ORIGINAL RESEARCH

Treatment of acute bacterial skin and skin structure infection with single-dose dalbavancin in persons who inject drugs

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Abstract

Background: Persons who inject drugs (PWID) are at increased risk of acute bacterial skin and skin structure infections (ABSSSIs), a growing healthcare concern. Multiple medical, social, and economic issues, including adherence and comorbidities, complicate the medical care of the PWID population, adversely affecting patient outcomes.

Methods: We assessed demographics and outcomes for the PWID population in a double-blind trial of 698 patients randomized to dalbavancin 1500 mg as a single intravenous (IV) infusion or as a 2-dose regimen (1000 mg IV on day 1; 500 mg IV on day 8) for ABSSSI. The primary endpoint was ≥20% reduction in erythema at 48–72 hours in the intent-to-treat population; clinical status was also assessed at days 14 and 28.

Results: There were 212/698 (30.4%) patients with a history of injection drug use in this clinical trial. Dalbavancin efficacy was similar between the single- and 2-dose therapy groups in the PWID and non-PWID populations at all timepoints. Dalbavancin

was well tolerated in the PWID population, with similar rates of adverse events as the non-PWID population.

Conclusion: Dalbavancin as a single-dose or 2-dose regimen had similar efficacy for the treatment of ABSSSI at all timepoints in the PWID and non-PWID populations. A single 30-minute IV infusion would eliminate the need for indwelling IV access. The convenience of a single dose supervised in a health setting may also optimize treatment adherence in the PWID population.

Keywords: dalbavancin, infectious disease, intravenous, methicillin-resistant *Staphylococcus aureus*, skin infection, staphylococcal, substance abuse.

Introduction

Acute bacterial skin and skin structure infections (ABSSSIs) are a significant global healthcare burden.[1] The incidence and severity of disease has increased in recent years, in parallel with the emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA).[1–3] ABSSSIs are associated with high morbidity and financial burden on healthcare systems[4]; in the United States (US), the proportion of invasive MRSA infections in persons who inject drugs (PWID) increased from 4.1% in 2011 to 9.2% in 2016.[5]

Dalbavancin, a novel lipoglycopeptide antibiotic with a long terminal half-life (14.4–15.5 days),[6] is administered as a 30-minute intravenous (IV) infusion as a single-dose or 2-dose regimen, eliminating the need for a peripherally inserted central catheter. The single-dose regimen may also optimize

adherence especially in the outpatient setting.[7] Dalbavancin is approved in the US and Europe as a single-dose or 2-dose treatment for adults with ABSSSIs caused by susceptible gram-positive organisms, and it has been evaluated in multiple phase 3 clinical trials of skin infection.[1,8–12] With activity against the gram-positive organisms most frequently implicated in ABSSSIs, including MRSA, dalbavancin provides a convenient and well-tolerated treatment option for the management of ABSSSI.[6]

Infectious diseases are a major health issue in PWID, who typically seek medical attention later in their disease course.[13] PWID are at higher risk of recurrent ABSSSIs,[7,14] necrotizing fasciitis, and infective endocarditis due to spread from skin and soft tissue abscesses into the bloodstream, and they are more likely to experience adverse outcomes associated with this disease.[15,16] Medical care for patients with a history of injection

drug use is complicated by medical, social, and economic issues that affect adherence.[13] Noncompliant patient behavior was the most common complication of therapy and an important predictor of poor outcome in hospitalized patients.[13] Safe and effective treatment options that optimize treatment adherence are needed for the PWID population with ABSSSIs.

This subgroup analysis sought to more fully characterize the demographics, baseline characteristics, safety, and efficacy of dalbavancin in the PWID and non-PWID population and as a single-dose therapy versus 2-dose therapy from a previously published global trial.[10]

Methods

Study design

This is a subanalysis of a previously published study (ClinicalTrials.gov NCT02127970).[10] It was a randomized, double-blind, phase 3 clinical trial in 698 adult patients with ABSSSI conducted between April 2014 and March 2015 at 60 centers across the US, Eastern Europe, Russia, and South Africa. All procedures performed in that study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards. The protocol and informed consent form were reviewed by the institutional review boards at each center and all patients provided written informed consent. Data reported in this manuscript are available within the article. Additional data from study NCT01808092 may be requested at http://www.allerganclinicaltrials.com/PatientDataRequest.htm.

Patients were randomized in a 1:1 ratio to receive either dalbavancin 1500 mg as a single IV infusion over 30 minutes followed by a placebo infusion a week later or 1000 mg IV followed by 500 mg IV a week later. Patients and study investigators were blinded to study treatment; the pharmacist was unblinded to the treatment to enable dose adjustments for patients with a creatinine clearance of <30 mL/minute who were not on regular dialysis. Patients were treated as outpatients or inpatients. Randomization was stratified on a number of factors, including the subtype of ABSSSI, with a cap of <30% for patients presenting with a major abscess.

Adjunctive antibacterial therapy with IV or oral metronidazole 500 mg every 8 hours was allowed when anaerobic pathogens were suspected; aztreonam was allowed for the empiric treatment of gram-negative pathogens or for the treatment of gram-negatives confirmed in a post-baseline culture. In this subgroup analysis, we compared outcomes for patients with and without a history of injection drug use.

Patients

For inclusion in the study, patients had an ABSSSI presenting as a major abscess, cellulitis, or traumatic wound/surgical site infection, with an area of erythema of ≥75 cm^2, as described

in the primary manuscript.[10] In addition to erythema, patients had to present with ≥2 localized signs or symptoms of ABSSSI, including purulent drainage, fluctuance, localized warmth, tenderness to palpation, and swelling/induration. Patients also had to present with ≥1 systemic sign of infection within the prior 24 hours, including an elevated body temperature ≥38°C (≥100.4°F), a white blood cell count >12,000 cells/mm^3 or ≥10% immature neutrophils on peripheral smear.

Patients were excluded if they received any antibiotic other than a single dose of a drug with a short half-life (i.e., ≤12 hours) in the previous 14 days. They were also excluded if they presented with gram-negative bacteremia, burns, diabetic foot infection, decubitus ulcer, infected devices, or venous catheter entry site infections, as well as additional criteria. Patients were included in the PWID group if they had prior or current injection drug use in their medical history, as collected at baseline visit. The relevant preferred term in the study was 'drug abuser' as coded using version 17.1 of MedDRA.

Outcome measures

The primary efficacy outcome measure was a comparison of the proportion of patients with ≥20% reduction in erythema associated with the infection at 48–72 hours after the start of treatment in the intent-to-treat (ITT) population. Any patient receiving supplementary rescue antibacterial therapy was considered a nonresponder. Secondary outcome measures included clinical status at day 14 (improvement in clinical signs and symptoms and ≥80% reduction in the area of the lesion) and day 28 (resolution of localized clinical signs and symptoms and ≥90% reduction in the area of the lesion) in the ITT and clinically evaluable (CE) populations. In addition to the inclusion and exclusion criteria, the CE population included patients who received no more than 1 dose of another systemic antibacterial with documented activity against the causative pathogen, received the appropriate adjunctive antibacterial therapy if the ABSSSI included one or more gram-negative aerobic or anaerobic pathogens on culture, and had a clinical assessment in the required time window. An investigator assessment of cure at days 14 and 28 in all CE patients was defined as a success if the patients showed resolution or improvement of all signs and symptoms to such a degree that no further antibacterial therapy was administered.

Safety assessments were performed at each visit throughout the study. In addition to screening for adverse events, physical and routine blood chemistry and hematologic examinations were performed.

Statistical analysis

Efficacy in the PWID population was evaluated by treatment arm, as was efficacy in the non-PWID population, and efficacy for single-dose versus 2-dose dalbavancin treatment was compared in PWID population treated in an outpatient setting. The 95% CIs were computed using the method of Miettinen

and Nurminen, with Cochran–Mantel–Haenszel stratum weights. Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables were used to analyze differences between the two populations. A post hoc analysis was performed using a 99% CI for the primary endpoint, comparing efficacy of the single-dose versus the 2-dose regimen in the PWID population.

Results

Patient demographics and disease characteristics

PWID population versus non-PWID population: Of the 698 patients randomized in the original study, 212/698 (30.4%)

patients had a history of injection drug use and 486/698 (69.6%) patients had no history of injection drug use (Table 1). In the PWID population, 208/212 (98.1%) described their use as ongoing at the time of study enrolment, 3/212 (1.4%) reported use within 12 months of study enrolment, and 1/212 (0.5%) reported use more than 12 months prior to study enrolment. PWIDs were more likely to be younger, male, Hispanic or Latino, and have a lower body mass index than patients without a history of injection drug use. These differences were all statistically significant (Table 1).

Patients with a history of injection drug use were almost exclusively treated as outpatients (98.6%) versus 36.4% of those without a history of injection drug use. The PWID population was more likely to have major abscess and traumatic wound/surgical site infection as the type of ABSSSI compared with the

Table 1. Baseline patient and disease characteristics, ITT population.

Characteristic	PWID (n=212)	Non-PWID (n=486)	*p*-value[a]
Age, y, mean (SD)	44.9 (11.1)	49.6 (15.9)	<0.0001
Male, n (%)	142 (67.0)	265 (54.5)	0.003
Ethnicity, n (%)			<0.001
Hispanic or Latino	87 (41.0)	24 (4.9)	
Other	125 (59.0)	462 (95.1)	
Race, n (%)			0.003
White	198 (93.4)	425 (87.4)	
Black or African American	8 (3.8)	51 (10.5)	
Other	6 (2.8)	10 (2.1)	
Hepatitis C, n (%)	92 (43.4)	11 (2.3)	<0.001
Diabetes, n (%)	7 (3.3)	69 (14.2)	<0.001
BMI, kg/m^2			<0.0001
Mean (SD)	26.0 (4.8)	30.1 (7.9)	
Median (range)	25.1 (18.0–42.6)	28.2 (15.9–70.6)	
BMI distribution, n (%)			<0.001
<25 kg/m^2	102 (48.1)	135 (27.8)	
25–30 kg/m^2	76 (35.8)	146 (30.0)	
>30 kg/m^2	34 (16.0)	205 (42.2)	
Location of trial center, n (%)			<0.001
North America	212 (100.0)	106 (21.8)	
Rest of world	0	380 (78.2)	
Creatinine clearance ≥30 mL/min, n/N (%)	210/211 (99.5)	477/485 (98.4)	0.29
Treated as outpatient, n (%)	209 (98.6)	177 (36.4)	<0.0001
Infection type, n (%)			<0.001
Major abscess	91 (42.9)	88 (18.1)	
Traumatic wound/surgical site infection	85 (40.1)	103 (21.2)	
Cellulitis	36 (17.0)	295 (60.7)	

(Continued)

Table 1.   (Continued)

Characteristic	PWID (n=212)	Non-PWID (n=486)	*p*-value[a]
SIRS,[b] n (%)	60 (28.3)	243 (50.0)	<0.0001
Temperature ≥38°C, n/N (%)	157/211 (74.4)	416/484 (86.0)	0.0002
WBC >12,000 cells/mm^3, n/N (%)	76/209 (36.4)	182/481 (37.8)	0.71
Immature neutrophils ≥10%, n/N (%)	9/183 (4.9)	93/348 (26.7)	<0.0001
Median infection area,[c] cm^2 (range)	289.0 (77–1620)	300.0 (56−4235)	0.49
Median CRP,[d] mg/L (range)	45.0 (1–300)	58.8 (0–300)	0.0412
Plasma lactate, mean (SD), mmol/L	1.5 (0.64)	1.8 (1.01)	0.08
>4 mmol/L, n/N (%)	0/193 (0.0)	13/429 (3.0)	0.012
Pathogen at baseline, n (%)	161 (75.9)	269 (55.3)	<0.0001
MRSA, n/N (%)	54/161 (33.5)	43/269 (16.0)	<0.0001
MSSA, n/N (%)	53/161 (32.9)	146/269 (54.3)	<0.0001
Streptococcus anginosus group,[e] n/N (%)	46/161 (28.6)	7/269 (2.6)	<0.0001
Streptococcus pyogenes, n/N (%)	7/161 (4.3)	29/269 (10.8)	0.020
Gram-negative aerobic organism, n/N (%)	19/161 (11.8)	28/269 (10.4)	0.75

BMI, body mass index; CRP, C-reactive protein; ITT, intent to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PWID, persons who inject drugs; SIRS=systemic inflammatory response syndrome; WBC, white blood cell.

[a]Differences between treatment groups were analyzed using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

[b]SIRS is defined as having ≥2 of the following: temperature <36°C or >38°C; heart rate >90 beats per min; respiratory rate >20 breaths per min; WBC count <4000 cells/mm^3 or >12,000 cells/mm^3 or >10% bands.

[c]Infection area measurements were available for 211 PWID patients and 484 non-PWID patients.

[d]CRP levels were available for 209 PWID patients and 486 non-PWID patients.

[e]*Streptococcus anginosus* group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

non-PWID population, which was more likely to have cellulitis. Significantly more patients in the non-PWID population had immature neutrophils ≥10% and met the criteria for diagnosis of systemic inflammatory response syndrome (SIRS) at baseline. There was no significant difference in the median infection area at baseline between the PWID and non-PWID populations. Likewise, there was no significant difference in the percentage of patients with a creatinine clearance of ≥30 mL/min. Compared with the non-PWID population, the PWID population was more likely to have infection with MRSA or *Streptococcus anginosus* group; the non-PWID population was more likely to have infection with methicillin-sensitive *S. aureus* (MSSA) or *Streptococcus pyogenes* (Table 1).

Baseline blood cultures were performed in all patients prior to initiating dalbavancin therapy. Bacteremia at baseline was identified in 6/212 (2.8%) patients in the PWID group (3 with MRSA, 1 with MSSA, 1 with *S. pyogenes*, and 1 with *Gemella morbillorum*) and 16/486 (3.3%) patients in the non-PWID group (1 with MRSA, 10 with MSSA, 1 with *S. pyogenes*, 1 with *S. pyogenes* and *Streptococcus agalactiae*, 1 with *Streptococcus mitis*, 1 with *Propionibacterium acnes*, and 1 with *Acinetobacter baumannii* complex). All patients with gram-positive bacteremia at baseline and follow-up blood cultures available had documented clearance of bacteremia, irrespective of history of injection drug use or single-dose versus 2-dose dalbavancin regimen.

There were 11 patients in the PWID subgroup on the 2-dose dalbavancin arm (11/107 [10.3%]) who received the first dose and did not receive the second dose: 4 due to loss to follow-up, 2 due to withdrawal of consent, 1 due to lack of efficacy, and 4 for other reasons (2 were incarcerated, 1 had gram-negative bacteremia in the setting of ongoing injection drug use, and 1 had progression of infection/sepsis). There were 10 patients in the non-PWID subgroup on the 2-dose dalbavancin arm (10/242 [4.1%]) who received the first dose and did not receive the second dose: 5 due to adverse events, 1 due to death not related to study drug, 1 due to loss to follow-up, and 3 for other reasons (2 had ABSSSI infection site that only grew gram-negative bacteria from baseline specimen, and 1 had toxigenic diphtheria).

PWID population: single-dose versus 2-dose therapy: The PWID subgroup included 105 patients in the single-dose group and 107 patients in the 2-dose group (ITT population).

At baseline, both groups had similar systemic and localized disease characteristics. Pathogens typically associated with ABSSSI were isolated from the blood or ABSSSI site at baseline in 78 patients (74.3%) in the single-dose group and 83 patients (77.6%) in the 2-dose group. *S. aureus* was the most commonly isolated pathogen, isolated in 47/78 (60.3%) patients in the single-dose group and 59/83 (71.1%) patients in the 2-dose group. With the exception of MRSA, which was isolated more often in patients in the 2-dose group (35/83 [42.2%]) versus the single-dose group (19/78 [24.4%]), pathogens isolated from the lesions or blood of the PWID subgroup were similar across treatment arms.

Outcomes

Based on the primary outcome of reduction in erythema at 48–72 hours, dalbavancin showed similar efficacy as a single-dose and as a 2-dose regimen in the PWID and non-PWID subgroups (Table 2). In the PWID subgroup, 89.5% of patients on the single-dose regimen were clinical responders versus 86.0% of patients on the 2-dose regimen (difference of 3.5% [95% CI: −5.6–12.7]). An additional analysis for the primary endpoint in the PWID subgroup was done with a tighter CI to keep the lower limit within −10%; noninferiority of the single-dose regimen to the 2-dose regimen was maintained even with a 99% CI (difference of 3.5% [99% CI: −8.7–15.9]). In the non-PWID subgroup, 77.9% of patients on the single-dose regimen were clinical responders versus 83.5% of patients on the 2-dose regimen. There was no significant difference between the single- or 2-dose regimens in the PWID or non-PWID subgroups. Secondary outcome success rates were also similar in the PWID and non-PWID subgroups in the CE population at days 14 and 28, with no significant difference between the single- or 2-dose regimens in either subgroup (Table 2).

The PWID subgroup was treated almost exclusively in an outpatient setting (209/212 [98.6%]). Dalbavancin had similar efficacy whether given as a single-dose or 2-dose regimen in the PWID subgroup treated as outpatients, with >95% success rates per the investigator assessment of cure at the end of treatment (day 14) and final visit (day 28) regardless of dosage regimen (Table 3).

Efficacy by baseline pathogen

Dalbavancin achieved similar clinical success rates in the PWID and non-PWID subgroups regardless of baseline pathogen (Table 4). Efficacy was also similar whether MRSA or MSSA was isolated as the causative pathogen, regardless of regimen (Table 4).

Safety

Dalbavancin was well tolerated by patients regardless of regimen or history of injection drug use. Treatment-emergent adverse events (TEAEs) occurred in approximately 20% of all patients (Table 5). The rates of TEAEs, drug-related TEAEs, serious TEAEs, deaths, and TEAEs leading to premature discontinuation of study drug were similar between the PWID and non-PWID subgroups and between the single- and 2-dose regimens. Serious TEAEs were observed in ≤2% of patients. One patient in each treatment group died during the study; neither death was related to dalbavancin. The most common TEAEs included nausea and headache, with similar rates across treatment groups (Table 5). The median duration of TEAEs in the PWID subgroup was 2.0 and 5.0 days for the single- and 2-dose regimens, respectively, with a time to onset of 6.0 and 10.0 days. By comparison, the median duration of TEAEs in the non-PWID subgroup was 3.0 and 2.0 days for the single- and 2-dose regimens, respectively, with a time to onset of 3.0 and 4.0 days.

Table 2.   Efficacy at various timepoints for PWID and non-PWID patients.

Outcome	PWID (N=212)		Non-PWID (N=486)	
	Dalbavancin Single-dose	Dalbavancin 2-dose	Dalbavancin Single-dose	Dalbavancin 2-dose
48–72 hours				
Treatment response (ITT), n/N (%)	94/105 (89.5)	92/107 (86.0)	190/244 (77.9)	202/242 (83.5)
Difference (95% CI)	3.5 (−5.6 to 12.7)		−5.6 (−12.7 to 1.4)	
Day 14				
Clinical success (CE), n/N (%)	78/87 (89.7)	78/85 (91.8)	189/215 (87.9)	192/217 (88.5)
Difference (95% CI)	−2.1 (−11.5 to 7.1)		−0.6 (−6.8 to 5.6)	
Day 28				
Clinical success (CE), n/N (%)	80/85 (94.1)	72/75 (96.0)	170/186 (91.4)	175/192 (91.1)
Difference (95% CI)	−1.9 (−9.7 to 6.0)		0.3 (−5.7 to 6.1)	
CE, clinically evaluable population; CI, confidence interval; ITT, intent to treat; PWID, persons who inject drugs.				

Table 3. Clinical response in the PWID population treated in an outpatient setting.

Outcome	Dalbavancin Single-dose		Dalbavancin 2-dose
48–72 hours			
Treatment response (ITT), n/N (%)	94/104 (90.4)		91/105 (86.7)
Difference (95% CI)		3.7 (−5.2 to 12.8)	
Day 14			
Clinical success (CE), n/N (%)	77/86 (89.5)		77/84 (91.7)
Difference (95% CI)		−2.1 (−11.6 to 7.2)	
Investigator assessment of cure (CE),[a] n/N (%)	83/86 (96.5)		81/84 (96.4)
Difference (95% CI)		0.1 (−6.7 to 7.0)	
Day 28			
Clinical success (CE), n/N (%)	80/84 (95.2)		71/74 (95.9)
Difference (95% CI)		−0.7 (−8.2 to 7.1)	
Investigator assessment of cure (CE),[b] n/N (%)	80/84 (95.2)		72/74 (97.3)
Difference (95% CI)		−2.1 (−9.3 to 5.2)	

CE, clinically evaluable population; ITT, intent to treat; PWID, persons who inject drugs.
[a]End of treatment investigator assessment scheduled for day 14–15.
[b]Final visit investigator assessment scheduled for day 28 (±2 days).

Table 4. Clinical status at day 14 by pathogen in PWID and non-PWID patients in the clinically evaluable population.

Pathogen, n/N (%)	PWID		Non-PWID	
	Dalbavancin Single-dose	Dalbavancin 2-dose	Dalbavancin Single-dose	Dalbavancin 2-dose
Staphylococcus aureus	36/40 (90.0)	45/49 (91.8)	76/83 (91.6)	86/88 (97.7)
MRSA	15/16 (93.8)	26/29 (89.7)	14/16 (87.5)	22/23 (95.7)
MSSA	21/24 (87.5)	20/21 (95.2)	62/67 (92.5)	64/65 (98.5)
Streptococcus agalactiae	0 (0)	0 (0)	3/3 (100)	2/3 (66.7)
Streptococcus anginosus group	21/26 (80.8)	13/13 (100)	3/3 (100)	2/2 (100)
Streptococcus anginosus	2/3 (66.7)	0 (0)	2/2 (100)	1/1 (100)
Streptococcus constellatus	7/8 (87.5)	4/4 (100)	0 (0)	1/1 (100)
Streptococcus intermedius	12/15 (80)	9/9 (100)	1/1 (100)	0 (0)
Streptococcus dysgalactiae	0 (0)	0 (0)	3/3 (100)	3/3 (100)
Streptococcus pyogenes	2/2 (100)	2/3 (66.7)	10/11 (90.9)	14/15 (93.3)
Enterococcus faecalis	0	0	3/3 (100)	7/7 (100)

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PWID, persons who inject drugs.

Discussion

Patients with a history of injection drug use have a similar efficacy and safety profile for the treatment of ABSSSI as those without a history of injection drug use with either the single- or 2-dose dalbavancin regimen. Clinical success by baseline pathogen is also similar in the PWID and non-PWID subgroups, with comparable efficacy in the treatment of MRSA as in MSSA.

With the emergence of MRSA as a causative pathogen in community-acquired ABSSSI, there is an increased need for empiric antibacterial therapy that covers MRSA and

Table 5.   Treatment-emergent adverse events (safety population).

Adverse event, n (%)	PWID (n=211)		Non-PWID (n=484)	
	Dalbavancin Single-dose (n=105)	Dalbavancin 2-dose (n=106)	Dalbavancin Single-dose (n=244)	Dalbavancin 2-dose (n=240)
Patients experiencing ≥1				
TEAE	22 (21.0)	23 (21.7)	48 (19.7)	46 (19.2)
Drug-related TEAE	9 (8.6)	5 (4.7)	16 (6.6)	21 (8.8)
Serious TEAE	2 (1.9)	1 (0.9)	5 (2.0)	4 (1.7)
Death	1 (1.0)	0 (0)	0 (0)	1 (0.4)
TEAE leading to premature discontinuation of study drug	1 (1.0)	0 (0)	5 (2.0)	5 (2.1)
TEAE ≥1%				
Headache	4 (3.8)	3 (2.8)	2 (0.8)	1 (0.4)
Nausea	3 (2.9)	1 (0.9)	9 (3.7)	6 (2.5)
Hypersensitivity	2 (1.9)	0 (0)	0 (0)	2 (0.8)
Infusion site extravasation	2 (1.9)	0 (0)	0 (0)	1 (0.4)
Skin abrasion	2 (1.9)	0 (0)	0 (0)	0 (0)
Diarrhea	1 (1.0)	2 (1.9)	3 (1.2)	0 (0)
Vomiting	1 (1.0)	1 (0.9)	5 (2.0)	2 (0.8)
Cellulitis	0 (0)	3 (2.8)	1 (0.4)	2 (0.8)
Chills	0 (0)	2 (1.9)	0 (0)	2 (0.8)
Dizziness	0 (0)	0 (0)	4 (1.6)	0 (0)
Localized infection	0 (0)	3 (2.8)	0 (0)	2 (0.8)
Nephrotoxicity on therapy[a]				
48–72 hours	2/98 (2.0)	0/97 (0.0)	3/235 (1.3)	7/234 (3.0)
Day 14	0/88 (0.0)	3/91 (3.3)	6/219 (2.7)	6/221 (2.7)

PWID, persons who inject drugs; TEAE, treatment-emergent adverse event.
[a]Nephrotoxicity defined as a 50% increase from baseline serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL.

can be given in an outpatient setting to minimize the risk of disease progression and the development of serious complications. When a patient requires hospital admission due to comorbidities, early discharge is encouraged and may considerably reduce the risks and costs of hospitalization.[7,17]

The safety of dalbavancin in phase 2/3 clinical trials is well established.[18] More recently, dalbavancin administered as a single 1500-mg IV dose was found to be noninferior to the 2-dose regimen given as 1000 mg followed by 500 mg one week later.[10] The use of a single dose providing the equivalent of a 10–14 day treatment course for ABSSSI could offer substantial advantages and help avoid hospitalization or allow an early hospital discharge. The current manuscript more fully elaborated on the demographics, baseline characteristics, efficacy, and safety of single-dose versus 2-dose dalbavancin regimens in the PWID subgroup of the main study.

Single-dose therapy may be particularly useful in populations with poor adherence or at high risk for loss to follow-up, where there is greater potential for the emergence of recurrent infection with resistant strains of bacteria. In our subgroup analysis, 10.3% of the PWID patients in the 2-dose dalbavancin arm did not receive the second dose on day 8, compared to 4.1% of the non-PWID patients in the 2-dose dalbavancin arm; this difference was statistically significant (p=0.047). The most common reasons for missing the second dose in the PWID subgroup were related to social circumstances that may be seen in this population: loss to follow-up (n=4), withdrawal of consent (n=2), or incarceration (n=2), while the most common reasons in the non-PWID subgroup were related to the infection or treatment and were due to investigator judgment to prematurely discontinue study drug: adverse events (n=5), or only gram-negative bacteria identified from ABSSSI infection site (n=2). Dalbavancin as the empiric single-dose treatment for

ABSSSI may be especially useful in the PWID population and in community settings where MRSA is prevalent.

The types of comorbidities in the PWID and non-PWID population in our study are similar to a smaller population in the United Kingdom.[19] Our analysis has also found that the PWID population is younger (mean age, 44.9 versus 49.6 years; $p<0.0001$) and more likely to be male (67.0 versus 54.5%; $p=0.003$) than the non-PWID population. Others have reported similar findings in PWID hospitalized for infective endocarditis, who are more likely to be younger and male than the overall patient group[20]; Chotai et al. also reported a mean age of 41 years and 73% male population in PWID hospitalized with soft tissue abscesses.[19] MRSA was found at higher rates in our PWID population compared to the non-PWID population (33.5 versus 16%; $p<0.0001$), as in other literature[21]; success rates were not significantly different by pathogen, consistent with the known activity of dalbavancin irrespective of the presence of methicillin resistance.

The PWID population, which is more likely to be nonadherent than the non-PWID population, could benefit from single-dose therapy with dalbavancin in a community setting, or in a hospital setting.[17] In hospitalized patients, nonadherence to oral antibiotics after discharge is an important predictor of poor outcome and relapse.[13] In a community setting, adherence can be further compromised; PWID are at higher risk of recurrent ABSSSIs[14] and more likely to have severe disease with adverse outcomes.[15,22] Reasons for outpatient antibiotic failure in PWID also include missed follow-up visits, noncompliance with antibiotic therapy, and documented line manipulation.[22] In our study, the PWID population was less likely to have SIRS and less likely to have a lactate level >4 mmol/L than the non-PWID population, further supporting outpatient therapy in the PWID population. Our analysis shows that dalbavancin 1500 mg administered as a single dose has success rates similar to the 2-dose regimen in the treatment of ABSSSI in the PWID subgroup, with similar success rates as the non-PWID subgroup.

Limitations include that this is a subgroup analysis of a larger study. There are demographic and clinical differences between the PWID and non-PWID subgroups, including that the PWID subgroup is from North America, younger, almost exclusively treated in the outpatient setting, with higher rates of MRSA, abscess and traumatic wound infection, and lower rates of diabetes, SIRS and bandemia than the non-PWID subgroup. The potential advantage of single-dose dalbavancin may also be underestimated as the single-dose dalbavancin regimen was compared with the simple 2-dose regimen in this study and was not compared with other antibiotic therapies with more complicated regimens. Due to the unique issues involved in the care of PWID and the clinical advantages of single-dose therapy for this serious indication, further analysis in this population is merited. The differences in clinical outcomes between the PWID subgroup and non-PWID subgroup and the PWID subgroup receiving single- and 2-dose regimens are small and unlikely to be relevant in a clinical setting.

As noted by Dunne et al. in the original study report of the overall patient group, approximately 90% of patients with ABSSSI and a positive culture at baseline had a gram-positive causative pathogen, and only 5% of patients received adjunctive antibacterial therapy with gram-negative coverage.[10] This differs considerably from the typical approach in hospitalized patients where there is frequent use of potentially unnecessary broad-spectrum antibiotic therapy.[23] In one study, a broad-spectrum antibacterial with gram-negative coverage was given in 61% of patients with cellulitis, 67% of patients with cutaneous abscess, and 80% of patients with skin and soft tissue infections with additional complicating factors, for a median of 3 days.[23] Given our findings that dalbavancin provides a beneficial clinical response regardless of baseline pathogen, dalbavancin offers a useful empiric therapy for patients with ABSSSI and especially for PWID. As a single-dose therapy, dalbavancin can ensure treatment adherence in this population and improve outcomes.

Conclusion

Single-dose dalbavancin has similar success rates to the 2-dose regimen for the treatment of ABSSSI in patients with a history of injection drug use compared to those without a history of injection drug use at all timepoints. A single, convenient 30-minute infusion may optimize therapy in the PWID population compared with alternative options that require prolonged patient adherence to a course of therapy. Further, by avoiding the need for indwelling IV access, which may be required with other IV antibiotics, the dalbavancin treatment regimen is not inadvertently enabling the potential for further drug abuse. Single-dose dalbavancin has the potential to improve clinical outcomes in patients with ABSSSI and a history of injection drug use and should be considered in this population when a susceptible pathogen is strongly suspected or isolated.

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