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ORIGINAL PAPER

Real-world experience with dalbavancin therapy in gram-positive skin and soft tissue infection, bone and joint infection

Selma Tobudic[1] · Christina Forstner[1,2] · Heinz Burgmann[1] · Heimo Lagler[1] · Christoph Steininger[1] · Ludwig Traby[1] · Mathias G. Vossen[1] · Stefan Winkler[1] · Florian Thalhammer[1]

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Abstract

Purpose Dalbavancin is a novel lipoglycopeptide with potent activity against several gram-positive pathogens, an excellent safety profile and a long elimination half-life.

Methods In this case series observed at the University Hospital of Vienna between 2015 and 2017, all adult patients with gram-positive infections who received at least one dosage of dalbavancin were screened ($n=118$). A total of 72 patients were included in the final analysis. The number of included patients stratified by the source of infection was: skin and soft tissue infection (SSTI) ($n=26$), osteomyelitis ($n=20$), spondylodiscitis ($n=14$), acute septic arthritis ($n=4$) and prosthetic joint infection ($n=8$).

Results In 46 patients (64%), clinical cure was detected at the end of dalbavancin therapy without additional antibiotic therapy. Of the 26 patients who received additional antibiotic therapy other than dalbavancin, 15 patients (21%) showed no clinical improvement under dalbavancin therapy, four patients (5%) had side effects (nausea $n=1$, exanthema $n=2$, hyperglycemia $n=1$), and in seven patients (10%) clinical improvement under dalbavancin therapy was detected but antibiotic therapy was de-escalated to an oral drug.

Conclusion We demonstrated high clinical effectiveness of dalbavancin for acute gram-positive infections primarily acute SSTI, acute septic arthritis, acute osteomyelitis and spondylodiscitis. In patients with biofilm-associated infection (chronic infection or joint prosthesis), source control was absolutely necessary for treatment success.

Keywords Dalbavancin · SSTI · Osteomyelitis · Vertebral osteomyelitis · Septic arthritis · Prosthetic joint infections

Introduction

Gram-positive bacteria are among the most important human pathogens associated with community-acquired and health-care-associated infections [1]. The most common gram-positive infections, which remain a substantial challenge, include skin and soft tissue infections (SSTIs) and wound infections, bloodstream infections, pneumonia, osteomyelitis, vertebral osteomyelitis, infective endocarditis, and device-related infections [2]. Dalbavancin is a novel lipoglycopeptide approved by European Medicines Agency (EMA) and the US Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in adults [3]. It is approved for the treatment of dalbavancin-susceptible gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and strains with intermediate sensitivity to vancomycin [4]. In vitro studies showed good activity of dalbavancin against several gram-positive pathogens, including *Staphylococcus aureus* (*S. aureus*), *Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus anginosus, Enterococcus faecium,* and *Enterococcus faecalis,* although clinical data regarding the clinical outcome in enterococcal infections are limited [5–8]. Resistance to staphylococci is rare, being reported in less than 1% of isolates [6, 9], but dalbavancin demonstrated poor activity against vancomycin-resistant *S. aureus* (VRSA) and no activity against VanA phenotype-resistant enterococci [10, 11]. Dalbavancin exhibits linear, dose-dependent

✉ Selma Tobudic
selma.tobudic@meduniwien.ac.at

[1] Division of Infectious Diseases and Tropical Medicine, Department of Medicine I, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria

[2] Institute Infectious Diseases and Infection Control, Jena University Hospital, Am Klinikum 1, 07747 Jena, Germany

pharmacokinetics with an elimination half-life of approximately 346 h, allowing a prolonged interval between two doses [12–15]. The approved dosage for dalbavancin for adults with ABSSSIs is a two-dose regimen of 1000 mg on day 1 followed by 500 mg on day 8 and single use of 1500 mg [3, 8, 16]. Due additionally, dalbavancin dose-regimens used in our university hospital include a two-dose regimen of 1500 mg on day 1 followed by 1000 mg on day 14 [17, 18], and a two dose-regimen of 1500 mg on day 1 followed by 1500 mg on day 8 [7, 16, 19, 20]. The prolonged use of dalbavancin for several weeks is well established in our clinical setting [7].

In the present study, clinical outcomes and safety of dalbavancin in the treatment of gram-positive infections in adults, such as skin and soft tissue infection (SSTI), osteomyelitis, vertebral osteomyelitis, prosthetic joint infection and acute septic arthritis, were retrospectively evaluated.

Materials and methods

This case series was performed at the University Hospital of Vienna, Austria, from January 2015 to December 2017. After approval by the local ethics committee in 2017 (No. 1445/2017), we retrospectively screened all adult patients treated by at least one dose of dalbavancin for SSTI, osteomyelitis, vertebral osteomyelitis, acute septic arthritis and prosthetic joint infection. SSTI was defined as acute or chronic. Acute SSTI was defined as erysipelas, major abscess, traumatic wound or surgical site infection. Erysipelas was defined by physicians using clinical and microbiological criteria. The need of a patient informed consent was waived by the local ethics committee due to the retrospective nature of the present study.

Patient demographics, causative pathogens, antimicrobial therapy employed in the treatment, and overall clinical outcome as judged by the investigators were collected. Dalbavancin data included indication, treatment regimen (regimen 1: 1000 mg on first day and 500 mg every 7 days, regimen 2: 1500 mg on first day and 1000 mg every 14 days, regimen 3: 1500 mg on first day, and on day 8 and in individual cases repetition of 1500 mg on days 56 and 63), duration of therapy and reporting of side effects [7]. The duration of therapy for a single regimen was calculated using the number of administrated dalbavancin doses: time (weeks) for regimen 1 = number of administrated doses × 1; time (weeks) for regimen 2 = number of administrated doses × 2; time (weeks). For regimen 3, the use of 1500 mg dalbavancin on day 1, followed by dalbavancin 1500 mg on day 8 was calculated as 8-week therapy. In case of prolonged therapy and use of 1500 mg on day 53 and day 64, duration of dalbavancin therapy was calculated as 16 weeks. The primary endpoint was defined as clinical cure or failure. Clinical cure was defined as resolution of all clinical signs and symptoms of infection, no additional antibiotic therapy required for the indication initially treated with dalbavancin and no microbiological relapse during the follow-up period of 6 months after completion of treatment. Failure of dalbavancin therapy was defined as no clinical improvement or worsening of current infection or new/recurrent signs and symptoms of infection requiring either a change or addition of antibiotic therapy, or microbiological relapse within 6 months after completion of (initial) treatment [7]. Change of antibiotic therapy was stratified by cause: no clinical improvement, side effect and antibiotic de-escalation to an oral drug. As secondary endpoint, number of patients (%) with clinical failure under dalbavancin therapy but resolution of clinical symptoms after antibiotic change in follow-up of 6 months was determined. Further secondary endpoints were defined as duration of dalbavancin therapy in weeks, number (%) of patients treated with combination therapy, number (%) of patients treated with dalbavancin as sequential therapy and side effects. Creatinine (mg/dl) as a measure of kidney function and liver enzymes (GPT and GOT, U/l) as a measure of hepatotoxicity were monitored at least at the beginning and the end of the dalbavancin therapy (7–14 days after last dose). Dalbavancin outcome was stratified by the causative pathogen isolated at the site of infection.

Results

Demographic data

In the final analysis, we included 38 men and 34 women with a median age of 56.5 years (range 18–92 years). The number of included patients stratified by the source of infection was: SSTI ($n = 26$), osteomyelitis ($n = 20$), vertebral osteomyelitis ($n = 14$), acute septic arthritis ($n = 4$) and prosthetic joint infection ($n = 8$). Table 1 shows the types of SSTI, cause of osteomyelitis and vertebral osteomyelitis, surgical interventions in the case of osteomyelitis, and the treatment strategies in the case of prosthetic joint infections.

Follow-up and clinical outcome

A total of 118 patients with gram-positive infections and at least one dosage of dalbavancin were screened and in 46 patients, long-term follow-up was not available due to an incomplete medical record (missing outcome data $n = 23$, missing microbiological data $n = 9$, missing documentation of exposure $n = 14$). These patients were excluded from further analyses. In the final analysis, 72 patients were included. In 46 patients (64%), clinical cure was detected under dalbavancin therapy without subsequent antibiotic therapy for the initial gram-positive infection. Of the 26 patients who were

Table 1 Patient and disease characteristics ($n=72$)

Age, years, median (range)	56.5 (18–92)
Male sex *n* (%)	38 (53)
SSTI, *n* (%)	26 (36)
Acute	21
Chronic	5
Osteomyelitis, *n* (%)	20 (28)
Cause of osteomyelitis	
Postoperative	8
Diabetic foot	9
Skin ulcera	1
Dental implant	1
Unknown	1
Surgical intervention	
Amputation	3
Debridement	2
Partial resection	1
Vertebral osteomyelitis, *n* (%)	14 (19)
Cause of vertebral osteomyelitis	
Postoperative	1
Hematogenous spread	8
Spine fracture by accident	1
Unknown	4
Acute septic arthritis, *n* (%)	4 (6)
Prosthetic joint infections, *n* (%)	8 (11)
Treatment strategy	
Total prosthesis replacement	4
Amputation	1
Debridement and change of mobile parts	1
No source control	2

n number, *SSTI* skin and soft tissue infection

switched to other antimicrobial treatment, 15 patients (21%) showed no clinical improvement under dalbavancin therapy, 4 patients (5%) had side effects (nausea $n=1$, exanthema $n=2$, hyperglycemia $n=1$), and in seven patients (10%), clinical improvement under dalbavancin was detected but therapy was changed to an alternative treatment other than dalbavancin due to the possibility to use an oral drug. Twelve of the 15 patients without clinical improvement under dalbavancin therapy (80%), also failed to achieve any clinical improvement after change to an alternative antibiotic regimen (Fig. 1). Dalbavancin was used in 14 patients (19%) as primary regime, in 39 patients (54%) as salvage treatment and in 19 patients (27%) as simplification due to outpatient parenteral treatment option.

Clinical outcomes stratified by source of infection

In patients with SSTI, clinical cure with dalbavancin therapy was detected in 20 of 26 patients (77%). In six patients, therapy was switched to a different antibiotic treatment (no clinical improvement $n=5$, side effects $n=1$). Resolution of clinical symptoms after antibiotic change was observed in two patients.

Of 20 patients with osteomyelitis, 13 (65%) patients had clinical resolution of their osteomyelitis with dalbavancin therapy. Only in one patient, resolution of clinical symptoms was achieved after change of antibiotic regimen. In 6 of 13 patients with osteomyelitis and clinical cure (46%), antibiotic therapy was combined with surgical intervention (debridement or amputation).

Seven of 14 patients (50%) with vertebral osteomyelitis had no clinical signs of infection under dalbavancin therapy and did not require further antibiotic treatment in the follow-up period of 6 months. The reasons for therapy change were no clinical improvement under dalbavancin therapy ($n=1$), antibiotic de-escalation to an oral drug ($n=4$) and side effects ($n=2$). After antibiotic change to another regimen, resolution of clinical symptoms and signs of infection was achieved in all seven patients. All patients with acute septic arthritis ($n=4$) showed clinical cure with dalbavancin therapy.

In patients with prosthetic joint infections, clinical cure as final outcome was documented in six of eight patients (75%) treated by combination of antibiotic therapy and surgical intervention (three-stage total prosthesis replacement (TPR) $n=1$, two-stage TPR $n=2$, one-stage TPR $n=1$, amputation $n=1$, debridement and change of mobile parts $n=1$). In three of six patients, dalbavancin therapy was deescalated to an oral drug. In two patients without surgical treatment and with previous long-term antibiotic therapy, dalbavancin achieved no clinical improvement (Table 2).

Table 3 includes all patients with no clinical improvement under dalbavancin therapy. Thirteen of 15 patients (87%) showed no clinical improvement with alternative antibiotics due to missing or incomplete source control (chronic wound, osteomyelitis, prosthetic joint infection). Diabetes mellitus was the most common comorbidity in this patient group.

Median duration (range) of dalbavancin therapy was: 2 weeks (2–16) for SSTI, 8 weeks (4–32) for osteomyelitis, 9 weeks (2–16) for vertebral osteomyelitis, 3.5 weeks (2–10) for acute septic arthritis and 12 weeks (6–32) for prosthetic joint infections. The most common regimen used was regimen 2 (initial dose 1500 mg and 1000 mg each 14 days) in 71% of patients. Clinical cure was seen in 11 of 17 patients (65%) using regimen 1, in 31 of 51 patients (61%) using regimen 2 and in 4 of 5 patients (80%) using regimen 3. All four patients with side effects were treated with regimen 2. In patients with osteomyelitis, prosthetic joint infection, vertebral osteomyelitis and acute septic arthritis dalbavancin was mainly used as sequential therapy (100%, 67%, 86%, and 100%, respectively). Dalbavancin was used as monotherapy in the majority of patients ($n=57$, 79%) (Table 4).

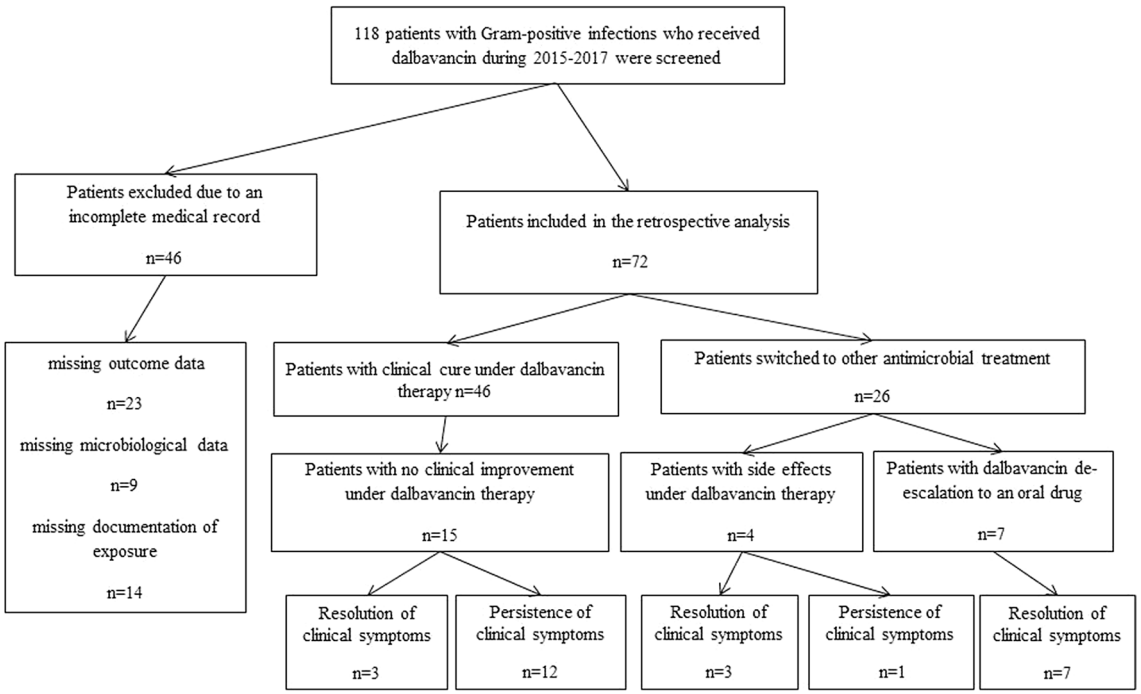

Fig. 1 Flow chart of the study population including follow up and clinical outcome

Table 2 Outcome of all patients after 6-month follow-up ($n=72$) treated with dalbavancin

Indication	Number of patients (%) with clinical cure under DALB	Number of patients (%) with antibiotic change stratified by reasons for change	Number of patients (%) with clinical failure under DALB therapy but resolution of clinical symptoms after antibiotic change
SSTI ($n=26$)	20 (77)	No clinical improvement, $n=5$ (19) Side effects, $n=1$ (4)	2 (8)
Acute ($n=21$)	20 (95)	No clinical improvement, $n=1$ (5)	1 (5)
Chronic ($n=5$)	0 (0)	No clinical improvement, $n=4$ (80) Side effects, $n=1$ (20)	1 (20)
Osteomyelitis, all ($n=20$)	12 (60)	No clinical improvement, $n=7$ (35) Side effects, $n=1$ (5)	1 (5)
Acute postoperative osteomyelitis ($n=7$)	7 (100)	–	0
Chronic osteomyelitis ($n=13$)	5 (38)	No clinical improvement, $n=7$ (54) Side effects, $n=1$ (8)	1 (8)
Vertebral osteomyelitis ($n=14$)	7 (50)	No clinical improvement, $n=1$ (7) Antibiotic de-escalation to an oral drug, $n=4$ (29) Side effects $n=2$ (14)	7 (50)
Acute septic arthritis ($n=4$)	4 (100)	–	0
Prosthetic joint infection ($n=8$)	3 (38)	No clinical improvement, $n=2$ (25) Antibiotic de-escalation to an oral drug, $n=3$ (38)	3 (38)

SSTI skin and soft tissue infection, *DALB* dalbavancin

No significant increase in creatinine (> 1.5× increase) and liver enzyme (> 3× increase) values between start and end of therapy was found.

Clinical outcome stratified by pathogen

Dalbavancin was most commonly applied in patients with staphylococcal infection (MSSA 25%, MRSA 8%, MSSE

Table 3 Characteristic of patients with clinical failure of dalbavancin treatment ($n = 15$)

Indication	Infected site	Pathogen	Prior other antibiotic therapy	Concomitant antibiotic	Resolution of clinical symptoms after switch from DALB to other treatment	Comorbidity
CWI	Foot	MRSA	Yes	No	No	IDDM PAOD
CWI	Hip	MSSE	Yes	No	No	NIDDM
CWI	Abdomen	MRSA	Yes	Moxifloxacin	No	Acne inversa
CWI	Inguinal	MSSA	Yes	No	No	Acne inversa
Postoperative acute SSTI	Breast	MRSA	Yes	No	Yes	Breast cancer
COM	Maxilla	*E. faecalis*	Yes	No	No	Dental implant
COM	Metatarsal	MRSE	Yes	Ciprofloxacin	No	NIDDM PAOD
COM	Metatarsal	*E. faecalis, S. sanguinis*	Yes	No	No	NIDDM PAOD
COM	Metatarsal	MSSA, *Streptococcus spp.*	Yes	No	No	IDDM
COM	Metatarsal	MRSA	Yes	No	No	NIDDM Lymphoma
COM	Tibia	MSSA	Yes	Moxifloxacin	No	PAOD cigarette smoking
COM	Tibia	MSSE	Yes	No	Yes	NIDDM; PAOD
COM	Calcaneus	MSSA	Yes	Clindamycin	No	IDDM
Vertebral osteomyelitis	Lumbal	*C. acnes*	Yes	No	Yes	No
Prosthetic joint infections	Hip	No pathogen found	Yes	Levofloxacin	No	No
Prosthetic joint infections	Knee	*S. anginosus*	Yes	No	No	No

C. acnes Cutibacterium acnes, *COM* chronic osteomyelitis, *CWI* chronic wound infection, *DALB* dalbavancin, *E. faecalis Enterococcus faecalis*, *IDDM* insulin-dependent diabetes mellitus, *MRSA* Methicillin-resistant *Staphylococcus aureus*, *MSSA* Methicillin-sensitive *Staphylococcus aureus*, *MSSE* Methicillin-sensitive *Staphylococcus epidermidis*, *NIDDM* non-insulin-dependent diabetes mellitus, *PAOD* peripheral arterial occlusive disease, *S. sanguinis Streptococcus sanguinis*, *SSTI* skin and soft tissue infection

7% and MRSE 4%), followed by streptococcal infection and infection caused by *Enterococcus faecalis* (*E. faecalis*).

Table 5 shows the outcome of patients stratified by the causative pathogen.

Discussion

This case series provides real-life experience of dalbavancin use for acute and chronic SSTI and for other off-label indications including bone and joint infections in our hospital. The main results of our study were that we found good safety of dalbavancin for short- and long-term treatment and high clinical cure rates in acute infection including erysipelas, acute septic arthritis, acute vertebral osteomyelitis, and acute osteomyelitis, but limited treatment success among chronic infections, particularly in cases with insufficient source control. In the last 3 years, several studies reported experiences with dalbavancin use [7, 8, 19, 21]. In the present work, the overall clinical cure rate (64%) under dalbavancin was lower compared with previous reports (84.1% by Bouza et al. and 89.5% by Wunsch et al.) [8, 19]. Noteworthy, in our case series, dalbavancin was used mainly as salvage treatment (54%) due to missing clinical success of the prior antimicrobial regimen and in off-label indications (54 patients, 75%). Only 14 patients (19%) received dalbavancin as primary treatment regimen. Additionally, it is known that change of antibiotic regimen occurs in clinical practice due to different reasons apart from missing clinical response. In fact, no clinical improvement was detected in 15 patients under dalbavancin, and only in 3 of those 15 patients (21%), clinical cure could be achieved by another antimicrobial regimen.

The management of bone and joint infection or of patients with chronic SSTI is very complex due to the biofilm life of bacteria and clinical success can only be achieved by source control in most cases [22]. Recently, high in vitro activity of dalbavancin against MRSA, MRSE and enterococcal biofilms was reported [23, 24]. However, in the present study, treatment success was particularly low in MRSA infections.

Table 4 Therapy regimen, duration of therapy in weeks, number of patients treated with combination therapy (dalbavancin + other antibiotic) and number of patients treated with dalbavancin as sequential therapy

Indication	Therapy regimen[a] (n)	Duration of DALB therapy (weeks) Median (range)	Number (%) of patients treated with combination therapy (DALB + other AB)	Number (%) of patients treated with DALB as sequential therapy
SSTI *n* = 26	1 (9) 2 (16) 3 (1)	2 (2–10)	2 (8)	11 (42)
Osteomyelitis *n* = 20	1 (2) 2 (17) 3 (1)	8 (4–32)	5 (25)	20 (100)
Vertebral osteomyelitis *n* = 14	1 (3) 2 (9) 3 (3)	9 (2–16)	5 (36)	12 (86)
Acute septic arthritis *n* = 4	1 (2) 2 (2) 3 (0)	3.5 (2–10)	1 (25)	4 (100)
Prosthetic joint infections *n* = 8	1 (1) 2 (7) 3 (0)	12 (6–32)	2 (33)	4 (67)

AB antibiotic, *DALB* dalbavancin, *n* number, *SSTI* skin and soft tissue infection

[a]Therapy regimen 1: 1000 mg on first day and 500 mg every 7 days; therapy regimen 2: 1500 mg on first day and 1000 mg every 14 days; therapy regimen 3: 1500 mg on first day, and on day 8 and in individual cases repetition of 1500 mg on days 56 and on day 63

Furthermore, treatment success was low in patients with diabetic foot syndrome (40%), with prolonged use of dalbavancin alone or in combination not being superior compared with other antibiotics. In patients with chronic osteomyelitis, clinical cure rates were 39% under dalbavancin and 46% after changing to a further regimen. In a recently published randomized clinical trial, dalbavancin achieved response rate as high as 97% in patients with osteomyelitis [16]. However, in this trial, dalbavancin was used as primary option for patients with a first episode of osteomyelitis and not for chronic cases. In accordance, we also detected a high clinical cure of 100% in patients with acute osteomyelitis.

For vertebral osteomyelitis, a randomized controlled trial demonstrated non-inferiority of 6-week compared with 12-week antibiotic therapy and very recently, it was shown that an early change to an oral drug is non-inferior to intravenous therapy in stable patients [25, 26]. In the present study, dalbavancin was a good treatment option when used as primary or sequential therapy in patients with microbiologically, radiologically, or histologically documented vertebral osteomyelitis. Only in a single patient, treatment was switched from dalbavancin to another antibiotic therapy due to missing clinical response after 6 weeks.

All patients with acute septic arthritis treated with dalbavancin showed clinical cure, but it has to be noted that all patients received dalbavancin as sequential therapy. The most important therapy for prosthetic joint infection is adequate source control including surgical and antibiotic therapy. Similarly as in other studies, for prosthetic joint infections, clinical success under dalbavancin was only reached when used in combination with surgical treatment [27].

The incidence of adverse events observed in this study was similar to that reported in randomized, controlled clinical trials and in real-life reports [7, 8, 16, 19, 21]. In our experience, dalbavancin had an excellent safety profile with no significant drug interactions. Patients were followed for 6 months after the last dose of dalbavancin. We observed acute reactions such as exanthema or hyperglycemia, but detected no long-term negative effects.

In terms of duration of dalbavancin therapy, patients in our hospital received prolonged therapy using different regimens. The rationale of regimen 2 over regimen 1 is to minimize the frequency of intravenous therapy, while maximizing the initial exposure. Initial dose (loading dose) 1500 mg is an approved dose and due to the long half-life > 14 days, a single maintenance dose of 1000 mg every 2 weeks is sufficient to exceed the MIC90 for target gram-positive pathogens. However, if a treatment duration ≥ 6 weeks is planned, then regime 3 is the better option [17, 18]. Our case series has some limitations as other similar studies based on real-life experience due to the retrospective analysis. First of all, the study conclusions are limited due to small number of patients. Second, long-term follow-up was not available in all cases. The decision to start with dalbavancin therapy or to switch to other drugs was mainly taken by physicians; therefore, there were no uniform criteria for using the drug.

In conclusion, we report excellent safety and high clinical effectiveness of dalbavancin for acute gram-positive

Table 5 Outcome of dalbavancin therapy stratified by species

Pathogen	All ($n=72$)
MSSA *n* (%)	27 (38)
Cure (DALB outcome) *n* (%)	18 (67)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	5 (19)
MRSA *n* (%)	6 (8)
Cure (DALB outcome) *n* (%)	0 (0)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	1 (17)
MSSE *n* (%)	5 (7)
Cure (DALB outcome) *n* (%)	3 (60)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	1 (20)
MRSE *n* (%)	3 (4)
Cure (DALB outcome) *n* (%)	3 (100)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	0
Enterococcus spp. *n* (%)	3 (4)
Cure (DALB outcome) *n* (%)	2 (67)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	0
Streptococcus spp. *n* (%)	11 (15)
Cure (DALB outcome) *n* (%)	6 (55)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	4 (36)
Cutibacterium acnes n (%)	3 (4)
Cure (DALB outcome) *n* (%)	2 (67)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	1 (33)
Mixed infection *n* (%)	4 (6)
Cure (DALB outcome) *n* (%)	3 (75)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	0
Unknown *n* (%)	10 (14)
Cure (DALB outcome) *n* (%)	9 (90)
Resolution of clinical symptoms after switch from DALB to other treatment *n* (%)	0

DALB dalbavancin, *MRSA* Methicillin-resistant *Staphylococcus aureus*, *MRSE* Methicillin-resistant *Staphylococcus epidermidis*, *MSSA* Methicillin-sensitive *Staphylococcus aureus*, *MSSE* Methicillin-sensitive *Staphylococcus epidermidis, n* number

infections primarily acute SSTI, acute septic arthritis, acute osteomyelitis and vertebral osteomyelitis. In patients with biofilm-associated infection (chronic infection or joint prosthesis), source control was absolutely necessary for treatment success.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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