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Original Research

Dalbavancin Use in Bone and Joint Infections

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ABSTRACT

Background: Dalbavancin (DAL) off-label use for treating bone and joint infections has increased especially as long-term intravenous access is not needed. Little is known about the effectiveness and safety of its use.

Methods: This retrospective, single-center, descriptive study included adults treated with DAL for bone or joint infections over a 4-year period (2019-2023). Patient demographics, infection type and location, pre-DAL antibiotic and surgical treatments, indication for DAL, and clinical outcomes were collected. Risk factor analysis for 1-year infection recurrence was performed.

Results: There were 58 patient encounters of bone and/or joint infections treated with DAL. The majority of patients were treated for osteomyelitis (81.0%) followed by native (8.6%) and peri-prosthetic (10.4%) joint infection. Fifty (86.2%) patients underwent surgical intervention, and 17 (68%) of the 25 patients with infected hardware had full hardware removal. The most common pathogen identified was *Staphylococcus aureus* (41; 70.7%), with methicillin-resistant *Staphylococcus aureus* isolated in 23 (40.0%) cases. Ten (17.2%) patients had recurrence within 1 year. Hardware removal was found to significantly decrease the risk of infection recurrence ($P = .026$). None of the peri-prosthetic joint infection patients had infection recurrence within 1 year.

Conclusions: Our findings support DAL as an effective treatment for bone and joint infection when combined with surgical debridement and hardware removal. Failure to remove infected hardware significantly increased the risk of infection recurrence within 1 year. Randomized controlled trials are needed to further support DAL as a novel treatment for orthopedic infections.

Introduction

Musculoskeletal infections, such as osteomyelitis and peri-prosthetic joint infections (PJIs) are some of the most difficult challenges facing orthopedic surgeons and infectious disease physicians in modern medicine. PJIs are rare in joint replacement with a 1%-2% incidence but remain a significant concern as arthroplasty volumes continue to increase [1-3]. Both bone and joint infections arise from an increasing number of antibiotic-resistant bacteria species, which require new means of treating efficiently and effectively [4]. Current practice to manage musculoskeletal infections includes surgical debridement and/or drainage of the infected tissue followed by administration of an extended course of intravenous (IV) antibiotics [5]. However, prolonged antibiotic use can lead to severe adverse effects for the patient and contribute to the further development of antibiotic resistance. Adverse drug reactions due to long-term IV antibiotic treatments for bone and joint infections are common, and this risk correlates with length of therapy [6-8]. In addition to concerns for patient well-being, there are considerable financial burdens faced by both patients and

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hospitals when it comes to long-term IV antibiotic treatments. Long-term treatments are associated with longer lengths of stay and often require daily IV antibiotic use, both of which significantly increase the cost of treatment to patients/hospitals [9,10]. Given these issues and the need for prolonged treatment for bone and joint infections, new approaches that offer more efficient antimicrobial administration at lower cost without sacrificing quality are at the forefront of clinical interest and patient safety.

Dalbavancin (DAL) is a lipoglycopeptide similar in structure and spectrum of activity to vancomycin that is indicated for acute bacterial skin and skin structure infections [11]. DAL has a prolonged half-life of 14.4 days in comparison to many of the IV antibiotics used to treat musculoskeletal infections that will typically require daily administration at a minimum [12]. This characteristic allows for once-weekly DAL infusion for 2 weeks to treat gram-positive bacterial infections [13]. This regimen is highly convenient for patients and attractive to hospital systems, as infusions can be performed at outpatient centers and do not require long-term hospital admission or peripherally inserted central catheter line placement. However, DAL is limited by its narrow indication for acute skin and soft-tissue infections. In recent years, off-label DAL use as treatment for bone and joint infections has increased as an alternative therapy for patients unable to receive traditional IV antibiotic treatments. One study showed that 91% of patients with osteomyelitis and/or PJI cases (n = 55) were cleared of infection following treatment [14]. A randomized controlled trial from 2016 supported DAL as non-inferior to current standards of care for bone infections with no orthopedic hardware involvement, and a literature review from 2021 also supported DAL to be effective in PJI cases when combined with prosthesis removal [15,16].

Evidence supporting DAL as a new form of treatment for bone and joint infections is scarce. The use of DAL might be particularly appealing in patients with contra-indications to long-term IV access. Our observational study investigated the safety and effectiveness of off-label use of DAL for complex orthopedic infections.

Material and methods

After receiving requisite institutional review board review, we performed a retrospective observational review of adult patients who received at least one dose of DAL for bone or joint infection between September 2019 and March 2023 at a single academic medical center. During this period, 1550 patients were treated with outpatient IV antibiotics for musculoskeletal infections. Forty-seven (5.2%) of 907 patients with osteomyelitis were treated with DAL, and 11 (1.7%) of 643 patients with septic arthritis (5 native, 6 prosthetic) were treated with DAL. Five (83.3%) of the 6 PJI patients underwent initial hardware removal. Two of these patients had static and articulating antibiotic spacers placed following hip and knee hardware removal, respectively. One patient had antibiotic beads placed following hip hardware removal, and the other two patients underwent respective hip and knee revision that utilized antibiotic cement. The remaining 1 PJI patient that did not undergo hardware removal was treated for septic arthritis of a prosthetic shoulder joint.

Demographic data were collected including patient age, sex, ethnicity, body mass index, comorbidities, history of IV drug abuse, and residential address. The address was used to calculate the national area of deprivation index (ADI), a percentile ranking of neighborhood-level socioeconomic status [17]. The least-deprived neighborhoods have an ADI of 1 while the most-deprived neighborhoods have a high ADI of 100. Infection type and location, treatment strategies, indication, DAL dosing, and treatment outcomes were also collected. Treatment outcomes included any inpatient admissions 90 days after DAL treatment for any reason, infection recurrence up to 90 days after treatment, infection recurrence up to 1 year after treatment, and death up to 1 year after treatment. DAL treatment was not protocolized at this institution, thus regimen details were made at the discretion of the treating infectious-diseases physician. Of note, the institution antimicrobial stewardship program typically recommended 2 once-weekly doses after initial IV antibiotic treatment for bone and joint infections based on previously reported dosing regimens for bone and joint infections [18].

For all cases, we recorded if pre-existing hardware was involved and whether hardware removal or debridement with implant retention was performed prior to DAL initiation. Micro-organisms identified from operative cultures were collected.

Treatment strategy data included surgical interventions prior to DAL treatment, which was stratified to surgical debridement cases and whether hardware or amputation was involved. Interventional radiology–guided biopsy or drainage of the infected area was included under surgical interventions. Finally, cases in which no surgical intervention was performed were noted.

Indications for off-label DAL use were collected from the infectious disease consultation notes including a history of or active intravenous drug abuse (IVDA), lack of insurance coverage or benefits, difficulties with home-infusion setup, history of non-adherence to antibiotic treatment, transitions to DAL from outpatient therapy due to unique complications, or any adverse reactions to initial outpatient antibiotics. DAL regimen data included the dosing, frequency, and if the patient completed the treatment regimen.

Data were collected via manual chart review of the electronic medical record. Continuous variables were analyzed using the Students' *t* test, and categorical variables were assessed using the χ^2 test or the Fisher exact test where appropriate. Statistical analyses were performed using Stata 15.0 statistical software (StataCorp; College Station, TX).

Results

Fifty-eight patients who received DAL during the study period at our institution were included in this study. Patient demographics are shown in Table 1. The mean age of the patient population was 44.3 ± 10.6 (SD) years, and the majority were Caucasian (40/58, 69.0%) males (41/58, 70.7%). This cohort had a high rate (25/58, 43.1%) of IVDA history and had a high national percentile ADI (81.2 ± 13.8 SD) indicating low socioeconomic status.

Table 2 identifies infection characteristics including causative agent and location of the infection. Osteomyelitis was the most common (47/58, 81.0%) infection, with vertebrae (12/58, 20.7%), tibia/fibula (11/58, 19%), and sternum (5/58, 8.6%) being the most prevalent sites. There were 6 (6/58, 10.4%) patients with prosthetic

Table 1
Categorical demographic data of patient cohort.

Demographics	N = 58
Age, mean ± SD, y	44.3 ± 10.6
Sex, n (%)	
Female	17 (29.3)
Male	41 (70.7)
Ethnicity, n (%)	
African American	11 (19.0)
Caucasian	40 (69.0)
Hispanic/Latino	7 (12.1)
BMI kg/m^2, mean ± SD	28.6 ± 6.4
History of IVDA, n (%)	25 (43.1%)
National ADI, mean ± SD, percentile (n = 51)	81.2 ± 13.8

ADI, area deprivation index; BMI, body mass index; IVDA, intravenous drug abuse; SD, standard deviation; Y, years.

Table 2
Infection characteristic statistics from patient population.

Infection location	
Osteomyelitis, n (%)	47 (81.0)
Vertebrae	12 (20.7)
Tibia/Fibula	11 (19.0)
Sternum	5 (8.6)
Hand	4 (6.9)
Foot	4 (6.9)
Radius/Ulna	4 (6.9)
Femur	2 (3.5)
Ileum	2 (3.5)
Scapula	1 (1.7)
Skull	1 (1.7)
Septic arthritis, n (%)	11 (19.0)
Native joint infection	5 (8.6)
Peri-prosthetic joint infection	6 (10.4)
Infection involved pre-existing hardware, n (%)	25 (43.1)
Micro-organisms identified, n (%)	
Operative cultures	
Staphylococcus aureus	41 (70.7)
MRSA	23 (40.0)
MSSA	18 (31.0)
Coagulase negative *Staphylococcus* spp	6 (10.3)
Streptococcus spp	4 (6.9)
Enterococcus spp	2 (3.5)
Corynebacterium	2 (3.5)
Other	12 (20.7)
Polymicrobial	13 (22.4)
No growth	7 (12.1)
Associated bacteremia	8 (13.8)
Staphylococcus aureus	7 (12.1)
MRSA	4 (6.9)
MSSA	3 (5.1)
Streptococcus	1 (1.7)

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Table 3
Pre-DAL treatments, indications, and regimen statistics for patient population.

Treatment strategy	N = 58
Surgical intervention, n (%)	
Infection required surgical debridement	50 (86.2)
Hardware removal	17 (29.3)
Amputation	1 (1.7)
IR-guided drainage/biopsy	5 (8.6)
No surgical or IR intervention	3 (5.2)
Antibiotics prior to DAL, n (%)	
Vancomycin	39 (67.2)
Ceftriaxone	32 (55.2)
Daptomycin	6 (10.3)
Cefepime	5 (8.6)
Cefazolin	5 (8.6)
Other	7 (12.1)
DOT prior to DAL, median (IQR), d	7 (3-15)
Dalbavancin indication, n (%)	
History of IVDA	25 (43.1)
Insurance related	17 (29.3)
Home infusion could not be set up	8 (13.8)
Non-adherence to antibiotics	4 (6.9)
Transition from OPAT due to complication	3 (3.4)
Adverse reaction to initial OP antibiotics	1 (1.7)
Dalbavancin regimen, n (%)	
Dose	
1500-mg dosing	55 (94.8)
1000-mg dosing	3 (5.2)
Frequency	
1 Dose treatment	8 (13.8)
2 Dose treatment	50 (86.2)
>2 Doses treatment	4 (6.9)
Completed DAL course	48 (82.8)

d, days; DAL, dalbavancin; DOT, days of therapy; IQR, interquartile range; IR, interventional radiology; IVDA, intravenous drug abuse; OP, outpatient parenteral; OPAT, outpatient parenteral antibiotic treatment.

joint infections and 5 (5/58, 8.6%) patients with native joint infections. Infections involving hardware were common (25/58, 43.1%). *Staphylococcus aureus* was the most common microorganism identified (41/58, 70.7%), and 23 (23/58, 39.7%) were methicillin-resistant *S. aureus*. Associated bacteremia was seen in 8 patients: 7 *S. aureus* and 1 *Streptococcus*.

Prior to DAL treatment, 50 patients (50/58, 86.2%) underwent surgical debridement. Seventeen (17/25, 68%) of the 25 patients with infected hardware had full hardware removal. The median (interquartile range) days of antibiotic therapy before DAL initiation was 7 (3-15), with vancomycin and ceftriaxone being the most common antibiotics administered. Patients received DAL rather than a traditional therapy due to a history of IVDA (25/58, 43.1%) and lack of insurance (17/58, 29.3%) as the most common indications. The majority of patients (86%) were prescribed 2, weekly, 1500-mg doses of DAL. Forty-eight (82.8%) patients completed their regimen as prescribed, with non-compliance being the most common reason for failure to complete regimen. Four patients received more than 2 weekly DAL doses decided by the consulting ID physician due to infection recurrence (2) and severity of infection (2). Table 3 displays treatment-related data.

Treatment outcomes are shown in Table 4. Ten (10/58, 17.2%) patients had recurrence within 1 year, with 8 of these occurring within 90 days of treatment. No patients with PJIs had recurrence. No deaths occurred within 1 year. No signs of hepatotoxicity or nephrotoxicity were reported by the patient cohort following DAL treatment.

Risk factor analysis revealed that patients who underwent hardware removal were less likely to have recurrence of infection (0% vs 35.4%; $P = .026$). Similarly, patients with hardware retention were more likely to have recurrence than not (40.0% vs 8.3%; $P = .024$). Risk factor analysis is shown in Table 5.

Discussion

DAL has strong activity against gram-positive pathogens with a uniquely long half-life of 14.4 days and is approved to treat acute skin and skin structure infection [13,19]. The long half-life and bactericidal activity against antibiotic-resistant gram-positive pathogens, including methicillin-resistant *S. aureus*, has resulted in an increased "off-label" use of DAL in the treatment of deeper tissue infections such as osteomyelitis and septic arthritis [14]. Our study investigated characteristics and outcomes for 58 patients that received DAL for bone or joint infections. Clinical success was determined if infection recurrence was not observed within 1 year of follow-up.

In our cohort, the most common patient indication for off-label DAL use was a history of IVDA (25/58, 43.1%). This correlates to indications for DAL treatment seen in other studies that have shown patient IVDA in roughly 30% of study populations [19,20]. Our study found 21 (84%) of 25 IVDA patients saw no recurrence of infection following DAL treatment. Our cohort came from a low socioeconomic background as shown by the mean national ADI above the 80th percentile. Given the general uniformity of these characteristics in this study population, no significant difference was found in rates of either IVDA or ADI for risk of recurrence.

Table 4
DAL treatment outcomes for study population.

Treatment outcomes, n (%)	N = 58
Inpatient admission in 90 days for any reason	10 (17.2)
Recurrence up to 90 days	8 (13.8)
Recurrence up to 1 year	10 (17.2)
Death up to 1 year	0 (0)

Table 5
Risk factor analysis for recurrence of infection within 1 year of treatment.

Risk factor	Recurrence (N = 10)	No recurrence (N = 48)	*P*-value
Age, mean ± SD, y	43.0 ± 4.7	44.5 ± 11.5	.340
Female, n (%)	4 (40)	13 (27.1)	.458
BMI, mean ± SD	30.7 ± 7.0	28.2 ± 6.3	.869
History of IVDA, n (%)	4 (40)	21 (43.8)	.557
National ADI, mean ± SD, percentile	82.1 ± 9.3	81.1 ± 14.5	.575
Hardware retained, n (%)	4 (40)	4 (8.3)	**.024**
Hardware removed, n (%)	0 (0)	17 (35.4)	**.026**
Pre-existing hardware, n (%)	4 (40)	21 (43.8)	.557
Failed to Complete DAL n (%)	2 (20)	8 (16.7)	.553
DOT before DAL, median (IQR), d	11.5 (7-28)	5.5 (3-12)	.099
PJI, n (%)	0 (0)	6 (12.5)	.303
Staphylococcus aureus, n (%)	8 (80)	33 (68.8)	.385

Statistically significant *P*-values ($< \alpha = 0.05$) are indicated with bold formatting in column 4.
ADI, area of deprivation index; BMI, body mass index; DAL, dalbavancin; DOT, days of therapy, IQR, interquartile range; IVDA, intravenous drug abuse; PJI, periprosthetic joint infection; SD, standard deviation; y, years.

Traditional outpatient parenteral antibiotic treatments are generally not viable options for this patient population, so the high success rate (21/25, 84%) without infection recurrence we observed offers support that DAL may have use as a unique alternative for these types of indications [21].

S. aureus was the most-common pathogen identified (41/58, 70.7%), and this is similar to other studies investigating DAL's use and effectiveness for treatment of osteomyelitis and PJIs [14,20,22]. *S. aureus* infections had a higher rate of recurrence (8/10, 80%) than other pathogens (2/10, 20%) although this was not statistically significant perhaps due to the low sample size of our cohort. However, current literature has shown *S. aureus* to be associated with bone infection recurrence even with initial treatment success at infection clearance [23]. Part of the mechanism responsible for this has been associated with the ability for *S. aureus* to internalize into osteoblasts following primary infection, which can lead to chronic and recurrent infections over long term even after treatment [24]. This evidence suggests that while *S. aureus* constituted most patients with recurrence in our cohort, this is a trend seen in standard care treatments and may not be caused by DAL use in these circumstances.

One finding of interest was the significant difference found between rates of hardware removal between those with infection recurrence (0/10, 0%) and no infection recurrence (17/48, 35.4%). From the risk factors tested to look for any signs that may influence treatment outcome following DAL infusion, hardware removal seems to be the only significant combination treatment measure along with DAL that helped influence positive outcome for the population with pre-hardware involvement. These findings correlate with a study that found a higher rate of treatment success in patients with hardware removed (16/21, 76.2%) than in those without (15/23, 65.2%) [25]. Our findings reiterate that antibiotic therapy should be combined with aggressive surgical treatment measures for higher infection clearance. Of note, none of the 8 patients in our study with retained hardware returned to the infectious diseases clinic, and thus, none transitioned to suppressive therapy. All 8 of these patients suffered from either substance abuse or non-compliance with the initial antibiotic therapy. Ultimately, 4 of these 8 patients (50%) experienced recurrence within 1 year of original surgery, which perhaps may have been prevented had suppressive therapy been added to their regimen.

Overall, 82.8% (48/58) of the population observed in this study saw no infection recurrence within a year. This is similar to rates of infection clearance to rates published using DAL to treat bone and joint infection [26]. One such study saw a successful 93% (39/42) clinical cure rate in their cohort, with 20 (20/21, 95.2%) osteomyelitis patients and 1 (1/2, 50%) septic arthritis patient seeing clinical success [27]. Another such study from 2019 followed DAL treatment outcomes for gram-positive infections which included bone and joint infections and found a lower clinical cure rate (46/72, 64% total: 3/8, 38% PJI) for its cohort [28]. Our study found greater success in the treatment of PJI patients both with DAL and in our single patient that saw clinical success without the need for hardware removal. One final interesting comparison can be made to a case report following successful treatment of *Corynebacterium striatum* PJI with long-term DAL. The patient described in that study underwent weekly 500-mg DAL infusions for 12 weeks, as well as surgical debridement and implant removal to clear the infection [29]. In our study, one patient had a PJI due to *Corynebacterium*. This patient underwent surgical debridement, removal of hardware, and placement of an antibiotic spacer and was treated with one dose of DAL (1500 mg) with no recurrence at 1 year. These previous studies have reported similar success rates and outcomes that reflect DAL as a safe and well-tolerated antibiotic when used in off-label settings [20,22,30]. This success rate is also encouraging when compared to a clinical success rate obtained in an earlier vancomycin study for bone and joint infections, which was lower at 66% (10/15) infection clearance [31].

Implications of the statistical outcomes are limited by the small population number that was included in this study, and this limitation is particularly evident in the number of PJI cases (n = 6). Another limitation is the subjective nature of infectious-diseases physicians that decide which patients were prescribed DAL. Future prospective studies would help to remove this bias. One last limitation was non-compliance with DAL treatment as 10 (17.2%) patients did not complete their recommended course. The overall size of this study, while small (N = 58), is one of the largest among retrospective reviews of DAL treatment for bone and joint infections. Despite these limitations, these findings and concomitant correlation from similar studies offer promising evidence that supports the further investigation of DAL as a novel antibiotic that can offer effective infection clearance at a higher accessibility rate to patients that suffer from bone and joint infections, especially those where prolonged IV treatment is not thought to be a safe option. Randomized controlled trials are needed to fully establish this novel antibiotic as an approved treatment option for deeper-lying infections such as osteomyelitis and septic arthritis.

Conclusions

Our observational data support DAL use in select patients unable to receive standard care therapy as a treatment option for bone and joint infections when accompanied with surgical debridement and infected hardware removal. Hardware retention was a significant risk factor for 1-year recurrence of infection, while hardware removal lowered this risk. DAL may be particularly useful in patients who have contra-indications to long-term IV access. Further investigation with randomized controlled trials is needed to support DAL as a clinically effective treatment option for bone and joint infection.

Conflicts of interest

J.B.S. receives royalties from Signature Orthopaedics; is in the Speakers bureau of or gave paid presentations for CurveBeam; is a paid consultant for Smith & Nephew and Medacta; is in the editorial/governing board of Journal of Arthroplasty; is a board member/made committee appointments for American Association of Hip and Knee Surgeons and American Joint Replacement Registry (AJRR). C.L.B.

receives royalties from DJO and Zimmer; is a paid consultant for MicroPort Orthopaedics; has stock or stock options in Avant-garde Health, BEKHealth, Clozex Medical, Excelerate Health Ventures, Green OR, Hayle Surgical, In2Bones SAS, MiCare Path, Plakous, Ride Health, ROM3 Rehab, LLC, Sleep Partners, LLC, and Sniffle; is in the editorial/governing board of Journal of Knee Surgery and Journal of Surgical Orthopaedic Advances; is a board member in/made committee appointments for American Association of Hip and Knee Surgeons, HipKnee Arkansas Foundation, and Southern Orthopaedic Association. B.M.S. receives royalties from MiCare Path, Sawbones/Pacific Research Laboratories, and Tightline Development LLC; is in the speakers' bureau/gave paid presentations for DJ Orthopaedics; is a paid consultant for DJ Orthopaedics and Johnson & Johnson; has stock or stock options in Joint Development LLC; is in the editorial/governing board JBJS-Br; is a board member at/made committee appointments for AAOS and American Association of Hip and Knee Surgeons. S.C.M. has stock or stock options in Delta Ortho LLC; is in the editorial/governing board of Journal of the American Geriatrics Society and SAGE; and is a board member at/made committee appointments for Fragility Fracture Network. The other authors declare no conflicts to disclose.

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CRediT authorship contribution statement

Liam P. Alderson: Writing – original draft, Formal analysis, Data curation. **Srivani Sanikommu:** Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Simon C. Mears:** Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **C. Lowry Barnes:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Benjamin M. Stronach:** Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Jeffrey B. Stambough:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jennifer McDonald:** Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Traci Motes:** Writing – original draft, Data curation. **Brett Bailey:** Writing – original draft, Investigation, Formal analysis, Data curation. **Ryan K. Dare:** Writing – original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

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