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BRIEF REPORT

Dalbavancin as Secondary Therapy for Serious *Staphylococcus aureus* Infections in a Vulnerable Patient Population

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We retrospectively evaluated off-label use of dalbavancin as secondary therapy in 32 patients with serious *Staphylococcus aureus* infections (endocarditis, osteomyelitis, septic thrombophlebitis, epidural infection) who were also persons who use drugs. The majority of patients (56%) had a clinical response to treatment. Only 1 patient who completed the intended dalbavancin course experienced a treatment failure.

Keywords. dalbavancin; *Staphylococcus aureus*; substance use.

Serious staphylococcal infections often require prolonged courses of intravenous antibiotic therapy. Dalbavancin, a lipoglycopeptide antibiotic with a long half-life, allows for weekly dosing, making it an appealing choice for patients requiring parenteral therapy, particularly in people who use drugs (PWUD). Retrospective case series are emerging regarding the efficacy and safety of dalbavancin in the treatment of deep-seated, Gram-positive infections [1, 2], though reports of its use in vulnerable patient populations such as PWUD remain scarce.

Outpatient parenteral antimicrobial therapy (OPAT) is widely used for the treatment of severe staphylococcal infections [3–5]. However, few studies have described enrolling PWUD, and more specifically persons who inject drugs (PWID), in standard OPAT programs [6–9].

Similar to programs developed at other institutions, we created a multidisciplinary inpatient team to provide a comprehensive care plan with coordinated medical treatment for PWUD, including consultation with nursing, psychiatrists, addiction medicine, acute pain management, and infectious disease (ID) specialists [10]. Despite these approaches, some patients are administratively discharged secondary to ongoing unsafe behaviors or leave against medical advice (AMA). These patients are at high risk of re-admission due to relapse of their incompletely treated infections or factors related to substance use. One study reported 43% of PWUD leaving AMA during hospitalizations between 2005 and 2011 [11], while another study documented significantly higher 30-day mortality in patients who were discharged AMA [12].

At our institution, PWUD who are discharged with parenteral antibiotics are offered close outpatient management including weekly ID clinic appointments, referral to an opioid replacement therapy clinic, and coordinated support; despite these measures, medication adherence remains a challenge. We described our clinical experience with the off-label use of intravenous (IV) dalbavancin for serious staphylococcal infections in this patient population.

METHODS

Setting and Study Population

This is a retrospective observational study conducted at a 413-bed university-affiliated urban teaching hospital, Harborview Medical Center (HMC), located in Seattle, Washington. It is a public safety net hospital for Seattle King County and a level 1 trauma and burn center for Washington, Wyoming, Alaska, Montana, and Idaho.

Dalbavancin was added to our institutional formulary in 2015 with restriction requiring approval from the ID team, antimicrobial stewardship, and the OPAT program. Clinical indications include bacteremia, complicated skin and soft tissue, or deep-seated infections for which conventional intravenous antimicrobial therapy is not recommended due to social circumstances. Situations that might warrant the use of dalbavancin include infections with organisms with no acceptable oral antibiotics and infections in patients who are discharged AMA or who are at high risk for administrative discharge because of behavioral issues and unsafe behaviors.

All patients ≥18 years old who were hospitalized between June 1, 2015, and September 30, 2017, for serious *Staphylococcus aureus* infections, who received initial conventional antibiotic treatment, and who were discharged on dalbavancin as secondary therapy were included. The initial dalbavancin dose was infused over 30 minutes on the day of hospital discharge, and duration of therapy was determined by the consulting ID physician. All patients were scheduled to return to the ID clinic for subsequent weekly infusions.

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The institutional review board of the University of Washington approved the study and waived written informed consent.

Data Collection and Analysis

Data collection was performed using REDCap [13], a data-reporting quality improvement tool linked to the University of Washington's Clinical Data Repository. From the electronic medical record (EMR), we collected data on patient demographics, medical comorbidities, microbiology, and antibiotics. Outcomes were collected through our EMR at follow-up visits and via a linked EMR to other clinics and hospitals.

Definitions

Active substance use was defined as the use of cocaine, heroin, or methamphetamine in any form within the last 30 days; information regarding use of other opiates was unavailable. A clinical response was defined as any patient who had a follow-up visit within 1 year at HMC or a neighboring hospital, linked through a common EMR, without evidence for an ongoing or relapsed infection, regardless of whether they completed the intended course of therapy. Loss to follow-up was defined as any patient not having a subsequent encounter to evaluate their infection at either the HMC ID clinic or another institution, linked via the EMR, within 1 year. Successful completion of total antibiotic course was defined as completion of total prespecified antimicrobial course, including dalbavancin and other subsequent oral antibiotics. All-cause readmission was defined as a hospital admission within 30 days from the previous hospital discharge in our shared EMR.

RESULTS

We identified 32 PWUD treated with dalbavancin for serious *Staphylococcus aureus* infections. The average age (interquartile range [IQR]) was 38 (25–50) years, 23 (72%) were male, 28 (88%) were Caucasian, 2 (6%) were Hispanic, and 2 (6%) were Native American. The majority of patients, 28 (88%), were PWID; 15 (47%) had hepatitis C, 15 (47%) were homeless, 1 had a history of diabetes, and 1 was HIV infected. The mean Charlson comorbidity index (IQR) was 0.8 ± 1.3 (0–2). The indications for antibiotic treatment are listed in Table 1. The majority of infections, 28 (88%), were due to methicillin-resistant *Staphylococcus aureus,* and 26 (81%) of the isolates were fluoroquinolone resistant.

Patients received an average of 13 days of antibiotic therapy before receiving dalbavancin; vancomycin was the most commonly prescribed antibiotic (84%). Peripherally inserted central catheter (PICC) placement was avoided in 15/32 (47%) patients. Twenty-two patients received a single dose, 7 received 2 weekly doses, 2 received 3 weekly doses, and 1 received 5 weekly doses of dalbavancin. The average hospital length of stay (LOS) was 12.2 ± 8.5 days. Overall, 17 (53%) patients completed the intended course of therapy. A clinical response was documented in 18 (56%) of patients, and 4 (13%) patients experienced a clinical failure. The remaining 10 (31%) patients were lost to follow-up and unevaluable. Six patients (19%) were re-admitted to the hospital within 30 days of discharge—none for adverse effects related to dalbavancin, 2 (6%) for treatment failures reported above, and 4 (13%) for reasons unrelated to their initial treatment.

Nine patients were treated for endocarditis (2 with methicillin-sensitive *Staphylococcus aureus* and 7 with methicillin-resistant *Staphylococcus aureus*), all involving the native tricuspid valve. Of these patients, 6 received a single dose of dalbavancin, and 3 received 2 doses. The average duration of inpatient therapy was 17 days. All patients had negative follow-up blood cultures before transition to dalbavancin. None of the patients with endocarditis were known to have failed treatment with dalbavancin, although 4 were lost to follow-up, and 5 were judged to have had a clinical response to treatment.

DISCUSSION

To our knowledge, this is the first study evaluating the secondary use of dalbavancin for treating complicated staphylococcal infections among PWUD in the OPAT setting. Our findings support the off-label use of dalbavancin as 1 option for the completion of antibiotic therapy for complicated *Staphylococcus aureus* infections among PWUD, following an initial period of conventional antibiotic treatment, including patients with infective endocarditis. Although PICC placement was often required for antibiotics during hospitalization, PICC placement was avoided in almost 50%, reducing the likelihood of catheter-associated complications such as secondary bacteremia, a recognized complication in the homeless PWID population [8]. We previously reported that medical respite can be an alternative treatment venue for homeless PWUD suffering from serious infections who require parenteral therapy [4]. However, OPAT is generally not an option for housed PWUD, and this then leads to prolonged hospitalizations solely for completion of parenteral antibiotic therapy.

Evidence supporting dalbavancin use outside of its currently approved indication for acute bacterial skin and skin structure infections (ABSSSIs) is limited despite its off-label use in clinical practice. An initial phase II study of dalbavancin compared with vancomycin for staphylococcal catheter-related bloodstream infections demonstrated higher efficacy of dalbavancin (87% vs 50%), although only 56% of vancomycin-treated patients had their catheter removed at baseline, compared with 93% of dalbavancin-treated patients [14]. A more recent retrospective multicenter study in Spain described the use of dalbavancin in 69 patients with prosthetic joint infection, osteomyelitis, catheter-related bacteremia, and ABSSSIs and reported a clinical efficacy of 84%, with reductions in hospital LOS and cost [1]. Other published clinical experience also documented a 93%

Table 1. Duration, Indication, Prior Treatment, and Outcomes of Patients Receiving Dalbavancin

Duration of Dalbavancin Therapy, wk		Weekly Dalbavancin Doses, mg	Successful Completion of Total Course	Type of Infection	Inpatient Antibiotics Used	No. of Days of Prior Antibiotic	Clinical Response	Reason for Dalbavancin Failure
Planned	Actual							
5	5	1500, 1000, 500, 500, 500	Yes	Osteomyelitis, extremity	Vancomycin, TMP-SMX	10	Yes	
3	3	1500, 1000, 1000	Yes	Bacteremia with infected thrombophlebitis	Vancomycin	6	Yes	
2	2	1000, 500	Yes	Osteomyelitis, extremity	Vancomycin	1	Yes	
3	2	1000, 500	No	Endocarditis	Ceftaroline	4	Yes	
2	2	1000, 500	No	Osteomyelitis, extremity	Vancomycin, doxycycline	17	Yes	
2	2	1000, 500	No	Endocarditis	Vancomycin	8	Yes	
1	1	1000	No	Bacteremia, flexor tenosynovitis	Vancomycin	10	Yes	
1	1	1000	Yes	Septic arthritis	Vancomycin	8	Yes	
1	1	1000	No	Endocarditis	Cefazolin	24	Yes	
1	1	1000	No	Osteomyelitis, spine	Vancomycin	3	Yes	
1	1	1000	Yes	Bacteremia	Vancomycin	3	Yes	
1	1	1000	Yes	Endocarditis	Vancomycin	32	Yes	
1	1	1000	Yes	Bacteremia	Vancomycin	8	Yes	
1	1	500	Yes	Bacteremia	Vancomycin	7	Yes	
1	1	1000	Yes	Osteomyelitis, spine	Vancomycin, ceftriaxone	18	Yes	
1	1	1000	No	Endocarditis, empyema	Vancomycin	24	Yes	
2	1	1000	No	Bacteremia	Vancomycin	16	Yes	
1	1	1000	Yes	Bacteremia	Vancomycin	9	Yes	
NA	3	1000, 500, 500	Yes	Septic arthritis, bacteremia	Vancomycin	20	No	Subsequent surgical debridement needed on day of first dalbavancin dose
2	2	1000, 500	No	Bacteremia with subdural & epidural abscess	Nafcillin	12	No	Development of vertebral osteomyelitis - 8 months later
3	1	1000	No	Osteomyelitis, spine	Vancomycin	29	No	Worsening back pain and bacteremia - 2 months later
2	1	1000	No	Osteomyelitis, extremity	Vancomycin	10	No	Subsequent surgical debridement needed - 4 months later
2	2	1500, 500	Yes	Endocarditis, infected thrombophlebitis	Vancomycin	20	Unknown	
2	2	1000, 500	Yes	Septic arthritis	Vancomycin	14	Unknown	
1	1	1000	Yes	Bacteremia with epidural phlegmon	Vancomycin	8	Unknown	
1	1	1000	Yes	Bacteremia	Vancomycin	7	Unknown	
2	1	1000	No	Bacteremia with epidural abscess	Vancomycin	13	Unknown	
1	1	1000	Yes	Bacteremia	Daptomycin	13	Unknown	
2	1	1000	No	Endocarditis	Cefazolin	13	Unknown	
2	1	1000	Yes	Endocarditis, empyema	Vancomycin	17	Unknown	
2	1	1000	No	Bacteremia with infected thrombophlebitis	Vancomycin, TMP/SMX	11	Unknown	
2	1	1000	No	Endocarditis	Vancomycin	13	Unknown	

Abbreviation: TMP-SMX, trimethoprim/sulfamethoxazole.

clinical success rate among 27 patients with endocarditis [2]. In both studies, information regarding drug use was not reported.

Barriers to dalbavancin use include the cost of the drug and the need for IV access for administration. The majority of the patients in this study received their first dalbavancin dose at the end of their inpatient hospitalization, incurring a substantial cost to our institution, though this may be offset by earlier hospital discharge and a shorter hospital LOS. Subsequent

dalbavancin doses were administered in the outpatient clinic; the majority of this cost was covered by individual patient insurance plans. Obtaining IV access in the outpatient setting for PWID may also be difficult, though of the patients reviewed here, none required clinic PICC placement or delay in treatment due to difficulty obtaining a peripheral IV.

There are several limitations to our study. First, various dalbavancin dosing regimens were used as there are no current standardized dose regimens for dalbavancin use in the treatment of non-ABSSSIs [1, 2]. A single randomized controlled trial demonstrates that 1500 mg of dalbavancin on day 1 and day 8 is effective for the treatment of debrided osteomyelitis [15]. Second, it is difficult to separate the effectiveness of the initial course of antibiotic therapy from any added benefit due to dalbavancin as all patients received both treatments. However, most patients included in this study had deep-seated *Staphylococcus aureus* infections that required prolonged courses of antibiotics, longer than the duration of their initial conventional treatment, suggesting that dalbavancin did contribute to their treatment outcomes. Third, our small sample size and single center limit generalization to other clinical settings. Finally, the low rate of treatment completion, high rate of loss to follow-up, and ability to track patients only in settings linked to our EHR hinder our ability to confidently assess the clinical effectiveness of dalbavancin. Unfortunately, this low rate of engagement in care and follow-up is common among PWUD [7, 16] and highlights the challenges in caring for this population. Among 101 housed and homeless PWID receiving OPAT without dalbavancin from our institution, we note a similar rate of clinical cure (49%) and a high rate of unknown outcome (47%) due to loss to follow-up [17].

In spite of these limitations, our study supports the use of weekly dalbavancin as a reasonable secondary therapeutic alternative to prolonged daily intravenous therapy for the treatment of serious staphylococcal infections among poorly resourced patients who are homeless or use drugs, for whom creating a safe and effective treatment plan can be challenging. Additional studies that employ innovative strategies to keep these hard-to-engage patients in care long enough to complete dalbavancin or alternative treatments are needed to validate this treatment strategy.

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