



Multicenter clinical experience of real life Dalbavancin use in gram-positive infections



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ARTICLE INFO

Article history:

Received 14 January 2019

Received in revised form 12 February 2019

Accepted 13 February 2019

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Dalbavancin
Osteomyelitis
PJI
Endocarditis

ABSTRACT

Dalbavancin, a lipoglycopeptide with prolonged half-life approved for the treatment of acute bacterial skin and soft tissue infections, can be used for the treatment of infections caused by gram-positive bacteria requiring long term treatment such as endocarditis, prosthetic joint infections (PJI) or osteomyelitis. Clinical data are limited in these settings.

Objectives: To evaluate indications, safety, tolerability and long-term outcomes of dalbavancin-treated patients.

Patients and methods Our multicenter, retrospective study includes patients who received dalbavancin in Austria from September 2016 to March 2018. 90-day outcomes and tolerability were determined.

Results: A total of 101 patients were included in 3 centers (57% male, median age 65 years). The treated infections were PJI (31%), osteomyelitis (29%), endocarditis (25%) and acute bacterial skin and soft tissue infections (12%). Concomitant use of other antimicrobial substances was common (63%). The mean total cumulative dose of dalbavancin was 3,357 mg ($\pm 2,283$ mg). Clinical success rate was 89%. Side effects occurred in 3/101 patients.

Conclusion: In this real-life study dalbavancin was primarily used in off-label indications for treatment of PJI, osteomyelitis and endocarditis. Success rate was high (89%), tolerability and safety were excellent in this setting. Dalbavancin may therefore be used in these off-label indications as alternative treatment approach.

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Introduction

Dalbavancin is a lipoglycopeptide approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients (Scott, 2015; Dunne et al., 2016a). It shows activity against a wide spectrum of gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. Its unique pharmacokinetic profile includes a prolonged elimination half-life of 14.4 days and good penetration into bone and synovial fluid (Chen et al., 2007; Bassetti et al., 2018; Dunne et al., 2015; Leighton et al., 2004). It has a favorable safety profile (Chen et al., 2007; Seltzer et al., 2003;

Dunne et al., 2016b; Leuthner et al., 2016) and was well tolerated in a phase I extended duration study (Dunne et al., 2015).

Dalbavancin offers potential for outpatient parenteral antibiotic therapy (OPAT) of patients with bacterial infections such as infective endocarditis or osteomyelitis which otherwise require long hospitalization due to daily administration of intravenous antibiotics over several weeks (Bassetti et al., 2018; Dunne et al., 2015). A recently published randomized trial found a 2-dose regimen of weekly dalbavancin to be effective and well tolerated for the treatment of osteomyelitis in adults (Rappo et al., 2019). A retrospective single-center study described the successful use of dalbavancin as OPAT in 27 patients with infective endocarditis (Tobudic et al., 2018).

However, data on the clinical efficacy and patients' outcome in a real life use of dalbavancin are still limited. We performed a retrospective multicenter study to evaluate indications, safety, tolerability and long-term outcomes of dalbavancin-treated patients.

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Patients and methods

We conducted a retrospective multicenter study at the Section of Infectious Diseases and Tropical Medicine, Medical University of Graz (center 1), the Danube Hospital Vienna (center 2) and the Department of Internal Medicine II, Medical University of Innsbruck (center 3). All patients receiving antibiotic therapy with dalbavancin from September 2016 to March 2018 were screened. Patients were excluded if their medical records were not available or incomplete.

Charts and electronic medical records were retrospectively reviewed and the following parameters were obtained: demographic information, type of infection, isolated pathogens, treatment regimen (dosage and number of administrations), reason for choosing dalbavancin, outpatient/inpatient setting, prior and concomitant antibiotic therapy, adverse events, serum creatinine levels before and after dalbavancin administration and 90-days outcome.

The follow-up period was 90 days after the last dose of dalbavancin. Clinical success was presumed when patients had no clinical, laboratory or microbiological evidence of persistent or recurring infection during the follow-up period. Clinical failure was defined as persistence of primary infection, relapse of primary infection or death as previously described (Bouza et al., 2017). Elevated serum creatinine levels were evaluated for reversibility. Acute kidney injury (AKI) was classified according to RIFLE criteria (Bellomo et al., 2004).

Statistical analysis was performed for descriptive purposes with the IBM SPSS software for Windows, version 23. For statistical analysis Mann–Whitney-U test and Cramer V test were used as appropriate. Statistical significance was defined by a 2-tailed p-value ≤ 0.05 . The study was approved by all three local ethics committees.

Results

Patients' characteristics

A total of 101 patients were included (44 female and 57 male) with a median age of 65 years (range 11–93 years). Two patients were younger than 18 years (11 and 15 years). 38 patients were included in center 1, 44 in center 2 and 19 in center 3. Demographic data, causative pathogens and dalbavancin treatment regimen are shown in Table 1.

Infections

The treated infections were prosthetic joint infections (PJI) (31%, n = 32), osteomyelitis (including vertebral osteomyelitis; 30%, n = 30), endocarditis (25%, n = 25; native valve n = 15, prosthetic valve n = 6, cardiac implantable electronic device n = 4), ABSSSI (11%, n = 11) and catheter related bloodstream infections (CRBSI) (3%, n = 3). Three patients who were diagnosed with endocarditis suffered from vertebral osteomyelitis as well.

Pathogens

Eighty-six patients (85%) received dalbavancin as targeted therapy, whereas 15 were treated empirically (15%). The most frequently isolated pathogens were coagulase-negative staphylococci (CNS) (33%, n = 28), methicillin-susceptible *Staphylococcus aureus* (MSSA) (16%, n = 14), methicillin-resistant *Staphylococcus aureus* (MRSA) (9%, n = 8), enterococci (8%, n = 7), streptococci (6%, n = 5) and *Propionibacterium acnes* (5%, n = 4). In 16 patients more than one gram-positive pathogen was isolated. In 5 patients gram-positive pathogens were detected along with gram-negative rods. These patients received dalbavancin in combination with antimicrobial agents covering the respective gram-negative bacteria.

Table 1

Demographic information (n = 101).

Variable	n (%)
Age, y, median (range)	65 (11–93)
Sex	
Male	57 (56.4)
Female	44 (43.6)
Infection type	
PJI	32 (31.7)
Osteomyelitis (including vertebral osteomyelitis)	30 (29.7)
Endocarditis	25 (24.8)
Native valve	15 (14.9)
Prosthetic valve	6 (5.9)
Cardiac implantable electronic device	4 (4)
ABSSSI	11 (10.9)
CRBSI	3 (3)
Pathogens	
CNS	28 (33)
MSSA	14 (16)
MRSA	8 (9)
Enterococci	7 (8)
Streptococci	5 (6)
<i>Propionibacterium acnes</i>	4 (5)
>1 gram-positive pathogen	16 (15.8)
Mixed infection (gram-positive plus gram-negative)	5 (5)
Dalbavancin regimen	
1 × 1500 mg	24 (23.8)
1 × 1500 mg d1 + d8	14 (13.9)
1 × 1500 mg d1 + d8 and in week 8	3 (3)
1 × 1000 mg d1 followed by 500 mg weekly	43 (42.6)
1 × 1000 mg every 14d	3 (3)
Other regimens	14 (13.9)

ABSSSI = acute bacterial skin and skin structure infections.

CRBSI = catheter related bloodstream infections.

CNS = coagulase-negative staphylococci.

MSSA = methicillin-susceptible *Staphylococcus aureus*.

MRSA = methicillin-resistant *Staphylococcus aureus*.

d = day.

Dalbavancin therapy

Dalbavancin was administered intravenously once in a dose of 1500 mg in 24/101 patients (24%). In 14/101 patients (14%) dalbavancin 1500 mg was administered on day 1 and day 8. Three patients (3%) were treated with 1500 mg on day 1 and on day 8 followed by 1500 mg in week 8. A starting dose of 1000 mg on day 1 followed by 500 mg weekly was used in 43 patients (43%). In 3 patients 1000 mg were administered every 14 days (3%). In 14 patients (14%) other regimens were used (Supplement 1)

The median number of administrations was 3 (range 1–32). The mean total cumulative dose of dalbavancin was 3,357 mg ($\pm 2,283$ mg standard deviation). Forty-nine patients (49%) were treated in an outpatient setting. The reasons for choosing dalbavancin treatment as documented by the treating physicians were: the long half-life of the drug in 58% of patients, treatment failure of previous antibiotic treatment in 12%, allergic reactions to other antimicrobial agents in 9%, resistance of pathogens to other substances in 8%, non-compliance of patients in 5%, side effects of prior therapies in 3% and other reasons in 5%

Concomitant use of other antimicrobial substances was observed in 64% (n = 64). The substances used were: rifampicin (22%, n = 14), fluoroquinolones (15%, n = 9 (levofloxacin n = 6, moxifloxacin n = 2, ciprofloxacin n = 1)), fusidic acid (16%, n = 10), betalactams (14%, n = 9), doxycycline (11%, n = 7) and trimethoprim/sulfamethoxazole (11%, n = 7). One patient received fosfomycin in combination with dalbavancin. One patient was treated concomitantly with linezolid for vertebral osteomyelitis due to enterococci. One patient received oral vancomycin to treat a *Clostridium difficile* infection. Five patients received two concomitant antimicrobial substances in addition to dalbavancin. The combinations were

rifampicin plus minocyclin, betalactam plus fucidic acid, betalactam plus fosfomycin, betalactam plus trimethoprim/sulfamethoxazole and fosfomycin plus doxycyclin.

Safety and tolerability

Adverse events occurred in 3/101 patients. One patient with multiple allergies in her medical history developed dyspnea and arterial hypertension (systolic blood pressure 200 mmHg) during the second administration of dalbavancin, therefore the infusion was immediately stopped. The patient was not treated with dalbavancin again. Another patient who was treated for endocarditis and vertebral osteomyelitis for 11 weeks complained of severe fatigue. The third patient was treated long term with weekly infusions for chronic mandibular osteomyelitis and developed vertigo that persisted even after the end of dalbavancin treatment. The patient was followed up for one year after dalbavancin was stopped. The symptoms persisted during this time. In 3/101 patients a reversible increase in creatinine ≥ 0.3 mg/dl from baseline occurred (AKI stage 1; in one patient who received 1500 mg on day 1 and day 8 and in two patients who received 1500 mg only once). No irreversible changes in kidney function tests occurred.

90. -day outcome

The patient who suffered from dyspnea and hypertension during the second dalbavancin administration was excluded from the outcome analysis. She suffered from sternal osteomyelitis. Of the remaining 100 patients six were lost to follow-up and their outcome could not be determined. Eighty-four of 94 patients (89%) had no evidence of infection at day 90 (Figures 1 and 2). Treatment failure occurred in 5/94 patients (5%), another 5/94 patients died (5%). The characteristics of patients with treatment failure and of patients who died are summarized in Tables 2 and 3. The median age of patients who died was 77 years compared to 63 years of all other patients ($p=0.057$).

There was no significant difference between patients who were cured compared to those who suffered treatment failure or death in regard to sex, concomitant antibiotic use, indication for dalbavancin, specific pathogen underlying the infection, number of dalbavancin administrations and dosing regimen.

Discussion

Dalbavancin has been approved for the treatment of ABSSSI in adult patients (Scott, 2015; Dunne et al., 2016a). It was first approved as a two-dose regimen (1000 mg on day 1, 500 mg on day 8) (Scott, 2015). Recently, single-dose dalbavancin (1500 mg) was

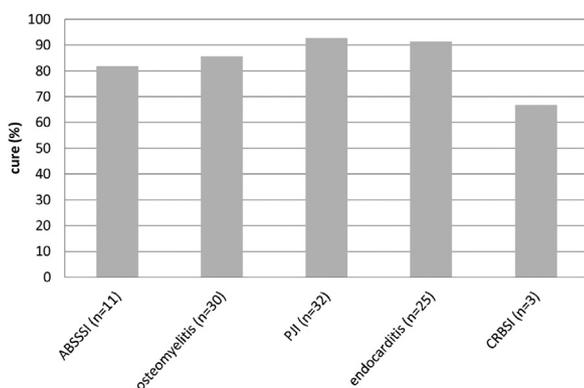


Figure 1. Percentage of cured patients in different indications for dalbavancin use.

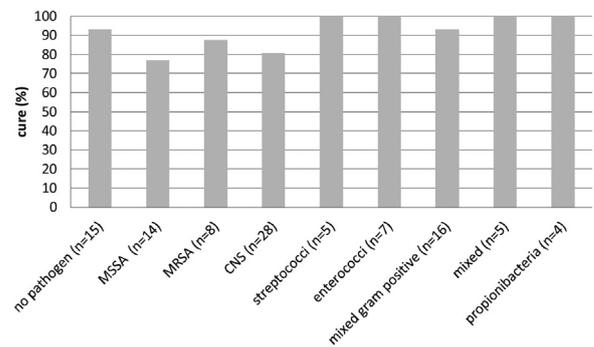


Figure 2. Etiology of infections and percentage of patients cured with dalbavancin.

demonstrated to be non-inferior to the original two-dose regimen (Dunne et al., 2016a; Rappo et al., 2019). Pharmacokinetic studies predicted that a regimen of 1500 mg on day 1 and on day 8 provides a comparable area under the curve (AUC) to 1000 mg on day 1 followed by four weekly doses of 500 mg (Dunne et al., 2015).

These pharmacokinetic properties turn dalbavancin into a treatment option for gram-positive infections requiring long term treatment such as osteomyelitis or endocarditis. Although clinical trials on complicated bacteremia and osteomyelitis are ongoing (NCT03091439, NCT03426761, NCT03148756) and one study on the treatment of osteomyelitis was recently published (Rappo et al., 2019), reports on the clinical use and therapeutic efficacy of dalbavancin in these indications are scarce (Tobudic et al., 2018; Bouza et al., 2017; Almangour et al., 2017). Bouza et al. (2017) conducted a retrospective multicenter study to evaluate clinical experience with dalbavancin in 69 patients in Spain. Long-term follow up was not feasible for all patients, hence the follow-up period was defined as at least one month after discontinuation of therapy. The overall clinical success rate of dalbavancin was high, also for serious gram-positive infections requiring long-term antibiotic therapy.

To our knowledge, our retrospective analysis comprising 101 patients is the most extensive study for this setting so far. The overall clinical success rate in our investigation was 89% which is comparable to the study from Bouza et al. (2017) reporting a cure rate of 84%. Treatment failure occurred in 5 patients in our study. In four of these patients surgical source control was not adequate for various reasons (e.g. patient refused surgery, infected tissue was not removed completely, surgery only performed after relapse). There was no difference in clinical characteristics or dalbavancin regimens between patients who were treated successfully and those who suffered treatment failure. We therefore speculate that treatment failure may have been caused by inadequate source control. Five patients died after their infection was treated with dalbavancin. In three patients death was unrelated to the initial infection (hospital acquired pneumonia, aspiration pneumonia, heart failure). In two patients dalbavancin treatment was not successful, leading to death due to uncontrolled infection (Table 3).

The rate of adverse events during dalbavancin treatment was low (3/101 patients) and led to treatment discontinuation only in one patient. All other patients could be treated as planned which is in line with previously published data underlining the utility of dalbavancin as a safe treatment option for patients in need of prolonged antibiotic treatment (Dunne et al., 2016b; Bouza et al., 2017). Even though dalbavancin is a lipoglycopeptide and may therefore cause renal impairment after application, none of the patients in our study developed severe and persisting renal failure. Twelve patients had a baseline creatinine level ≥ 1.3 mg/dl (maximum 1.99 mg/dl). There was no significant increase in creatinine levels after dalbavancin treatment in any of these patients. However, in patients with severely impaired kidney

Table 2
Characteristics of patients with treatment failure.

Age	Indication	Pathogen	Dosing	Applications	Concomitant antibiotics	Comment
42	Endocarditis (native valve)	CNS	1 × 1500 mg	1	Rifampicin	Surgery performed only after relapse of infection, Patient suffered from Chri-Du-Chat Syndrom
30	ABSSSI involving breast implant	CNS	1 × 1500 mg	1	Rifampicin	During initial surgery exchange of implant and only partial removal of infected tissue
57	PJI	CNS	1 × 1000 mg, 500 mg weekly	13	Trimethoprim/sulfamethoxazole	Pat refused surgery, suppression of infection only, persistent abscess
73	PJI	Unknown	1 × 1000 mg, 500 mg weekly	12	Fosfomycin, Tetracycline	Pat refused surgery, persistent signs of infection
88	ABSSSI (pace maker in situ)	CNS	1 × 1500 mg	1	–	Pace maker exchange performed

CNS = coagulase negative staphylococci.

ABSSSI = acute bacterial skin and soft tissue infection.

PJI = prosthetic joint infection.

Pat = patient.

Table 3
Characteristics of patients with lethal course of disease.

Age	Indication	Pathogen	Dalbavancin Dosing	Applications	Antibiotics prior to Dalbavancin	Concomitant antibiotics	Days btw last Dalbav. & date of death	Comment
86	Shoulder arthritis	MSSA	1 × 1000 mg, 500 mg weekly	4	Azithromycin (3d), amoxicillin/clavulanic acid (14d)	Ceftazidim	3	Heart failure
88	Post-OP osteomyelitis	CNS, enterococci	1 × 1500 mg	1	Not documented	Fusidic acid	42	HAP due to Pseudomonas
77	ABSSSI, bacteremia	MRSA	1 × 1000 mg, 500 mg weekly	8	Fosfomycin (6d), linezolid (6d)	Ertapenem, Cefepim	68	Aspiration associated HAP
70	Endocarditis, Gluteal abscess	MSSA	1 × 1000 mg followed by 1 × 500 mg	2	Amoxicillin/clavulanic acid (5d)	–	9	Due to persistent bacteremia discontinuation of dalbavancin and switch to betalactam therapy; cause of death: sepsis
76	CRBSI	CNS	1 × 1500 mg	1	Amoxicillin/clavulanic acid (duration unknown), piperacillin/tazobactam (duration unknown)	–	10	Sepsis

d = days.

MSSA = methicillin sensitive *Staphylococcus aureus*.

HAP = hospital acquired pneumonia.

ABSSSI = acute bacterial skin and soft tissue infection.

MRSA = methicillin resistant *Staphylococcus aureus*.

CNS = coagulase negative staphylococci.

CRBSI = catheter related bloodstream infection.

function dalbavancin may not be the treatment of choice and should only be administered after critical assessment of risk-benefit ratio.

Several different dalbavancin regimens were used in our study. Most patients (43%) were treated by 1000 mg i.v. on day 1, followed by 500 mg i.v. once weekly, which is in line with the report from Spain by Bouza and colleagues (Bouza et al., 2017). However, 14% of patients were treated with 1500 mg i.v. on day 1, followed by 1500 mg i.v. on day 8 as was indicated by an in vitro study predicting sufficiently high dalbavancin concentrations in bone using this regimen (Dunne et al., 2015). There was no significant difference in outcome between the different regimens used in our study. However, the groups were too small and treatment failures were fortunately too low to draw conclusions on the optimal dosing regimen.

In our study, all endocarditis patients were treated with other antimicrobial agents before switching to dalbavancin for completion of the treatment course. Nine patients were treated with dalbavancin 1500 mg i.v. only once. Eight patients received a

loading dose of 1000 mg i.v. followed by weekly administration of 500 mg. This is in contrast to a recent publication on dalbavancin use in the treatment of endocarditis in which most patients were treated with a regimen of 1500 mg i.v. loading dose, followed by 1000 mg i.v. biweekly (Tobudic et al., 2018). In this study 92% of patients were treated successfully with dalbavancin.

Our study conclusions are limited by the retrospective nature of our study. In addition, long term follow up was not available in 6 cases. Finally, the decision to use dalbavancin was made by the treating physicians. Therefore, no uniform criteria to commence dalbavancin were applied.

In conclusion, in this real-life study dalbavancin was used primarily off-label for treatment of PJI, osteomyelitis and endocarditis. Nevertheless, success rate was high (89%) and tolerability and safety were excellent in this setting. Dalbavancin may therefore be a useful treatment alternative for gram-positive infections requiring long term treatment such as PJI, osteomyelitis and endocarditis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Transparency declarations

IZS, RK, OJ have served on the speaker's bureau of Angelini. JP received consulting fees from Gilead and travel grants from Angelini, Gilead, MSD and Pfizer. AL received travel grants from Angelini. All other authors have none to declare.

The data were presented in part at the meeting of the Austrian Society of Internal Medicine in Salzburg, Austria in September 2018 and at the meeting of the Austrian Society of Infectious Diseases in Saalfelden, Austria in April 2018.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ijid.2019.02.013>.

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