Effectiveness, safety and cost analysis of dalbavancin in clinical practice

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ABSTRACT

Objectives Dalbavancin is approved for the treatment of complicated skin and soft tissue infections. However, there is growing evidence that other gram-positive infections could be treated with this antibiotic. A study was undertaken in a tertiary hospital in Spain to evaluate the effectiveness and safety of dalbavancin in off-label indications and the potential healthcare cost savings.

Methods A retrospective observational study including all patients treated with dalbavancin in our hospital from October 2016 to August 2019 was carried out. Demographic, clinical and safety variables were collected. Effectiveness was assessed using the clinical and microbiological resolution of the infection and the absence of hospital admissions due to the same infection in the following 3 months.

Results A total of 102 patients were included (69.9% men, n=71; median age 72.5 years (range 56.0–84.0)). Treatment was off label in 71 cases (69.6%). The most frequent off-label indications were catheter-related bacteraemia (15.7%, n=16) and endocarditis (13.6%, n=14). All patients had previously received antibiotics. The main reason for switching to dalbavancin was patient discharge (79.4%, n=81). Dalbavancin was administered during hospitalisation in 66.7% of the patients and in the outpatient setting in 13.7%. The median reduction in length of hospital stay was 14 days per patient. A saving of about 4550 Euros per patient was estimated. 89 patients (93.7%) had clinical and microbiological resolution of the infection at the end of the study. One patient did not finish the dalbavancin infusion due to an allergic reaction.

Conclusions Our results suggest that dalbavancin is a safe and effective alternative to the off-label treatment of gram-positive infections. Its dosage facilitates early discharge and outpatient management of these patients.

INTRODUCTION

Dalbavancin is a lipoglycopeptide antibiotic indicated for the treatment of adult patients with acute bacterial skin and soft tissue infections (SSTI) in the USA and Europe. It is active against gram-positive microorganisms, including different species of multiresistant microorganisms such as methicillin-resistant *Staphylococcus aureus*.[1]

The most relevant pharmacokinetic characteristic is its long half-life (348 hours), which allows a single-dose administration of 1500 mg or a two-dose administration of 1000 mg and 500 mg separated by 1 week. Therapeutic levels are maintained for 15 days.[2] Such dosing allows an early discharge of hospitalised patients who require intravenous antibiotic therapy and reduces the frequency of outpatient hospital visits for parenteral antibiotics, while ensuring therapeutic compliance.

Aside from SSTI, dalbavancin could have potential use in other gram-positive infections due to the increase in resistance and its convenient dosage. This is reflected in studies which included patients with endocarditis,[3 4] osteomyelitis[5] or bacteraemia.[4]

The main objective of this study is to evaluate the use of dalbavancin in a tertiary hospital and its effectiveness and safety in clinical practice. The secondary objective is to evaluate the potential healthcare-related cost savings.

METHODS

Patient selection and study design

A retrospective observational study was performed. All adult patients who started treatment with dalbavancin in our centre between October 2016 and August 2019 were included. Patients were identified via electronic medical records.

The demographic and clinical data collected were sex, age, baseline creatinine blood level, antibiotic allergies, isolated microorganisms and previous use of antibiotics, including duration.

The dalbavancin-related variables applied were indication, dosage, place of administration (outpatient or hospital ward), number of doses received in each, purpose, adverse effects (AEs), concomitant antibiotic prescription and duration.

Effectiveness and safety

Effectiveness was evaluated using the clinical and microbiological resolution of infection. Treatment failure was defined as a persistent primary infection and/or need for antibiotic therapy rescue, relapse during the 3-month follow-up period after the last dalbavancin dose or infection-related death.[1] Patients who did not receive the whole dalbavancin dose, died of other causes or were lost during the follow-up period were not included in this analysis.

To measure safety, dalbavancin-related AEs were recorded through the electronic medical records.

Reduction of hospitalisation and cost analysis

To estimate reduction in hospitalisation days, the therapy days were considered equivalent to the dalbavancin regimen period once the patient was discharged, considering that intravenous administration was the most appropriate alternative in our patients (failure of previous treatments and low adherence). The duration of dalbavancin therapy was defined based on the exposure days once the dose was administered.

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To carry out the cost analysis, days equivalent to the dalbavancin regimen received were calculated for daptomycin. The daptomycin dose was calculated at 10 mg/kg/day for a 70 kg patient, as an intravenous antibiotic with similar indications and spectrum. The period of this regimen was established considering the mean dalbavancin treatment duration in our patients. The public antibiotic prices used were those reported by the Spanish Ministry of Health.

Hospitalisation-related costs (325 Euros is the estimated price for a day of hospitalisation in Spain[6]) and costs of parenteral antibiotic administration at the outpatient hospital (120 Euros per 2 hours[1]) were calculated. The mean number of hospitalisation days of patients included in the study and the number of administrations given at the outpatient hospital were used to complete the mean duration of dalbavancin therapy.

Statistical analyses

All parameters were described according to the nature of the variables. Measurements of central tendency (mean or median) and dispersion (SD or IQR) were included for quantitative variables and absolute and relative frequencies for qualitative variables. Statistical analyses were performed using SAS V.9.4 by an independent statistician.

Ethics

The study was approved by the Ethics Committee of 12 de Octubre University Hospital (Madrid, Spain), which waived the requirement for informed consent due to the study design.

RESULTS

During the study period 102 patients started treatment with dalbavancin (69.6% men, n=71; median age 72.5 years (range 56.0–84.0); and baseline creatinine 1.0±0.5 mg/dL). Of these, 11.8% were allergic to at least one antibiotic (n=12). Most of the dalbavancin-treated infections were caused by *Staphylococcus aureus* (70.6%, n=72). The demographic and clinical characteristics of the study population are shown in table 1.

All patients were treated with antibiotics before starting dalbavancin. The median duration of previous antibiotic therapy was 18.5 days (range 13–29.8).

The most frequent dalbavancin-treated infections were SSTI (30.4%, n=31), catheter-related bacteraemia (15.7%, n=16) and endocarditis (13.7%, n=14) (table 2). Dalbavancin was prescribed for treating off-label indications in most cases (69.6%, n=71).

In 68 patients (66.7%) the dosages used were as follows: a single dose of 1500 mg (n=60) or 1000 mg the first day followed by 500 mg 1 week later (n=8). The remaining patients received alternative dosages (see table 2). Median dalbavancin therapy duration was 14.0 days per patient (range 14–26.3). Additionally, 16.7% of the patients (n=17) received oral antibiotics in combination with dalbavancin. The median duration of concomitant antibiotic therapy was 14.0 days per patient (range 5–28). The most commonly used antibiotics were oral moxifloxacin (n=8) and linezolid (n=4).

The reasons for switching to dalbavancin were hospital discharge (79.4%, n=81), toxicity of the previous therapy (8.8%, n=9), to ensure adherence (5.9%, n=6), poor venous access to receive prolonged intravenous treatment (4.9%, n=5) and microbiological resistance (1%, n=1).

Effectiveness

A total of 102 patients were considered for this analysis. However, seven did not meet the inclusion criteria: one patient did not receive the entire dalbavancin dose due to an allergic reaction, three died from a non-infectious-related cause, and three were lost in the follow-up period. Therefore, 95 patients (93.1%) were included in this analysis. Among them, 89 (93.7%) had clinical and microbiological resolution of the infection, with no relapses in the 3-month follow-up period. However, six patients (6.3%) experienced clinical failure. The infection was not resolved in one patient, another died due to the infection and four relapsed during the follow-up period. The outcomes are shown in table 2.

Table 1 Demographic characteristics of the study population and isolated microorganisms

Characteristic	n (%)
No of patients	102 (100)
Age (years)*	72.5 (56.0–84.0)
Sex	
Men	71 (69.6)
Baseline creatinine (mg/dL)†	1.0±0.5
Antibiotic allergies	
Not known	90 (88.2)
Penicillin	5 (4.95)
Aminoglycosides	2 (1.95)
Quinolones	2 (1.95)
Tetracycline	2 (1.95)
Rifaximin	1 (1)
Isolated microorganisms	
Staphylococcus spp	72 (70,6)
No microbiological isolations	11 (10.7)
Enterococcus spp	10 (9.7)
Streptococcus spp	4 (4)
Corynebacterium spp	1 (1)
Cutibacterium spp	1 (1)
Enterococcus spp + *Streptococcus* spp	1 (1)
Enterococcus spp + *Staphylococcus* spp	1 (1)
Staphylococcus spp + *Streptococcus* spp	1 (1)

*Median (IQR).
†Mean±SD.

Safety

Dalbavancin-associated AEs occurred in 3.9% of patients (n=4) and presented as a cutaneous rash (n=1), nausea and vomiting (n=1), infusion reaction (shivering that disappeared after decreasing the administration rate) (n=1) and hypersensitivity (n=1). The patient with hypersensitivity had an eruptive exanthema reaction and dalbavancin administration was stopped.

Reduction in hospitalisation and cost analysis

Regarding the place of administration, 68 patients (66.7%) received dalbavancin during hospitalisation, 14 (13.7%) in the outpatient hospital, 19 patients (18.6%) received some doses during hospitalisation (17 patients received the first dose, one patient received two doses and one received four doses) and the rest of the doses in the outpatient hospital, and one patient received the first dose when hospitalised and the following at his nursing home.

The median reduction in hospitalisation stay was 14 days per patient (range 7–84). This decrease in hospital stay translated into an economic saving of 4450 Euros per patient.

Considering the median duration of dalbavancin therapy and reduction in hospitalisation in our study, the potential cost savings per patient would be 3477.78 Euros compared with

Table 2 Dalbavancin indication, dosage, duration of previous antibiotic, concomitant antibiotic use and its duration, and result

Indicationn (%)	Duration of previous antibiotic (days)*	Dalbavancin dosage				Concomit antantibioticn (%)	Duration of concomit antantibiotic (days)*	Successn (%)	Notincludedn (%)
		Initialdose(mg)	Subsequent dose(s)	Days forsubsequent dose(s)	N (%)				
Skin and soft tissue infections 31 (30.4)	18.5 (13–29.8)	1500			60 (58.8)	Moxifloxacin 8 (7.8) Linezolid 4 (3.9) Ciprofloxacin2 (2) Trimethoprim/ sulfamethoxazole 1 (1) Cefditoren 1 (1) Cloxacillin 1 (1)	14 (5–28)	89 (93.7)	7 (6.9)
Catheter-related			1×1500 mg	15	14 (13.7)				
Bacteraemia 16 (15.7)			2×1500 mg	15	3 (2.9)				
Endocarditis			6×1500 mg	15	2 (1.9)				
14 (13.7)			1×1500 mg	7	1 (1)				
Bacteraemia with			5×1500 mg	30	1 (1)				
suspected endocarditis 11 (10.8)				15	1 (1)				
Prosthetic joint			1×500 mg	15	1 (1)				
infection 11 (10.8)			1×1000 mg	15	1 (1)				
Osteomyelitis			2×500 mg	7	1 (1)				
11 (10.8)			5×500 mg	7	1 (1)				
Bacteraemia		1000	500 mg	7	8 (7.8)				
5 (4.9)			-	-	3 (2.9)				
Septic arthritis			5×500 mg	7	2 (1.9)				
2 (1.9)			2×500 mg	7	1 (1)				
Febrile syndrome			3×500 mg	7	1 (1)				
without focus 1 (1)			4×500 mg	7	1 (1)				

*Median (range).

treatment with daptomycin during hospitalisation or 812.78 Euros compared with receiving daptomycin at the outpatient hospital (table 3).

DISCUSSION

In this study we observed a high percentage of off-label dalbavancin use. Most of our patients achieved clinical success, with infection resolution and no relapses in the 3-month follow-up period after finishing treatment. In the patient series published by Bouza *et al* a cure rate of 88% (n=54) was recorded,[1] and in the study by Wunsch *et al* the cure rate was 89% (n=84).[7] Both studies also showed a high off-label use of dalbavancin (78.3% and 89%, respectively). These results are in line with those observed in our study.

The patient who died in our study after receiving dalbavancin was at the end of life. Despite this, the antibiotic was administered. Recent studies have estimated that the use of antibiotic therapy at the end of life is common, with frequencies between 27% and 88% depending on the population.[8] However, in most cases this practice does not increase survival.[9]

Although most of the dosages used in our study were those indicated on the label, we observed a wide variability in the rest. This may be due to the sequential therapy administered with dalbavancin in many of the off-label indications, considering its long half-life. Thus, dalbavancin levels are maintained during the necessary treatment time with a weekly or every two weeks administration.[2 10] Further investigations should be carried out to standardise the optimal dosage of this antibiotic in off-label indications that are common in clinical practice.

Daptomycin was chosen as a comparator due to the complexity of our study population (multiple previous lines of antibiotics, toxicity and/or failure with previous antibiotic therapies, age and polypharmacy, resistance). Therefore, the cost-saving analysis cannot be extrapolated to less complex patients who may have more cost-effective therapeutic options.

The potential economic savings observed in our study are related to the reduction in the number of hospitalisation days. Early hospital discharge also reduces the risk of acquiring healthcare-related infections, which is higher for longer stays.[11] Dalbavancin treatment also allows for early venous catheter removal, which reduces the risk of catheter-related infections.[12] Linezolid is an oral antibiotic with activity against resistant gram-positive microorganisms. However, when prescribing oral antibiotics, patients must understand the importance of finishing the cycle and treatment compliance. Additionally, AEs frequently appear in such prolonged treatments. Some recent clinical trials have compared intravenous versus switching to oral antibiotic therapies for treating endocarditis[13] or bone and joint infections[14] and have shown that switching to oral antibiotic therapy was non-inferior to continued intravenous treatment.[13 14] Therefore, oral antibiotic therapy should be considered as an alternative to intravenous antibiotics in individual cases.

In our study, AEs were uncommon and mild. All had been previously described in the literature with similar frequencies.[1 7] The patient who presented with hypersensitivity did not have

Table 3 Cost comparison of 14 days of antibiotic treatment with dalbavancin versus daptomycin per patient

Place of administration	Antibiotic dose and cost	Healthcare-related cost	Total cost	Cost difference
Hospitalisation	Dalbavancin 1500 mg 2531.94€	1 hospitalisation day 325€	2856.94€	3477.78€
	Daptomycin 700 mg 1784.72€	14 hospitalisation days 4550€	6334.72€	
Outpatient hospital	Dalbavancin 1500 mg 2531.94€	1 administration 120€	2651.94€	812.78€
	Daptomycin 700 mg 1784.72€	14 administrations 1680€	3464.72€	

What this paper adds

What is already known on this subject

- Dalbavancin is approved for the treatment of complicated skin and soft tissue infections.
- Dalbavancin could have potential use in other gram-positive infections due to its convenient dosage and the increase in bacterial resistance.

What this study adds

- Our study shows that dalbavancin is a safe and effective alternative for treating complicated infections in a real-life setting.
- Cost minimisation analysis indicates that using dalbavancin would be justified in healthcare settings due to the reduction in the number of hospitalisation days and the saving of outpatient hospital resources.

any known allergy. Hypersensitivity reportedly occurs in less than 2% of patients who receive this antibiotic, so the rate of this AE would be within the expected range.

The main limitation of our study is its retrospective nature. All our patients had previously received antibiotics, so it is difficult to know whether success was only due to the antibiotic under study. Additionally, the follow-up period should be longer for some infections. Despite its advantageous dosage and consequent savings in healthcare-related costs, the policy of rational use of antibiotics in every hospital should also be considered. On the other hand, dalbavancin is a recently commercialised drug and clinical experience is limited. Therefore, close monitoring of patients who have received dalbavancin is recommended as its long-term safety remains unknown.

CONCLUSION

Our results show that the potential use of dalbavancin extends beyond the authorised indication in clinical practice with a high percentage of effectiveness. Its main advantage is the dosage, allowing early discharge and outpatient management of patients. Dalbavancin also has a favourable safety profile in the short term. Long-term safety and effectiveness studies and dosage optimisation in off-label indications are warranted.

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