None	41
3	MRSA; GGS	Right 4th toe	Debridement	Vancomycin + P/T day 1–3	1500 mg weekly × 2	None	Yes	Yes	None	39
4	MRSA	Left thumb distal and middle phalanges	I and D	Vancomycin + P/T day 1–2	1500 mg weekly × 2	None	Yes	Yes	None	40
5	Culture negative	T12–L2 and L4–5; HW infection	Debridement; HW removal	Vancomycin + Rifampin day 1–40	1500 mg weekly × 2	Ciprofloxacin + Rifampin	Yes	Yes	None	30
6	Culture negative	T9–10	Debridement	Daptomycin + ertapenem day 1–4	1500 mg weekly × 2	Levofloxacin	Yes	Yes	None	38
7	Unknown	Cervical vertebra	Debridement; washout; HW replaced	None	1500 mg weekly × 2 All given OP	Ertapenem	Yes	Yes	None	PA
8	MRSA	L4–5	Debridement; L3–S1 fusion	Daptomycin day 1–24	1000 mg × 1 followed 1 week later by 500 mg weekly × 1	Rifampin	Yes	Yes ^a	None	18
9	MSSA	T11–12	Debridement; abscess drainage; T11–12 laminectomy	Cefazolin + Rifampin day 1–39	1000 mg × 1 followed 1 week later by 500 mg weekly × 2	None	Yes	Yes	None	21
10	MRSA	Toe	Debridement	Vancomycin day 1–20	1000 mg × 1 followed 1 week later by 500 mg weekly × 2	None	Yes	Yes (at 1 month)	None	22
11	MSSA	L4 to S3 epidural abscess; diskitis OM (L5–S1)	Debridement; hemilaminectomy	Vancomycin + meropenem day 1–2; Oxacillin day 3–26	1000 mg × 1 followed 1 week later by 500 mg weekly × 3	None	Yes	Yes	None	30
12	MRSA	Left ankle with abscess	Toes to TMA to BKA to AKA – bilaterally	Daptomycin day 1–14	1000 mg × 1 followed 1 week later by 500 mg weekly × 3	None	No (bilateral AKA)	N/A	None	28
13	MSSA	Left 2nd and 3rd metatarsal bones	Debridement	Daptomycin day 1–21 ^b	1000 mg × 1 followed 1 week later by 500 mg weekly × 3	None	Yes	Yes	None	28
14	MSSA	Septic sacroiliac joint with OM	Debridement	Vancomycin day 1–2; Cefazolin day 3–15	1000 mg × 1 followed 1 week later by 500 mg weekly × 4	None	Yes	Yes	None	34
15	MSSA	L1–2 and L5–S1; left paraspinal myositis/OM	None	Vancomycin day 1–3; Cefazoline day 3–6	1000 mg × 1 followed 1 week later by 500 mg weekly × 4	None	Yes	Yes	None	36
16	MRSA	L2–3	Debridement	Vancomycin day 1–20	1000 mg × 1 followed 1 week later by 500 mg weekly × 4	None	Yes	Yes	None	36
17	MRSA	Left elbow	HW removal	Vancomycin + Rifampin day 1–6	1000 mg × 1 followed 1 week later by 500 mg weekly × 4	Rifampin	Yes	Yes	None	36
18	MSSA	Right knee	Debridement	None	1000 mg × 1 followed 1 week later by 500 mg weekly × 5 All given OP	None	Yes	Yes	None	PA

19	MRSA	L3–4	Debridement; laminectomy	Daptomycin failure	1000 mg × 1 followed 1 week later by 500 mg weekly × 6 All given OP	None	Yes	Yes	None	PA
20	MSSA	L1–2 and T12	None	Vancomycin and Daptomycin failure ^b	1000 mg × 1 followed 1 week later by 500 mg weekly × 10 All given OP	Rifampin	Yes	Yes	None	PA
21	MRSA	left ischial OM	Debridement	None	1000 mg × 1 followed 1 week later by 500 mg weekly × 13 All given OP	None	Yes	Yes	None	PA
22	MSSA	T12–L1	Laminectomy; irrigation; HW placed	Vancomycin + P/T day 1–2; Cefazolin day 3–7	1000 mg × 2 followed 1 week later by 500 mg weekly × 3	Rifampin	Yes	Yes	None	35
23	MSSS	Right knee	HW replacement	Cefazolin day 1–24	1500 mg × 1 followed 2 weeks later by 500 mg weekly × 1	None	Yes	Yes	None	18
24	MRSA	Left 1st MTP and 1st proximal phalanx OM	None	Linezolid + P/T day 1–7	1500 mg × 1 followed 2 weeks later by 500 mg weekly × 2	None	No (BKA)	N/A	None	35
25	MSSA	Right wrist septic joint/OM	Debridement; abscess drainage	Vancomycin + Rifampin day 1–8	1500 mg × 1 followed 2 weeks later by 500 mg weekly × 3	Rifampin	Yes	Yes	None	34
26	MRSA; GAS; CoNS	Right mid and hindfoot	Debridement	Vancomycin day 1–12; Daptomycin day 12–32	1500 mg × 1	None	Yes	Yes	None	10
27	MRSA; anaerobic GNR	Left foot	No	Vancomycin day 1–26	1500 mg × 1	Oral metronidazole	Yes	Yes	None	16
28	MSSA	T11 OM with paraspinal abscess	Abscess drainage	Vancomycin day 1–3; Oxacillin day 4–16; Cefazolin day 17–34	1500 mg × 1	None	Yes	Yes ^c	None	8
29	MRSA	Right foot	None	Vancomycin day 1–28	1500 mg × 1	None	No (TMA)	N/A	None	14
30	MRSA	C4–5	Abscess drainage	Vancomycin 1–55	1500 mg × 1	None	Yes	Yes	None	15
31	MSSA	Medial clavicle OM	Debridement	Vancomycin + ceftriaxone day 1–2; Cefazolin day 3–10	1500 mg × 1	None	Yes ^d	Yes ^e	None	32

AE = adverse events; AKA = above-knee amputation; BKA = below-knee amputation; C = cervical spine; CoNS = Coagulase-negative staphylococcus; d = days; GAS = group A streptococcus; GGS = group G streptococcus; GNR = gram-negative rods; HW = hardware; I and D = incision and drainage; LOS = length of stay; MSSA = methicillin-susceptible *Staphylococcus aureus*; MSSS = methicillin-susceptible *Staphylococcus saccharolyticus*; MRSA = methicillin-resistant *Staphylococcus aureus*; L = lumbar spine; MTP = metatarsophalangeal; N/A = not applicable; OM = osteomyelitis; OP = outpatient; PA = prevented admission; P/T = piperacillin-tazobactam; S = sacral spine; T = thoracic spine; TMA = transmetatarsal amputation.

^a This is a second course of dalbavancin. Patient failed previous course of antibiotics including dalbavancin most likely due to the lack of debridement which was performed later before the second course of antibiotic therapy.

^b Penicillin allergic patients.

^c This is a 5-month follow-up evaluation from the end of therapy.

^d Plan was 1000 mg × 1 followed 1 week later by 500 mg weekly × 4. Patient received 1000 mg dose at discharge and never returned for subsequent doses. Patient did have wound closure 1 month from original debridement, surgeon noted 5 cm wound, good granulation and no erythema in surrounding area.

^e This is a 6-month follow-up evaluation from the single dalbavancin dose.

adherence, eliminates the need for prolonged central intravenous access and its potential complications, and becomes an alternative option when central-line placement is not feasible or should be avoided for long-term antibiotic administration in outpatient settings (Dunne et al., 2015). In contrast to vancomycin, dalbavancin does not require routine monitoring for serum drug concentration (Agarwal et al., 2017; Dunne et al., 2015). Further, in a safety, tolerability and pharmacokinetic phase I study, dalbavancin is safe and tolerable after a 1000 mg loading dose followed by 500 mg for 7 additional weekly doses with no apparent drug accumulation (Dunne et al., 2015).

A single case report is available for the use of dalbavancin in the treatment osteomyelitis (lumbar osteomyelitis) and showed that 8 weeks of dalbavancin was initially effective to clear the infection; however, it did not appear to prevent infection recurrence 3 months after the last dose (Almangour et al., 2017). The authors concluded that this recurrence was more likely a reinfection with a new strain of MRSA than a relapse. In this case, no adverse events were observed. More recently, safety and tolerability of dalbavancin in the treatment of different gram-positive infections have been described, among which, 12 patients were treated for osteomyelitis. Comparable to our results, clinical success was achieved in 91.7% of patients (Bouza et al., 2018). No clinical trial data is available for the use of dalbavancin in the management of osteomyelitis; however, a phase II clinical trial is currently ongoing (Clinicaltrials.gov, n.d.).

Major limitations of this study are the lack of comparison group, the retrospective non-randomized nature of the design, as well as the inclusion of various dalbavancin dosing regimens, duration of initial antibiotics preceding dalbavancin, and anatomical sites of infections. Standard antibiotics were given prior to the receipt of dalbavancin with a median duration of 20 days which may bias the reported therapeutic outcome. Additionally, the retrospective nature of safety outcome reporting and the fact that adverse events had to be defined in the medical record as attributable to the drug make under-reporting highly likely. These factors may limit the precision of the given conclusion. However, it includes 3 medical centers with large sample size and it is the first to report the potential utility of dalbavancin in patients with osteomyelitis with well-described study population, intervention, and follow up.

While awaiting the results from the ongoing phase II randomized controlled trial, 2-arm observational studies are needed to further assess the safety and effectiveness of dalbavancin compared to standard of care antibiotics usually employed in treating osteomyelitis and identifying the optimal dalbavancin dosing regimen for the treatment of bone infections.

5. Conclusion

In the present multicenter study, dalbavancin appears to be safe and effective in the treatment of osteomyelitis, provides cost-saving opportunities by shortening LOS, and allows for more convenient dosing administration for long-term antibiotic therapy in outpatient setting. Further evidence is needed to validate these findings.

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