Original article

Dalbavancin versus standard of care for the treatment of osteomyelitis in adults: A retrospective matched cohort study

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ABSTRACT

Objective: To assess the safety and effectiveness of dalbavancin compared to standard of care (SOC) in the treatment of osteomyelitis in adults.

Method: A retrospective cohort study of patients with osteomyelitis due to S. aureus treated with dalbavancin was conducted. Patients who received at least 2 doses of dalbavancin for the treatment of osteomyelitis between January 1, 2015 to January 31, 2018 in a single center in Texas, USA were identified and matched in 1:1 ratio with controls who received SOC. The primary efficacy outcome was the clinical success at the end of treatment. Secondary efficacy outcome was the clinical success continued for at least 3 months after the completion of the antimicrobial therapy.

Results: During study period, 21 patients received dalbavancin for the treatment of osteomyelitis; however, only 11 patients were eligible for inclusion and matched to 11 others who received SOC. Primary outcome was achieved in all 11 patients who received dalbavancin and all those patients subsequently attained the secondary outcome. In SOC group, primary outcome occurred in 82% (9/11) of patients in which 8 out of 9 patients subsequently achieved the secondary outcome. No adverse reaction noted in either group.

Conclusion: Dalbavancin appears to be safe and effective for the management of osteomyelitis in adults. Further studies are needed to confirm these findings.

1. Introduction

Osteomyelitis is a local inflammatory reaction characterized by a progressive destruction of the bone caused by pyogenic organisms and considered one of the most challenging to treat infectious diseases. It can be acute or chronic and can develop as a result of hematogenous seeding, contiguous spread with or without vascular insufficiency, or direct inoculation of the organism to the bone (Fritz & McDonald, 2008; Spellberg & Lipsky, 2012). Gram-positive bacteria are the predominant etiologic pathogens in osteomyelitis with *Staphylococcus aureus* (*S. aureus*) being the most commonly identified (Darley & MacGowan, 2004; Hatzenbuehler & Pulling, 2011).

To achieve acceptable rate of cure, 6 weeks of parenteral or oral antimicrobial therapy is recommended for the management of osteomyelitis caused by gram-positive microorganisms (Berbari et al., 2015; Carek, Dickerson, & Sack, 2001; Li et al., 2019; Spellberg & Lipsky, 2012). For osteomyelitis caused by methicillin-susceptible *S. aureus* (MSSA), penicillinase-resistant penicillins or cefazolin are the standard antimicrobial treatment options whereas intravenous vancomycin and alternatively daptomycin are recommended first for osteomyelitis caused by methicillin-resistant *S. aureus* (MRSA) (Berbari et al., 2015; Zimmerli, 2010). The applicability of these options, however, may be limited by several factors including drug allergy, adverse reactions, elevated minimum inhibitory concentrations (MIC), antimicrobial resistance, infection relapse, and treatment failure. Hence, there is a substantial need to explore the effectiveness and safety of other antimicrobial options to treat osteomyelitis caused by *S. aureus*.

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Dalbavancin is a semisynthetic lipoglycopeptide, approved by the US Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by certain susceptible gram-positive organisms including MSSA and MRSA ("Dalvance [package insert]. Parsippany, NJ: Durata Therapeutics; 2014,"). Dalbavancin is bactericidal *in vitro* against *S. aureus* primarily through the inhibition of bacterial cell wall biosynthesis (Dunne et al., 2015) For ABSSSI, the recommended dalbavancin dosage regimen is 1500 mg given intravenously as a single dose or as 1000 mg followed 1 week later by 500 mg to be administered over 30 min infusion ("Dalvance [package insert]. Parsippany, NJ: Durata Therapeutics; 2014,"). Dalbavancin showed high bone concentrations in animal and phase I clinical trials, has long half-life allowing for weekly dosing interval, potent activity against several gram-positive organisms, and favorable safety profile after multiple weekly dosing for up to 8 weeks (Dunne et al., 2015; Jones, Sader, & Flamm, 2013; Solon, Dowell, Lee, King, & Damle, 2007). These factors emphasize the need to explore the potential utility and clinical effectiveness of dalbavancin in the management of osteomyelitis. We report here, to best of our knowledge, the first observational study of dalbavancin compared to the standard of care (SOC) for the treatment of osteomyelitis caused by *S. aureus*.

2. Method

A retrospective cohort study of patients with osteomyelitis due to *S. aureus* treated with dalbavancin was conducted. Patients who received at least 2 doses of dalbavancin for the treatment of osteomyelitis between January 1, 2015 to January 31, 2018 in a single center in Texas, USA were identified. Our initial search included all patients who received dalbavancin then the records were searched to identify only those who received dalbavancin for the treatment of osteomyelitis caused by *S. aureus*. Clinical, microbiologic, and laboratory findings should be supported by imaging studies to confirm the diagnosis of osteomyelitis. Patients ≥ 18 years of age with osteomyelitis due to *S. aureus* who received at least 2 doses of dalbavancin, and who were evaluated for clinical outcome at end of therapy and after at least 3 months following the completion of the treatment course were included. Patients were excluded if they received more than 7 days of empiric or SOC targeted therapy before the initiation of dalbavancin. Patients were also excluded if they received only one dose of dalbavancin or if they did not undergo evaluation for clinical outcome at end of treatment or after at least 3 months following the completion of the treatment course.

Once dalbavancin cohort was identified, record was searched for patients with osteomyelitis due to *S. aureus* who received SOC therapy. For MSSA, the SOC therapy is nafcillin, oxacillin, or cefazolin. For MRSA, the SOC therapy is vancomycin or daptomycin. To be eligible for inclusion, patient with osteomyelitis due to *S. aureus* should have received the SOC therapy for at least 2 weeks and underwent clinical evaluation at end of therapy and after at least 3 months following the completion of the treatment course. Once identified, patients who received SOC were matched in 1:1 ratio to patients in dalbavancin group. Patients were matched according to the phenotypic susceptibility pattern of *S. aureus* (MSSA versus MRSA), presence of previous osteomyelitis, diabetes mellitus, documented peripheral vascular diseases, surgical intervention including debridement, incision and drainage, and amputation for this episode of osteomyelitis, as well as involvement of orthopedic hardware.

The primary efficacy outcome was the clinical success at the end of treatment. Secondary efficacy outcome was the clinical success continued for at least 3 months after the completion of the

antimicrobial therapy. Clinical success is defined as the absence of signs and symptoms associated with the infection per evaluation by treating clinicians. Also, it should not include the need of additional debridement, surgical interventions, alteration of the initial antimicrobial therapy, or repetitive courses of therapy during the follow-up period. Follow-up assessments also include adverse reactions of dalbavancin. To report any adverse reaction in this study, it had to be clearly documented in the medical records at the discretion of treating clinicians as attributable to the antibiotic used.

For statistical analysis, we used chi-square test to compare categorical variables and the Student *t*-test for continuous variables. Due to the limited number of patients who were treated with dalbavancin for osteomyelitis, no power calculation was conducted. The study was approved by the institution review board.

3. Results

During study period from January 1, 2015 to January 31, 2018, 21 patients received dalbavancin for the treatment of osteomyelitis; however, only 11 patients were eligible for inclusion. Seven patients were excluded as they either received single dose of dalbavancin or >7 days of empiric or SOC targeted therapy before the initiation of dalbavancin. Three more patients were excluded due to the inability to find appropriate matched controls. Those 11 eligible patients were matched to 11 others who received SOC for the treatment of osteomyelitis. Characteristics of all eligible patients are listed in Table 1. All osteomyelitis cases in both groups were classified as acute. In dalbavancin group, hematogenous spread was the source of infection in 2 patients while the rest were contiguous. In SOC group, all infections were from contiguous sources. Total dalbavancin dose for the entire course of treatment ranging between 3 and 7.5 g with median [interquartile range (IQR)] of 3 (0.5) gram. The most commonly used regimen was two 1500-mg administered intravenously one week apart (5 cases). One patient received a single 1500-mg followed 2 weeks later by 500 mg weekly for 3 weeks. The rest of patients received a dose of 1000-mg followed a week later by 500-mg weekly for 4 weeks (2 patients), 5 weeks (1 patient), 10 weeks (1 patient), and 13 weeks (1 patient). In SOC group, patients received either vancomycin or daptomycin for MRSA and cefazolin for MSSA infections. In this group, the mean and median (IQR) duration of therapy were 44 and 42 (5) days, respectively. In dalbavancin group, the mean and median (IQR) duration of empiric therapy before the initiation of dalbavancin were 2.5 and 2 (5) days, respectively. In SOC group, mean and median (IQR) to appropriate targeted therapy for MSSA were 4.8 and 5 (2.5) days, respectively. The mean doses of

Table 1
Characteristics of eligible patients.

	Dalbavancin-treated group (n = 11) % (n/N)	SOC-treated group (n = 11) % (n/N)	P-value
Mean age (years)	50.8	53.9	0.664
Mean weight (kg)	95	98.8	0.726
Gender (male)	81.8 (9/11)	72.7 (8/11)	0.611
MSSA	45.5 (5/11)	45.5 (5/11)	MC
DM	45.5 (5/11)	45.5 (5/11)	MC
Surgical intervention	81.8 (9/11)	81.8 (9/11)	MC
PVD	0 (0/11)	0 (0/11)	MC
Orthopedic hardware	18 (2/11)	18 (2/11)	MC
Previous osteomyelitis	9 (1/11)	9 (1/11)	MC

DM = diabetes mellitus; KG = kilogram; MC = matching criteria; MSSA = methicillin-susceptible *Staphylococcus aureus*; PVD = peripheral vascular disease; SOC = standard of care.

vancomycin and daptomycin were 22.3 mg/kg/day and 7.3 mg/kg/day, respectively. The mean dose of cefazolin was 5.4 g/day. The mean vancomycin trough was 16 mg/dl. Foot was the most common site of osteomyelitis in SOC group (7 patients) while the rest were tibia, knee, hip, and shoulder, one patient each. Table 2 provides specific information about each dalbavancin-treated patient.

Primary outcome was achieved in all 11 patients who received dalbavancin and all those patients subsequently attained the secondary outcome. In SOC group, primary outcome occurred in 82% (9/11) of patients in which 8 out of 9 patients subsequently achieved the secondary outcome. No significant difference was shown between the two groups in primary outcome (p = 0.138) and secondary outcome (p = 0.062). No adverse events were noted or required treatment discontinuation in both groups.

4. Discussion

In this retrospective analysis of 11 patients treated with dalbavancin for osteomyelitis compared with matched controls treated with SOC therapies, more patients achieved clinical success at end of therapy and at 3 months follow-up in dalbavancin group compared to SOC group; however, the difference is not statistically significant. No adverse events noted in both groups. The most commonly used dalbavancin regimen was two 1500-mg intravenous infusions given 1 week apart. This two-dose regimen can result in dalbavancin exposure that exceeds $MIC_{99.9}$ of 0.12 μg/ml for S. aureus for 8 weeks and can achieve area under the curve (AUC) similar to that of 1 g followed by 500 mg weekly for 4 additional weeks (Dunne et al., 2015).

S. aureus remains the most common etiologic pathogen in osteomyelitis (Carek et al., 2001; Lew & Waldvogel, 2004; Zimmerli, 2010). There are few options currently available to treat osteomyelitis caused by this pathogen. Nafcillin, oxacillin, and cefazolin are the SOC for the management of osteomyelitis caused by MSSA while intravenous vancomycin and alternatively daptomycin are the first line options currently used for the management of osteomyelitis caused by MRSA (Berbari et al., 2015; Hatzenbuehler & Pulling, 2011; Liu et al., 2011; Spellberg & Lipsky, 2012; Zimmerli, 2010). Other options such as ceftaroline and tigecycline are in vitro active against S. aureus including MRSA; however, there are very limited clinical data available for the safety and effectiveness with prolonged treatment courses of these

agents to treat osteomyelitis (Griffin, Harting, & Christensen, 2013; Lalikian, Parsiani, Won, Chang, & Turner, 2017). Linezolid, although can achieve adequate bone concentrations necessary to eradicate several gram-positive pathogens and demonstrated successful clinical outcomes in case reports and series (Falagas, Siempos, Papagelopoulos, & Vardakas, 2007), its bacteriostatic activity as well as the adverse reactions associated with prolonged treatment courses are concerning and may limit its clinical utility in bone infections. Other factors including drug allergy, elevated MIC, infection relapse, antimicrobial resistance, and treatment failure may further limit the pharmacotherapeutic options for the treatment of osteomyelitis.

Dalbavancin has promising pharmacokinetic/pharmacodynamic and safety data to be considered in the treatment of osteomyelitis caused by S. aureus. Dalbavancin demonstrated high bone concentration in animal and phase I clinical trials (Dunne et al., 2015; Solon et al., 2007). The mean non-infected cortical bone to plasma AUC penetration ratio of dalbavancin was reported at 13.1% (Dunne et al., 2015). This is higher than the mean ratio of 7% previously reported for vancomycin (Graziani, Lawson, Gibson, Steinberg, & MacGregor, 1988). Measured dalbavancin bone concentration 12 h after a single 1 g dose was 6.3 μg/g and remained high at 4.1 μg/g after 14 days (Dunne et al., 2015). Further, when MIC_{90} of the sampled isolates were compared in antimicrobial surveillance program, dalbavancin (MIC_{90} of 0.06 μg/ml) demonstrated 8-fold more potent activity against S. aureus compared to daptomycin and 16-fold compared to vancomycin (Jones et al., 2013). Given the terminal half-life of 14.4 days (Dunne et al., 2015), dalbavancin allows for infrequent (weekly), more convenient dosing administration schedule. Therefore, it can overcome the need for long-term central intravenous access for antimicrobial administration and its associated complications especially when central intravenous access in outpatient settings should be avoided. It can also provide opportunities to reduce length of stay and treatment costs (Almangour, Perry, Terriff, Alhifany, & Kaye, 2019). Unlike vancomycin, dalbavancin does not require routine serum drug concentration monitoring for safety and effectiveness. Lastly, in phase I clinical study, dalbavancin appeared to be safe and did not accumulate after 1 g loading dose followed by 500 mg for 7 additional weekly doses (Dunne et al., 2015). This is particularly important in osteomyelitis given the need for multiple weekly dosing.

Very few clinical data are currently available that specifically addressed the safety and effectiveness of dalbavancin in the

Table 2
Dalbavancin eligible patients.

Patient (n = 11)	Site of infection	Specimen for culture	Surgical intervention	Total dalbavancin received (g)	Primary outcome reached	Secondary outcome reached
1	Right 4th metatarsophalangeal osteomyelitis	Bone tissue/abscess	ID	3	Yes	Yes
2	Right 4th toe	Wound	Debridement	3	Yes	Yes
3	Left thumb distal and middle phalanges	Wound	ID	3	Yes	Yes
4	Thoracic spine 9–10	Bone tissue	Debridement	3	Yes	Yes
5	Cervical vertebra	Bone tissue	ID; washout; HW replacement	3	Yes	Yes
6	Lumbar spine 1–2 and lumbar spine 5-Sacral spine 1; left paraspinal osteomyelitis	Blood	No	3	Yes	Yes
7	Left elbow	Bone tissue and wound	HW removal	3	Yes	Yes
8	Right knee	Wound/Joint	Debridement	3.5	Yes	Yes
9	Lumbar spine 1–2 and Thoracic spine 12	Bone tissue and blood	No	6	Yes	Yes
10	Left ischial osteomyelitis	Wound	Debridement	7.5	Yes	Yes
11	Right wrist septic joint/osteomyelitis	Abscess	Debridement; abscess drainage	3	Yes	Yes

DM = diabetes mellitus; HW = hardware; ID = incision and drainage; N/A = not applicable.

treatment of osteomyelitis. In a case report, 8 weekly doses of dalbavancin were used to treat a patient with lumbar osteomyelitis. Although patient achieved clinical cure at end of treatment, recurrence of MRSA, which was likely a reinfection with a different strain, occurred 3 months after the last dose. Patient did not experience adverse reaction attributable to dalbavancin (Almangour, Fletcher, Alessa, Alhifany, & Tabb, 2017). In a retrospective study of 31 patients with osteomyelitis, 90% of patients achieved clinical success with dalbavancin with no adverse events noted (Almangour et al., 2019). Similar efficacy outcome was achieved in another retrospective study when dalbavancin was used in 12 patients with osteomyelitis (Bouza et al., 2018). A more recent multicenter retrospective study included 19 patients with bone and joint infections who received a median of 2 dalbavancin doses showed 90% success and improvement (Morata et al., 2019). Comparable efficacy outcome was also shown in a retrospective study included 30 patients with osteomyelitis (Wunsch et al., 2019). A first, recently published phase II randomized controlled trial compared dalbavancin 1500 mg IV on days 1 and 8 to SOC showed 97% and 88% clinical cure at day 42 in dalbavancin group and SOC therapy group, respectively, which continued for up to 1 year (Rappo et al., 2019). *S. aureus* was the most common causative pathogen in these studies.

In addition to the retrospective nature of the design, the small sample size is among the major limitations of this study. This is primarily due to the limited number of patients who were treated with dalbavancin for osteomyelitis, the strict inclusion criteria, and the limited availability of appropriate matched controls. Under-reporting of safety outcome is likely due to the retrospective nature of the study design and the fact that adverse event had to be reported in the medical record as related to the antibiotic used. However, this is the first observational study to compare dalbavancin to SOC for the management of osteomyelitis in adult patients with carefully selected matched controls.

In conclusion, dalbavancin appears to be safe and effective option for the management of osteomyelitis in adults. Further studies are needed to confirm these findings and to compare safety and effectiveness of different dosing regimens.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

The study was approved by the institution review board of Hendrick Health System, Abilene, TX (USA).

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