

Dalbavancin dosage regimens in the treatment of gram-positive infections: a case series and review of the literature

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Abstract

Background: Dalbavancin is approved by the United States Food and Drug Administration (FDA) for one-dose or two-dose regimens in the treatment of acute bacterial skin and skin structure infections (ABSSSIs). This agent may also be utilized off-label for invasive gram-positive infections, but there are no standard dosage recommendations for off-label use (1). We evaluated different dosage regimens used in real-life experiences.

Methods: Medication administration data at ProMedica Health System and The University of Toledo Medical Center was reviewed to identify patients treated with dalbavancin to evaluate the efficacy and safety of common dosing regimens for both invasive and noninvasive gram-positive infections. The primary outcome was treatment failure defined as recurrence or hospitalization due to the same infection within one year. Baseline characteristics between successfully treated and failed groups were compared.

Results: Throughout the 5 years (2016-2021), 131 patients who received dalbavancin were enrolled. 82 (63%) of patients had ABSSSIs. Forty-nine (37%) fell under the category of invasive gram-positive infections. Forty-one patients (31%) of them had failure of treatment.

Of the patients who failed treatment, twenty-three patients received one dose of intravenous dalbavancin, and eighteen patients received at least two doses of dalbavancin. Adverse events were noticeable for one patient with transient rash on the hand and one patient had non *Clostridioides difficile* diarrhea.

Conclusion: Dalbavancin has been a safe and convenient option for the treatment of gram-positive infections. A regimen of two doses or more of dalbavancin may offer a better outcome than one dose only for both invasive and non-invasive gram-positive infections.

Keywords: Dalbavancin, Dosage, Intravenous antibiotics

1. Introduction

Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), are common pathogens implicated in osteoarticular infections, infective endocarditis, bloodstream infections, and acute bacterial skin and skin structure infections. Vancomycin has historically been deemed the drug of choice for the treatment of these infections when caused by MRSA and penicillin-resistant enterococcus species (2). Dalbavancin is a long-acting lipoglycopeptide antibiotic that interferes with cell wall synthesis to prevent peptidoglycan cross-linking and has an approximate half-life of 8.5 days (3). In contrast to the nephrotoxic effects often associated with glycopeptides, dalbavancin has a favorable renal profile and does not require dose adjustments in those receiving regularly scheduled hemodialysis but for those with a CrCl of <30 ml/min dose reduction is warranted (3,4). Intravenous dalbavancin was originally approved by the United States Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible gram-positive organisms (4). The FDA has approved two dosing regimens of dalbavancin for the treatment of ABSSSIs. The first is a one-dose regimen including a single 1500 mg infusion, and the second is a two-dose regimen comprising of a 1000 mg dose and a subsequent 500 mg dose administered one week later, with dose adjustment for patients with renal impairment (4). Several trials have proposed that dalbavancin could be a plausible option for the treatment of invasive gram-positive infections since administration and monitoring are more convenient than traditional IV or highly bioavailable oral therapy, but ideal treatment regimens for invasive gram-positive infections were not specified and it was determined that randomized controlled trials are needed to determine if dalbavancin is non-inferior to current standard of care (5, 6, 7). Dalbavancin is often infused every week in an outpatient setting for prolonged courses, may have fewer adverse effects, and currently does not require therapeutic drug monitoring; however, there is current inconsistency in dosage regimens prescribed by providers (1). This study aims to describe the outcomes of patients who were treated with Dalbavancin for gram-positive infection among two health systems in northeast Ohio and Michigan.

2. Methods

Study Design

This is a retrospective, non-randomized, observational study that was performed after obtaining Institutional Review Board approval at the University of Toledo Medical Center and ProMedica Health System. All patient data were deidentified to safeguard patients' confidentiality. Electronic health records were reviewed for all patients who were treated with dalbavancin for the management of gram-positive infections between 2016 and 2021. Dalbavancin orders were used to collect data, and administration was verified by documentation in the charts. The dosage regimens utilized were reviewed, and overall outcome, recovery, failure of treatment, and death rates were compared between them.

Inclusion/Exclusion Criteria

We included adults (≥ 18 years of age or older) treated with at least one dose of dalbavancin for gram-positive infections that were diagnosed by infectious diseases physicians or other providers in the facilities that did not have infectious diseases providers between 2016 and 2021 at the University of Toledo Medical Center and ProMedica Health System and excluded those who were lost to follow-up (they did not have clinic follow up notes or admission notes for one year).

Primary and Secondary Outcome Measures

The primary outcome was treatment failure defined as recurrence of infection (as determined by any additional procedures or clinic visits related to the infections) or re-hospitalization for the same infection for one year after the final dose of dalbavancin. Secondary outcomes were treatment success, all-cause mortality, any adverse events, and correlating them with certain dosage patterns. Success of treatment was defined as no recurrence of the infection and no re-hospitalization for the same infection for one year. All-cause mortality was defined as any cause of death among the study group in one year after dalbavancin administration.

3. Results

132 patients who received dalbavancin during our pre-specified time period were identified. One patient was excluded due to being lost to follow-up. The median age of patients was fifty-eight. The number of intravenous drug users was twenty-four, Charlson comorbidity index mean of 3.47. Fifty-eight patients were females with a ratio of

Table 1: patient characteristics

Patient characteristics	Number
Age range	(20-98) median 58
Sex male/female ratio	73/58(56%/44%)
Intravenous drug users	25(18%)
Charlson comorbidity index	Mean 3.47
Underlying diseases:	
Diabetes mellitus	48(36%)
End-stage renal disease on hemodialysis	2(1%)
Chronic kidney disease	22(16%)
HIV	3(2%)
Malignancy	6(4%)
Morbid obesity	9(6%)
Hepatitis C	12(9%)
Peripheral vascular disease	16(12%)
Type of infection:	
Acute bacterial skin and skin structure infection	82(62%)
Vertebral osteomyelitis	11(8%)
Osteoarticular infections(non-vertebral)	33(25%)
Infective endocarditis	6(4%)
Bloodstream infections	9(6%)
Hardware-associated infections:	14 (10%)
Periprosthetic joint infection	0

Table 2: microbiologic diagnosis and failure rate

Microbiologic diagnosis	Total Number of patients	Number of patients who failed treatment
Methicillin-resistant Staphylococcus aureus	33	11(33%)
Methicillin susceptible staphylococcus aureus	21	7(33%)
Streptococcus species	10	3(30%)
Enterococcus faecalis (susceptible to vancomycin)	9	3(33%)
Coagulase-negative staphylococcus	11	0 (0%)

44%. Other baseline patient characteristics are outlined in Table 1.

116(88%) patients received antibiotics before starting Dalbavancin. 62 (47%) patients received 3-5 days of IV Vancomycin before receiving IV dalbavancin. 29% (18) patients who received IV vancomycin had a failure of treatment.

The commonly used dosage regimens were: 77 patients received one dose of 1500 mg of dalbavancin, and 29% (23/77) of them had failure of treatment. 53 patients received at least 2 doses of 1500 mg of dalbavancin; 17 of them had treatment failure. One patient received renally adjusted dalbavancin but failed treatment for MRSA diabetic foot infection with osteomyelitis and required 6 weeks of IV vancomycin.

Microbiologic diagnosis was not obtained in 47 (35%) patients as they had ABSSIs with cellulitis as a major diagnosis. On the other hand, microbiologic diagnosis was obtained in patients who had invasive infections or infected wounds. The results of cultures are outlined in Table number 2.

Most of the patients had one diagnosis, but some patients had more than one diagnosis such as having infective endocarditis, vertebral osteomyelitis, and bacteremia. The results are broken down by diagnosis to determine failure of treatment by recurrence of infection or re-hospitalization within one year in the following paragraphs.

Acute bacterial skin and skin structure infections:

82 patients had ABSSSIs, 30 patients with ABSSI had infection recurrence. 69 patients received one dose of 1500 mg of dalbavancin with recurrence in 23 (33%) patients. Eight patients received 1500 mg on day 1 and day 8 with recurrence in 6 patients. 5 patients received 1000 mg on day 1 and 500 mg on day 8 with failure of treatment in one patient. Details included in table 3.

Diabetic foot infections:

23 patients had diabetic foot infections and 17 of them had associated foot osteomyelitis. 17 patients received antibiotics before dalbavancin (vancomycin in 9 patients). Failure of treatment occurred in 11 patients.

Vertebral osteomyelitis:

11 patients diagnosed with vertebral osteomyelitis, discitis and 6 of them also had

Table 3: Acute bacterial skin and skin structure infections

	Patients with successful treatment	patients who failed treatment in one year
Number of patients with ABSIs total (82)	52 (63%)	30 (37%)
Age average	59	60.5
Male/female ratio	27/25 (51%/48%)	12/18 (40%/60%)
Intravenous drug usage	6(11%)	1(2%)
Charlson comorbidity index mean	3	4.4
Previous antibiotics received	Vancomycin Cephalexin sulfamethoxazole/trimethoprim Doxycycline Clindamycin Levaquin Minocycline Augmentin cefazolin	Vancomycin Cephalexin Ceftriaxone Levofloxacin Dicloxacillin Amoxicillin Omnicef Aztreonam Clindamycin SMX/TMP Piperacillin/tazobactam
Microbiologic al diagnosis	No cultures MRSA MSSA Enterococcus faecalis Coagulase-negative staphylococcus Group B Streptococcus	MRSA MSSA Coagulase-negative staphylococcus Corynebacterium striatum Enterococcus faecalis Streptococcus pyogenes

epidural abscess received dalbavancin as outpatients after initially receiving either IV vancomycin or IV daptomycin while inpatient. 6 patients had a history of intravenous drug use. 6 patients had spinal surgery for source control. Cultures grew MRSA in 5 patients, MSSA in 4 patients, one with streptococcus Mitis, and one with negative cultures. Recurrence happened in one out of the four patients with MSSA infections, While for MRSA infections, four patients received two doses of 1500 mg of dalbavancin with no recurrence of infection, one patient received only

Table 4: patients with vertebral osteomyelitis

	patients with treatment success	patients who failed treatment in one year
Number	8(72%)	3(27%)
Age range (26-68) mean	45	43
Male /female ratio	6/2 (54%/18%)	3/0 (27%/0)
Intravenous drug usage	4(36%)	2(18%)
Charlson comorbidity index average	2	2
Previous antibiotics received	vancomycin daptomycin	vancomycin
Microbiologic diagnosis		
MRSA	4(36%)	1(9%)
MSSA	3(27%)	1(9%)
Negative cultures	1(9%)	0
Streptococcus mitis	0	1(9%)
Dosage regimen received:		
One dose of 1500 mg of Dalbavancin	1(9%)	2(18%)
One dose of 1500 mg on day 1 and 1500 mg on day 8	4(36%)	0
One dose of 1000 mg on day 1 and 500 mg doses weekly n=5	3(27%)	1(9%)

1 dose of 1500 mg and had a failure of treatment. Details in table 4.

Non vertebral osteoarticular infections:

Thirty-three patients were diagnosed with osteoarticular infection, with failure of treatment in 13 patients. Seven patients received one dose of dalbavancin 1500 mg and five of them failed treatment. 26 patients received two doses, and 8 patients failed treatment.

Infective endocarditis:

Six patients with infective endocarditis were treated with dalbavancin, including two patients with left-sided endocarditis. All six of these patients had a history of IV drug use. Two patients had MRSA right-sided endocarditis, and four patients had MSSA endocarditis (two patients

Table 5: patients with osteoarticular infection

	patients with successful treatment	patients who failed treatment in one year
Number	20(60%)	13(40%)
Age range (26-93) mean	53	56
Male /female ratio	15/5 (45%/15%)	5/8 (15%/24%)
Intravenous drug usage	1(3%)	7(21%)
Charlson comorbidity index Average	3.35	5.7
Previous antibiotics received.	Vancomycin Cefepime (MRSE, Strep viridans) Cephalexin (MSSA) Piperacillin/tazobactam Clindamycin	Clindamycin Minocycline Vancomycin
Median duration of therapy Prior to dalbavancin (4 days)	Doxycycline Augmentin Cefazolin Linezolid Ceftriaxone	Bactrim Linezolid
Microbiologic diagnosis	MRSA MSSA MRSE (Methicillin-resistant <i>staphylococcus epidermidis</i>) <i>Streptococcus viridans</i> Coagulase-negative staphylococcus Group B Streptococcus	MRSA MSSA <i>Enterococcus faecalis</i> <i>Streptococcus pyogenes</i> <i>Corynebacterium striatum</i>
Dosage regimen received:		
One dose of 1500 mg of dalbavancin	2	5
One dose of 1500 mg on day 1 and 1500 mg on day 8	18	7
One dose of 750 mg on day 1 and 375 mg on day 8 (renal dosing)	0	1
Hardware present (prosthetic joints =0)	4 total 3 (hardware was retained) 1 (hardware was removed)	1 (infection resolved after the hardware was removed and linezolid was given for 14 days post-op)

had MSSA mitral valve endocarditis and two patients had MSSA right-sided endocarditis). The dosage regimen was split between whether cultures grew MSSA or MRSA. MSSA mitral valve endocarditis patients were treated with 1 dose of Dalbavancin of 1000 mg followed by 5 doses of 500 mg. Two patients had a failure of that regimen and had one of them had mitral valvular surgery for source control followed by intravenous nafcillin for 6 weeks.

MRSA endocarditis was treated with 1 dose of Dalbavancin 1500 mg followed by 4 doses of

500 mg. MRSA endocarditis patients had metastatic foci of infection (pulmonary septic emboli and sternoclavicular septic arthritis that required Incision and drainage) Relapse and clinical failure were seen in 1 out of 2 patients with MRSA endocarditis and one of them had tricuspid valve surgery as seen in table 6.

Bloodstream infections:

In this study, we found nine patients with secondary bacteremia, all treated with dalbavancin as planned for their primary diagnosis

Table 6: patients with Infective endocarditis

	Number of patients with treatment success	Number of patients who failed treatment in one year
Number	3(50%)	3(50%)
Age mean	37	31
Male /female ratio	1/2 (33%/66%)	2/1(66%/33%)
Intravenous drug usage	3(50%)	3(50%)
Charlson comorbidity index mean	3	3
Previous antibiotics received	nafcillin (MSSA) 2 days cefazolin (MSSA) 3 days vancomycin (4 days) (MRSA)	Vancomycin (3 days)
Microbiologic diagnosis:		
MRSA	1(33%)	1(33%)
MSSA	2(66%)	2(66%)
Dosage regimen received:		
One dose of 1500 mg of dalbavancin followed by 4 doses of 500 mg	1(33%)	1(33%)
One dose of 1000 mg on day 1 followed by 4 doses of 500 mg	2(66%)	2(66%)

(6 with endocarditis and 3 with vertebral osteomyelitis).

Safety:

Adverse effects were limited to one patient with mentioned rash in both hands that was transient and spontaneously resolved and one patient had diarrhea but tested negative for *Clostridioides difficile*. 14 patients have died; however, deaths were unrelated to the original infection. Etiologies were (advanced age (4 patients died at hospice and comfort care, two patients died from COVID-19 complications, two patients' death was related to complications of chronic obstructive pulmonary disease, one patient due to congestive heart failure, one patient due to advanced liver cirrhosis,

Table 7: patients with secondary bacteremia (bloodstream infections)

	patients with successful treatment	patients who failed treatment in one year
Number	6 (66%)	3(33%)
average age	37	31
Male /female ratio	2/4(22%/44%)	2/1(22%/11%)
Intravenous drug usage	4(44%)	3(33%)
Charlson comorbidity index	3	3
Previous antibiotics received	Vancomycin Cefazolin nafcillin	vancomycin
Microbiologic diagnosis		
MSSA	3(33%)	2(22%)
MRSA	2(22%)	1(11%)
Streptococcus species	1(11%)	0
Dosage regimen received:		
One dose of 1500 mg of Dalbavancin	1(11%)	0
One dose of 1500 mg on day 1 and 1500 mg on day 8	2(22%)	0
One dose of 1500 mg of Dalbavancin followed by 4 doses of 500 mg	1(11%)	1(11%)
One dose of 1000 mg on day 1 followed by 4 doses of 500 mg	2(22%)	2(22%)

end-stage renal diseases in two patients, and two patients died from metastatic malignancies).

4. Discussion

Gram-positive organisms are a major cause of infections ranging from acute bacterial skin and skin structure infections to Infective endocarditis and osteoarticular infections. Over the years, different resistant organisms have emerged and

gained more attention such as MRSA, causing invasive infections which are becoming increasingly difficult to treat. For many years, lipopeptides such as vancomycin and in recent years daptomycin have been the mainstay for treating drug-resistant Gram-positive systemic infections. For certain conditions, such as endocarditis and osteoarticular infection, patients who are not candidates for oral antibiotics require regular daily infusions that must be given over several weeks. For that purpose, patients must be set up with infusion centers or home health infusion agencies which are costly, and multiple daily dosages can be cumbersome for nursing staff and patients themselves. Insertion of midlines or peripherally inserted central catheter lines and their maintenance is an additional burden for the patients' nursing staff for PICC line dressing changes and care. In view of these factors, dalbavancin and oritavancin have recently emerged as two promising, convenient candidates for the treatment of deep-seated gram-positive infections (4,8).

Dalbavancin has also shown promise in the treatment of infective endocarditis, osteomyelitis, and SSTIs. Francesca et al. showed cure rates of dalbavancin around 89% for osteomyelitis and 83% for endocarditis (5). With specific regard to endocarditis, dalbavancin has the highest evidence of cure among lipoglycopeptides based on six retrospective studies and a small number of case reports. Treatment success rates in the six retrospective studies ranged from 72% to 100%. However, a 72% success rate was observed in the study by Dinh et al., in which dalbavancin was used in a significant proportion of patients as rescue therapy; 26.6% of all patients in the study received dalbavancin for clinical and/or microbiological failure on prior therapy (9). In the other five studies, where the role of dalbavancin in many cases (where documented) was consolidation therapy after blood culture clearance rather than as a rescue strategy, treatment success rates were 91% to 100% (in those for which follow-up data were available (10)). In our study, there were only six patients with native valve infective endocarditis and three of them had treatment failure despite receiving multiple doses of dalbavancin (a total of five doses). In terms of adverse events, dalbavancin was well tolerated in the evaluated studies. Rates of reported adverse events in these studies ranged from 0% to 11% (1,5,11) which correlates with the low rate of adverse events in our study, it was reported in 2 patients only (transient rash and mild diarrhea). In 2019, Rappo

et al. did a prospective randomized comparative clinical trial in patients with osteomyelitis. Many patients in this trial had a gram-positive organism isolated from bone and the dalbavancin group had high clinical cure rates at day 42, sustained through 1 year. All patients had surgical intervention for source control. The simple 2-dose regimen was suitable for an outpatient setting, such as emergency rooms, infusion centers, and hospital outpatient departments (7). In a retrospective study, dalbavancin appeared to be a well-tolerated option for vertebral osteomyelitis (12). In our study, Vertebral osteomyelitis and non-vertebral Osteoarticular infections have shown favorable results in our study with success rates of 72% (8/11) and 60% (20/33) respectively. Dalbavancin has been an effective regimen for the treatment of acute bacterial skin and skin structure infections with a success rate of 63% (52/82) recurrence was noticeable in patients diagnosed with lower extremity cellulitis at 60% (18/30). 116(88%) patients received antibiotics before starting Dalbavancin. 62 (47%) patients received 3-5 days of IV Vancomycin before receiving IV dalbavancin. 29% (18) patients who received IV vancomycin had a failure of treatment.

Our study has limitations being retrospective and numbers are too small to be statistically significant, lack of standardized dosing for infections, and no standard of care arm comparator but its strengths are it is a multi-center study that spans several hospitals over 5 years' time, and it reflects the real-time experience and the variations in dosing based on the prescriber's preference. Based on our case review. There has been no standard dose for the treatment of invasive gram-positive infections with dalbavancin.

5. Conclusion

The body of evidence regarding treatments with lipoglycopeptides seems to be increasing but they are still in their initial stages. In our cohort of patients who received dalbavancin, favorable outcomes occurred in patients with osteoarticular infections and vertebral osteomyelitis who received two doses or more of dalbavancin, but the numbers were too small to be statistically significant.

However, dalbavancin did not show promising results for the management of our cohort of patients with Infective endocarditis. Despite multiple dosing regimens used for variable infections dalbavancin has been shown to be a

safe option with minimal adverse effects. Since this was a retrospective case series study, other studies are needed to assess the best dosing regimen of dalbavancin for the treatment of invasive gram-positive infections.

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