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Short Communication

Clinical experience with dalbavancin for the treatment of deep sternal wound infection

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ABSTRACT

Objectives: Deep sternal wound infection (DSWI) is a complication of major heart surgery with high morbidity as well as prolonged antimicrobial treatment and hospital length of stay (LoS). Dalbavancin is a new lipoglycopeptide antibiotic active against Gram-positive micro-organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), with a long half-life. This small case series assessed the feasibility of dalbavancin for the treatment of DSWI.

Methods: This was retrospective, observational, cohort study of patients treated with dalbavancin for DSWI over a 2-year period (March 2016 to April 2018) in two cardiac surgery departments in Italy. All patients with DSWI underwent surgical accurate debridement. Dalbavancin was administered during the hospital stay or in an outpatient facility.

Results: Among 15 patients enrolled in the study, MRSA was isolated in 7 (47%), methicillin-resistant *Staphylococcus epidermidis* in 6 (40%) and other coagulase-negative staphylococci in 2 (13%). Dalbavancin was administered by two infusions in 9 patients (60%), whereas 5 patients (33%) received a median of four doses. Fourteen patients received a first dose of 1000 mg followed by 500 mg, whereas one patient received two doses of 1500 mg each. All patients were defined as clinically cured. The median hospital LoS was 13 days (interquartile range, 8–18 days). At 6 months after discharge, 14 patients (93%) showed no relapse of DSWI, whereas 1 patient recurred with a diagnosis of DSWI caused by another pathogen (*Candida* sp.).

Conclusion: Dalbavancin may be an alternative option for DSWI caused by Gram-positive bacteria when first-line treatments are contraindicated or as salvage treatment.

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1. Introduction

Deep sternal wound infection (DSWI) is an infrequent but life-threatening infection complicating major heart surgery that affects between 0.7–3% of patients undergoing cardiac surgery. Common risk factors for DSWI are obesity, diabetes and use of an internal mammary artery for coronary artery revascularisation. Gram-positive cocci, including *Staphylococcus aureus*, are a predominant cause of DSWI accounting for 80% of cases [1–4].

Recent improvements in surgical management have dramatically reduced the fatality rate of DSWI. However, DSWI is still associated with high morbidity and healthcare-associated costs, estimated to be as much as US$35 000–500 000 for each case of DSWI, mainly due to the requirement for prolonged antimicrobial treatment and re-operation as well as a prolonged hospital length of stay [5–9].

Dalbavancin is a new semisynthetic bactericidal lipoglycopeptide synthesised from a fermentation product of *Nonomuraea* sp. that is indicated for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs). Its mechanism of action against susceptible Gram-positive micro-organisms is due to inhibition of cell wall synthesis through binding to D-alanyl-D-alanine groups on the end of the nascent cell wall peptidoglycan, thus preventing cross-linking (transpeptidation

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and transglycosylation) of the disaccharide subunits resulting in bacterial cell death.

This drug has the unique pharmacokinetic property of a terminal half-life of 187.4 h that allows for once-weekly administration [10]. Dalbavancin has a spectrum of activity similar to other glycopeptides, demonstrating bactericidal activity against a variety of Gram-positive pathogens. Thus far, dalbavancin appears to be more active in vitro than either teicoplanin, vancomycin, linezolid or quinupristin/dalfopristin against all tested *Staphylococcus* spp., including methicillin-resistant *S. aureus* (MRSA) [11].

Dalbavancin has been poorly assessed in the treatment of DSWI. Dalbavancin showed similar efficacy to vancomycin in an animal model of mediastinitis and sternal osteomyelitis [12]. Clinical experience of dalbavancin in DSWI is limited to a case report of a patient treated with dalbavancin after failing treatment with vancomycin and rifampicin [13].

In the small case series reported here, the feasibility of dalbavancin for treatment of DSWI was assessed.

2. Methods

This was retrospective, observational, cohort study of patients treated with dalbavancin for DSWI from March 2016 to April 2018. The study protocol was approved by the local ethics committee (Comitato Etico indipendente Area Vasta Emilia Centro). Written informed consent was not required owing to the observational retrospective nature of the study.

2.1. Setting

The study was conducted in the cardiac surgery departments of Maria Cecilia Hospital (Cotignola, Ravenna, Italy), one of the largest centres in Italy performing approximately 1100 open heart surgery per year, and Villa Torri Hospital (Bologna, Italy) performing approximately 350 cardiac procedures per year.

2.2. Population

Consecutive adult patients (age ≥18 years) admitted to one of the study centres for DSWI complicating major heart surgery and receiving dalbavancin as definitive treatment were included in the study.

2.3. Management of deep sternal wound infection

All patients undergoing major heart surgery were managed in a dedicated outpatient service. The suspicion of DSWI was based on pain, cellulitis, purulent drainage, erythema or wound dehiscence, or on chest computed tomography images when present. The diagnosis of DSWI was based on the US Centers for Disease Control and Prevention (CDC) criteria [14] and was defined as either: (i) organisms cultured from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration; (ii) evidence of mediastinitis seen during a surgical operation or histopathological examination; or (iii) a combination of at least one of the following features: fever (>38.8 °C) with no other recognised source after extensive diagnostic work-up, chest pain or sternal instability plus at least one of the following: (a) purulent discharge from the mediastinal area, (b) organisms cultured from blood or discharged from the mediastinal area or (c) mediastinal widening on radiography. DSWIs were classified according to the El Oakley criteria [15]. All patients underwent surgical accurate debridement, wire removal when present and application of vacuum-assisted closure. Deep tissue sampling for microbial cultures was performed during surgical debridement for all patients. Dalbavancin was administered during the hospital stay or in a dedicated outpatient service.

2.4. Data collection

Data were collected using a case report form and the integrity of the data was systematically checked. The following variables were collected at enrolment: demographic variables (sex, age); co-morbidities according to the Charlson comorbidity score; and data of the index surgical intervention, including underlying disease, indication, EuroSCORE II [16], duration of cardiopulmonary bypass and post-surgical complications including arrythmias, neurological, respiratory and renal complications, or bleeding. Infection data included date of diagnosis of DSWI, microbiological results and treatment. Outcome variables included death, hospital length of stay (LoS), relapse of DSWI within 6 months after treatment, and hospital re-admission.

2.5. Statistical analysis

Categorical variables were analysed as absolute numbers and their relative frequencies. Continuous variables were analysed as the median and interquartile range (IQR). Categorical variables were compared using the χ^2 test or Fisher's exact test, whereas continuous variables were compared using the Mann–Whitney *U*-test or two-tailed Student's *t*-test, when appropriate.

3. Results

During the study period, 15 patients were treated with dalbavancin for DSWI. Patients demographics, underlying diseases and characteristics of the index surgical intervention are shown in Table 1. Briefly, 7 patients (47%) were male and the median (IQR)

Table 1
Characteristics of the study population ($N = 15$).

Characteristic	*n* (%)[a]
Male sex	7 (47)
Age (years) [median (IQR)]	65 (57–70)
Diabetes mellitus	7 (47)
Chronic renal failure (moderate/severe)	2 (13)
Charlson comorbidity index [median (IQR)]	6 (2–8)
Index surgical procedure	
CABG	7 (47)
Valvular replacement	5 (33)
Aortic valve	4 (27)
Mitral valve	1 (7)
Aortic aneurysm surgery	2 (13)
Combined CABG + aortic valve replacement	1 (7)
Timing of surgery	
Elective	12 (80)
Urgent	2 (13)
Emergent	1 (7)
EuroSCORE at surgery [median (IQR)]	2 (1–7)
NYHA classification at surgery	
I	3 (20)
II	8 (53)
III	2 (13)
IV	2 (13)
Blood transfusion	
Red blood cells	7 (47)
Platelets	3 (20)
Duration of cardiopulmonary bypass (min) [median (IQR)]	73 (42–104)
Post-surgical complications	
Atrial fibrillation	2 (13)
Tamponade	1 (7)
Stroke	0 (0)
Delirium	1 (7)
Acute renal failure	0 (0)
Pneumonia	0 (0)
Length of ICU stay (days) [median (IQR)]	2 (2–3)

IQR, interquartile range; CABG, coronary artery bypass graft; NYHA, New York Heart Association; ICU, intensive care unit.
[a] Data are *n* (%) unless otherwise stated.

age was 65 years (57–70 years). Most patients (7; 47%) underwent isolated coronary artery bypass grafting (CABG), whereas 6 patients (40%) underwent valvular replacement (1 aortic valve replacement in combination with CABG). Finally, two patients were treated with aortic surgery (one urgent and one emergent intervention). Post-surgical complications were limited to two cases (13%) of atrial fibrillation, one case (7%) of cardiac tamponade with the need for resternotomy and one case (7%) of post-surgical delirium.

3.1. Characteristics of deep sternal wound infections

Characteristics of the DSWIs are summarised in Table 2. Overall, DSWI was diagnosed 42 days (IQR 26–126 days) after the index surgical procedure. Fourteen patients were re-admitted to hospital and one patient was still hospitalised at time of DSWI diagnosis. All patients underwent surgical debridement and were thereafter treated with vacuum-assisted closure therapy for a median of 13 days (IQR 8–15 days). Intraoperative samples were positive in all cases, as follows: MRSA, 7 cases (47%); methicillin-resistant *Staphylococcus epidermidis*, 6 cases (40%); and other coagulase-negative staphylococci, 2 cases (13%). In two cases (13%) blood cultures were positive for MRSA and the result was consistent with intraoperative samples. Empirical treatment consisted of teicoplanin (6; 40%), daptomycin (5; 33%), vancomycin (2; 13%) or a combination of teicoplanin and piperacillin/tazobactam (2; 13%). The reason for dalbavancin use as definitive treatment were: lack of oral antibiotics based on susceptibility test results (5; 33%); decision of the attending physician (5; 33%); previous failure with other treatments (3; 20%) or history of allergy to other drugs (2; 13%). All isolates were tested for susceptibility to dalbavancin before starting therapy and none were found to be dalbavancin-resistant. All nine patients (60%) with mediastinitis types I, II and III were treated with two infusions of dalbavancin of 1000 mg and 500 mg (14 days of treatment). Five patients (33%) with types IV and V mediastinitis received a median (IQR) of 4 (4–5) weekly dalbavancin doses, the first dose at a dosage of 1000 mg and the following at a dosage of 500 mg, and one patient (7%) with type IV mediastinitis received two doses of 1500 mg each. The median hospital LoS was 13 days (IQR 8–18 days). Eight patients received the first dose of dalbavancin during their hospital stay and the remaining patients received dose(s) during an outpatient visit.

Table 2
Characteristics and outcome of cases of deep sternal wound infection (DSWI) treated with dalbavancin ($N = 15$).

Characteristic	n (%)[a]
Timing after surgery (days) [median (IQR)]	42 (26–126)
Classification according to El Oakley criteria	
Type I	1 (7)
Type II	4 (27)
Type IIIA	1 (7)
Type IIIB	3 (20)
Type IVA	1 (7)
Type IVB	1 (7)
Type V	4 (27)
Reason for dalbavancin use as definitive treatment	
Lack of oral antibiotics based on susceptibility test results	5 (33)
Decision of the attending physician	5 (33)
Previous failure with other treatments	3 (20)
History of allergy to other drugs	2 (13)
Microbiology	
Methicillin-resistant *Staphylococcus aureus*	7 (47)
Methicillin-resistant *Staphylococcus epidermidis*	6 (40)
Other coagulase-negative staphylococci	2 (13)
Outcome	
Death during follow-up	0 (0)
Relapse of DSWI within 6 months	1 (7)
Relapse with microbiological failure	0 (0)

IQR, interquartile range.
[a] Data are n (%) unless otherwise stated.

3.2. Outcomes

Patients were followed for 6 months after the end of dalbavancin treatment. One patient relapsed after 97 days, underwent a new surgical debridement and the deep tissue cultures were positive for *Candida albicans*. The remaining 14 patients (93%) showed no relapse of DSWI, did not received any further course of antibiotics and were not re-admitted to hospital for other causes.

4. Discussion

In this retrospective study, 15 patients received dalbavancin as definite treatment of DSWI. Overall, they showed a good clinical outcome in terms of resolution of infection (15/15; 100%) and relapse (1/15; 7%). To the best of our knowledge, this is the first clinical experience of the use of dalbavancin for the treatment of DSWI, with the exception of a single case report [13]. In the registration trials, surgical site infections were included in the study but no data on DWSI were reported [17].

Previous studies on dalbavancin showed a potential role of this antibiotic in the treatment of several infection types other than ABSSSIs [18,19]. In the study by Tobudic et al., dalbavancin was used as primary or sequential treatment for Gram-positive infective endocarditis with a clinical success of 92.6% [20]. Similarly, in a small randomised trial, dalbavancin was more effective than vancomycin in the treatment of catheter-related bloodstream infection [21]. Lastly, in real-life clinical experience, dalbavancin has been administered for the treatment of various type of infections, including osteomyelitis, prosthetic joint infection, bloodstream infection, endocarditis and ABSSSI with clinical success rates of 72–100% [17].

DSWI is a life-threatening complication of patients undergoing major heart surgery. DSWI is also associated with increased healthcare costs, possibly related to the prolonged intravenous (IV) antibiotic treatment that is often prescribed in this situation [22]. A unique characteristics of dalbavancin is the extremely long half-life that allows a once-weekly dose regimen. According to this feature, patients treated with dalbavancin may be discharged earlier than other patients treated with IV glycopeptides or lipopeptides. In the current study, the median hospital LoS for patients with DSWI was 13 days (IQR 8–18 days), which was lower than that commonly reported in the literature for this complication [5,8].

This study is limited by the small sample size and the absence of a direct comparison between antimicrobial agents. However, the success rate and the relatively low relapse rate indicate that dalbavancin may be an alternative option for DSWI caused by Gram-positive bacteria when first-line treatments are contra-indicated or as a salvage treatment.

5. Conclusion

In this study, dalbavancin was used for the treatment of DSWI in 15 patients with favourable outcomes. Further larger comparative studies are needed to assess the cost efficacy of dalbavancin for the treatment of DSWI.

Funding

None.

Competing interests

None declared.

Ethical approval

The study protocol was approved by the local ethics committee (Comitato Etico Area Vasta Emilia Centro). Written informed consent was not required owing to the observational retrospective nature of the study.

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