Le Infezioni in Medicina, n. 2, 250-256, 2023
doi: 10.53854/liim-3102-14

Dalbavancin in catheter-related bloodstream infections: a pilot study

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Article received 15 January 2023, accepted 2 May 2023

SUMMARY

Background: Catheter-related bloodstream infections (CRBSI) represent a frequent complication of vascular catheterization, with high morbidity, mortality, and associated costs. Most infections are caused by Gram-positive bacteria; thus dalbavancin, a new long-acting lipoglicopeptide, may have a role in early patient discharge strategies optimizing treatment and reducing overall costs.
Methods: In this small pilot feasibility study, we assessed the efficacy and safety of a "single step" treatment strategy combining dalbavancin administration (1500 mg IV single dose), catheter removal, and early discharge in adult patients admitted to medical wards in a three-year period.
Results: We enrolled sixteen patients with confirmed Gram-positive CRBSI, with a mean age of 68 years and relevant comorbidities (median Charlson Comorbidity index=7). The most frequent causative agents were staphylococci, with 25% of methicillin-resistant strains, and the majority of infected devices were short term central venous catheter (CVC) and peripherally inserted central catheter (PICC).
Ten out of sixteen patients had been treated empirically before dalbavancin administration. The mean time from dalbavancin administration to discharge was 2 days; none of the patients had adverse drug-related reactions; at 30- and 90-day follow-up, no patients have been readmitted to the hospital due to bacteraemia recurrence.
Conclusions: Our results indicate that single-dose dalbavancin is highly effective, well-tolerated, and cost-saving for Gram-positive CRBSI.

Keywords: Dalbavancin, Catheter-related bloodstream infections, antimicrobial stewardship program.

INTRODUCTION

Dalbavancin is a long-acting semisynthetic lipoglycopeptide antibiotic, strongly bactericidal, currently approved only for the treatment of ABSSSI (acute bacterial skin and skin structure infections). Its broad spectrum is a very attractive feature, given that dalbavancin has shown activity against many Gram-positive microorganisms, in particular *Staphylococcus aureus* but also coagulase-negative staphylococci, *Streptococcus pneumoniae*, β-haemolytic streptococci and vancomycin-susceptible *Enterococcus faecalis* [1-6].
Plasma concentrations of dalbavancin guarantee its bactericidal activity for 14 days after administration of a single 1500 mg dose [1-3]. Despite this

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peculiarity, ABSSSIs remain the only approved indication for dalbavancin, although this setting appears the least interesting for its pharmacokinetic and pharmacodynamic (PK/PD) properties.
Intravascular devices are fundamental in the management of hospitalized patients for delivery of drugs and fluids, nutritional and blood products; such wide use, however, exposes patients to multiple risks, the most common of which are infections. The organisms involved in catheter-related bloodstream infections (CRBSI) belong to normal skin resident flora at the insertion site (mostly coagulase-negative staphylococci, *S. aureus* including methicillin-resistant (MRSA) strains, and enterococci), which may lead to colonization of the catheter tip and subcutaneous space, leading to bacteraemia and sepsis. The diagnosis of CRBSI is based on clinical manifestations of infection (*i.e.* fever, chills, and/or hypotension) along with a positive culture of blood from a peripheral venipuncture and clear evidence that the catheter is the source of infection [7, 8].
The incidence of CRBSI ranges from 0.2 to >2 per 1000 catheter days [9-11]. CRBSI are a common cause of nosocomial infections resulting in substantial morbidity, mortality, increased length of hospital stay, and healthcare costs [12].
Once a CRBSI is suspected, empiric antimicrobial therapy should be administered after appropriate cultures are obtained, and catheter removal should be considered whenever possible, depending on the catheter type (short-term vs long-term vs implanted devices) and ease of new device insertion, the severity of underlying illness, presence of sepsis. Some authors suggest that up to 14 days of antibiotics should be administered for *S. aureus* bacteraemia [13, 14]. The unusually long half-life of a single dose of dalbavancin implies that it could be used efficiently as monotherapy or as a consolidation treatment for CRBSI.
Hence, the management of CRBSI with catheter removal and early discharge shortly after administration of a single dose of dalbavancin might be a reasonable and cost-effective strategy.
The goal of our pilot study is to assess the feasibility of a "single dose dalbavancin approach".

PATIENTS AND METHODS

Patients' characteristics
Between January 1st, 2020, and December 31, 2022, we collected all cases of guidelines-defined diagnosis of CRBSI from Pordenone and San Vito al Tagliamento (Italy) medical wards. The two hospitals, a hub 400-bed and a spoke 200-bed facilities, are the largest acute care hospitals of the local healthcare system (Azienda Sanitaria Friuli Occidentale, Italy) and serve a population of 320.000 inhabitants in Northeast Italy; the medical wards (overall 150 beds capacity) manage cardiological, onco-haematological and respiratory diseases; a structured antimicrobial stewardship program allows for daily medical rounds with attending physicians and phone consultation 24/7.
Patients enrolled met the following inclusion criteria: age ≥18 years and microscopic presumptive Gram-positive CRBIs. Exclusion criteria were: pregnancy and breastfeeding, informed consent not available from patient or legal representative, absence of clinical information from patient or electronic record (*i.e.* immigrants, denial of previous electronic medical records), an alternative focus of infection, hypersensitivity/allergy to glycopeptides; of note, previous ongoing antibiotic treatment was not an exclusion criterion.
The following data were collected during patient interviews or from the electronic medical record: sex, age, BMI, co-morbidities (and age-adjusted Charlson comorbidity index), active malignancy either solid or haematological, diabetes, immunosuppression, chronic renal failure (Kidney Disease: Improving Global Outcome KDIGO >3).
The following data were obtained from hospital records: type of device (short-term central venous catheter - CVC, peripherally inserted central catheter – PICC, Midline catheter), time of clinical suspicion, time of blood cultures, empiric antibiotic treatment instituted, microorganism responsible, susceptibility testing results, drug-related adverse events, infusion discontinuation, discharge date.

Informed consent
All patients provided informed consent for drug administration to treating physicians before participation. The informed consent for using personal clinical data for the study purpose was collected from all participants. Data were anonymized before storage and analysis.

Case definition
Catheter related bloodstream infection was defined as microorganism growth from at least one percutaneous blood culture and from catheter tip

culture. Alternatively, two blood samples (one from a catheter hub and the other from a peripheral vein) were required to meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP) [7].

Microbiological assessment

We collected simultaneous blood cultures from catheter and peripheral venipuncture in all patients enrolled; catheters were removed after dalbavancin administration, and the tips were sent for culture. More precisely, blood cultures (BCs) were collected at baseline from peripheral venipuncture and central/midline catheter, as follows: two sets (4 bottles) from a peripheral vein were obtained from all patients with a suspected CRBSI and repeated at 48-72 hours if clinically indicated at least one set (2 bottles) was collected through the central/midline catheter.

A single venipuncture was used to draw two BC sets. Each set consists of a 10 mL aerobic bottle (BacT/Alert FA Plus) and a 10 mL anaerobic bottle (BacT/Alert FN Plus) (bioMérieux, Marcy l'Etoile, France). When the standard aerobic and/or standard anaerobic blood culture incubated bottles gave a positive signal, the time to positivity was recorded. Gram staining was then performed and microscopic presumptive identification signalled to the attending clinician. An aliquot of positive blood cultures was plated onto solid media and incubated for at least 24 hours; identification was carried out with MALDI-TOF MSI (bioMérieux) according to laboratory-defined standard procedures.

Blood samples were simultaneously processed and the time to positivity of each culture was recorded. If indicated, the catheter tip was removed and sent to microbiology laboratory for quantitative cultures. Catheter colonization was considered if >1000 CFU/mL were recovered from the tip cultures by Cleri's technique [7].

Treatment protocol

Empiric antibiotic therapy was started by physicians at CRBSI suspicion and switched to dalbavancin after microscopic Gram-positive presumptive identification.

Patients were treated with a single IV infusion of 1500 mg dalbavancin in 500 mL 5% dextrose and infused in 60-90 minutes. The intravascular catheter was removed after dalbavancin administration, as soon it was judged safe by treating team (no need to further IV therapies, switch to oral drugs whenever possible, stable oral fluids and food intake, no early severe adverse events, catheter/vascular thrombosis absent at Doppler assessment). Patients were discharged without any further antibiotic treatment.

Drug safety evaluation included assessment of vital signs during dalbavancin administration and one hour thereafter; recording of any reported symptom until discharge; laboratory assessment of renal and liver function until discharge; clinical assessment before and during infusion, at discharge and at the end of treatment period by treating physician or infectious diseases consultant.

At discharge, patients and caregivers were provided contact information in case of symptoms recurrence or possible adverse drug reaction (ADR), and a 30-day clinical follow-up was scheduled.

Doppler ultrasound was systematically performed by attending physicians at the time of clinical suspicion of CRBSI.

Transthoracic echocardiogram (TTE), and transoesophageal echocardiogram (TEE) secondly were performed to rule out endocardial involvement upon cardiologic advice in *S. aureus* and *E. faecalis* bacteraemia [7].

The primary endpoint was clinical success at the end of treatment (EOT), defined as follows: sign and symptoms resolution with no requirement of new systemic antibiotics, no readmission to the hospital within 30 days, and no complications associated with the development of bacteraemia, particularly from *S. aureus.*

Secondary endpoints were drug-related adverse events, and hospital readmission within 30 days for infection recurrence.

RESULTS

During the study period, a total of sixteen infectious episodes occurred and were treated with a single dose dalbavancin.

Patients' and catheters' characteristics are depicted in Table 1: 56.2% of patients were male, with a mean age of 68 years (range 39-94 years); 62.5% of patients were >65 years old. Mean Charlson index was 7 (3-14). Seven out of the 16 patients (43.7%) had active solid neoplasm and one patient had chronic myeloid leukaemia, five (31.2%) had chronic renal disease, 12.5% were diabetic, 25% had systemic and/or cerebral vascular disease;

one patient was active intravenous drugs user.
Admission diagnoses were mostly sepsis (25%, 4 patients), respiratory failure (19%), and cancer-related complications (19%); the remaining diagnoses are outlined in Table 1.

Table 1 - Patients' and catheters' characteristics.

Patient characteristics	*Number (total 16)*
Sex (men/women)	9/7
Age – mean (range)	68 (39-94)
BMI – mean (range)	24.6 (17.7-30.4)
Charlson comorbidity index median (range)	7 (3-14)
Comorbidities: – Malignancy (either solid tumour or haematologic) – Chronic kidney disease – Vascular disease systemic and/or cerebral – Diabetes – Obesity – Active IV drugs use	 8 5 4 2 2 1
Diagnosis at hospital admission: – Sepsis – Respiratory failure – Heart failure/acute coronary syndrome – Chronic decompensated renal failure – Liver failure – Neoplasm – Various	 4 3 1 2 1 3 2
Catheter type – Short term cvc – Midline – PICC	 10 4 2
Aetiology – MSSA – MRSA – MSSE – MRSE – S. capitis – En*terococcus faecalis*	 5 1 3 3 3 1
Empiric treatment: – Daptomycin – Oxacillin – Vancomycin – Ceftaroline – Ceftriaxone	 4 3 1 1 1
Adverse drug reaction	0/16
Infection recurrence at 30 days follow-up	0/16
LOS after dalbavancin administration – mean days (range)	2 (0-6)

In 75% empiric antibiotic therapy was begun at admission. The majority of infections occurred in short-term CVCs (62.5%), whereas 25% in midline, and 12.5% PICC.
Samples were collected both from catheter and peripheral blood in all patients; all catheters were removed after dalbavancin administration, and tips sent for culture.
Out of sixteen CRBSI evaluated in this study, 6 were *S. aureus* infections, 6 *Staphylococcus epidermidis*, 3 *Staphylococcus capitis*, 1 *E. faecalis*. Four out of 15 staphylococci were methicillin-resistant [3 methicillin resistant *Staphylococcus epidermidis* (MRSE), 1 MRSA].
Clinical success at the end of the 30-day follow-up period was 100%.
None of the patients required a new intravascular device. Six out of 16 patients were assessed by TTE, only one by TEE. All echocardiograms were performed between seven and 14 days of bacteraemia onset, and resulted negative. Doppler ultrasound was performed in all patients with none being positive for catheter-related thrombosis (0/16).
Drug safety profile assessment was favorable with no infusion interruptions due to adverse effects; during the 30-day follow-up period, there were no reported ADRs or complications, and no recorded mortality.
No patients were readmitted within 30 days of the original diagnosis.
Ten out of 16 patients received empiric antibiotic therapy before dalbavancin, for a mean of three days: among them, four patients were treated with daptomycin, three with oxacillin; the remaining patients were administered vancomycin (1 pt), ceftaroline (1 pt) and ceftriaxone (1 pt).
Mean time from clinical suspicion of CRBSI to empiric antibiotic therapy was 3 days (range 0-7 days) and mean time from dalbavancin administration to discharge was two days (range 0-6 days). From the start of empiric antibiotic therapy to discharge, patients remained hospitalized overall for 51 days.
We conducted a further follow-up at 90 days based on electronic medical records: of the 16 patients, four died, all from metastatic cancer. Four out of 13 patients were re-hospitalized, one of them, with advanced dementia, for new bacteraemia after 60 days; the isolated organism of the second episode (*S. epidermidis*) was different from that of the first episode (*S. capitis*).

DISCUSSION

Catheter-related bloodstream infections are frequent healthcare-associated infections with a costly impact on the healthcare system, given the massive use of intravascular devices in every therapeutic setting. New treatment approaches, alongside increased prevention efforts, are required in an era of scarce financial resources and need for rapid patients' turnover: outpatient parenteral antibiotic therapy (OPAT) and long-acting antimicrobials are therefore a valuable option to exploit, as part of a structured antimicrobial stewardship program.

In an era of aging population, pressure on healthcare services is increasing, treatments are increasingly effective but with a negative impact on the homeostasis of most fragile patients: elderly, cancer patients, and patients with chronic renal failure are different but somehow similar populations in terms of risk factors for healthcare-associated infections (immune suppression, frequent access to acute care, multiple medical procedures); nevertheless, vascular catheters are unavoidable in these settings to manage long term therapies [3, 15-17]. In oncology setting, CRBSI, besides requiring more prolonged and costly therapies for their treatment, may hinder oncologic care protocols and cause additional mortality [18].

Of note, in our series half of patients were diagnosed with advanced/metastatic cancer, 62% were over 65 years old and one-third had chronic renal failure.

First of all, none of the patients reported a recurrence of bacteraemia requiring hospitalization in the first 30 days after treatment, in agreement with literature data: in a phase II RCT in 2005, of 67 patients affected by Gram-positive CRBSI, thirty-four were treated with vancomycin and 33 were treated with dalbavancin. At 14-day dalbavancin showed ad higher clinical success rate compared with the comparator (87% versus 50%) and no relapse was found in the dalbavancin group [19].

One of the main points of this work is the total absence of adverse drug reactions reported. The safety of dalbavancin is also a highlight, given that it was found to have fewer adverse events than comparator agents [2]. The excellent safety profile was confirmed in several real-life studies evaluating dalbavancin use also in off-label settings in which the overall proportion of adverse effects ranged from 0-13%. Furthermore, serious adverse drug reactions are reported to be less than 3% [20]. Dalbavancin is a safe drug even in patients with renal and hepatic impairment; it demonstrates linear pharmacokinetic properties, low likelihood for drug–drug interactions, and a very long elimination half-life. Overall, it has a favourable risk-benefit profile, mostly mild or moderate adverse events, lower than comparator drugs [2]; additionally, its administration schedule guarantees optimal compliance even in high-risk populations (for example IV drug users). For all these reasons, dalbavancin is increasingly used in other infections requiring long-term therapies, such as bone and joint infections, infective endocarditis, and bacteraemia, with good results and an excellent safety profile [1, 12, 21, 22].

In patients treated with standard antibiotic regimen, the overall hospital length of stay would be approximately 175 days, based on current guidelines [23]. Considering that the average length of stay for medical device-related infections is 12.7 days, the average cost of a CRBSI can therefore be estimated at 13.000 euros. The total costs for the Italian healthcare system serving a population of 60 million, would then be estimated at 80 million euro annually [22].

In Italy, no literature estimates the costs of CRBSI through the DRG system (Diagnosis-Related Groups). In recent Italian work, the cost of a CRBSI varies from €4,080 up to € 14,800 [9].

Prompt diagnosis and early treatment are crucial to reduce morbidity and mortality and optimizing healthcare financial resources.

Over the years, considerable efforts have been made to reduce CRBSI rates: infection control strategies alongside antimicrobial stewardship programs play a pivotal role in reducing healthcare-associated complications, guiding appropriate use of antibiotics, and placing new coming drugs in an appropriate setting.

Bed shortage in medical wards is periodically critical, namely in flu season and recently during the COVID-19 pandemic; also, the characteristics of population, with a large representation of over 65 years old with multiple comorbidities, contribute to the increasing need for hospital admission for acute or chronic decompensated diseases.

For all these reasons, shortening patients' hospital stay with alternative strategies of treatment like OPAT, new therapeutic schemes, and new long-acting drugs, is highly desirable.

From a healthcare perspective, shortening hospitalization and reducing the time in place for intravascular catheters allows prevention of more complications, such as infections, MDRO acquisition, drug-related toxicities, muscle loss, falls, delirium, and pressure sores in elderly patients; this also results in a reduction of nursing care load and allows re-allocation of personnel resources in much-needed settings. Prevention of all types of hospital-associated complications should be a priority for modern healthcare systems and might be an additional quality asset to promote hospitals [8].

Avoidance of long hospitalizations, besides economic and healthcare system considerations, has huge advantages for patients too: they can rapidly return to their home environment and resume normal activities including work, and their quality of life improves. Moreover, patients' perception of the healthcare system and satisfaction increase.

Based on these considerations, we have implemented in our reality a treatment scheme for CRBSI that included dalbavancin single dose administration, removal of the device immediately afterward, and rapid discharge with follow-up. This "single-step therapeutic approach" has proven, in our patient series, to have a favourable risk-benefit and cost profile. This could be part of a new structural organization, derived from the growing epidemiological needs and the scarcity of economic resources, in which high quality and efficacy of care are matched to a global financial resources optimization, considering all aspects of healthcare systems and all settings in a broader picture, not only sectorial costs (drug vs hospital stay vs devices).

Our study has several relevant limitations: first, the small sample size and the absence of a control group with "standard of care" therapy cannot allow drawing definitive conclusions. Second, two third of patients had already an empiric regimen with anti-Gram-positive drugs and this might have impacted on observed positive results of dalbavancin. This was a single-centre feasibility study; thus, the results may not be widely generalizable.

In conclusion, a "single step approach" - single dose dalbavancin administration, immediate catheter removal, and early discharge - resulted in a 30-day absence of bacteraemia recurrences without adverse drug-related events in a limited case series of CRBSI treatments. Despite its apparent high immediate cost, dalbavancin is a safe and cost-effective therapeutic choice for Gram-positive CRBSI treatment once the overall costs have been considered. Additional prospective clinical trials are needed.

Competing interests

No conflict of interest must be declared for any of the authors.

Funding

No fund was used for this study.

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