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Review

Current trends in the real-life use of dalbavancin: report of a study panel

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ABSTRACT

Dalbavancin is a novel lipoglycopeptide antibiotic with a chemical structure similar to teicoplanin. Dalbavancin has been approved and marketed since 2014 in the USA and 2015 in the European Union for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs) caused by Gram-positive cocci. ABSSSIs include infectious syndromes such as erysipelas, cellulitis, major cutaneous abscesses that require incision and drainage, and both surgical and traumatic wound infections. In current clinical practice, dalbavancin is also used for cardiac implantable electronic device-related soft tissue infection and other prosthetic infections, and therefore when the presence of biofilm is a concern. In this review, we aimed to highlight our experience with the use of dalbavancin for some of the most hard-to-treat Gram-positive infections, as well as a promising strategy in terms of pharmacoeconomic effectiveness. We describe our current real-life clinical practice with the use of dalbavancin, depicting a few representative clinical cases in order to share our own practice in the hospital setting.

1. Introduction

Dalbavancin is a novel lipoglycopeptide antibiotic whose main feature is a very long half-life. Its chemical structure is similar to teicoplanin, with some differences affecting its function. The most important addition to dalbavancin is an extended lipophilic side chain, not present in teicoplanin, that allows dalbavancin to better anchor to the bacterial cell membrane, enhancing its potency, prolonging its half-life and allowing for extended dosing intervals [1]. Dalbavancin also possesses an amidated carboxyl side group that enhances the agent's anti-staphylococcal activity [2]. Specifically, its mechanism of action against susceptible Gram-positive bacteria is due to inhibition of cell wall synthesis through binding to D-alanyl-D-alanine groups on the nascent cell wall peptidoglycan, thus inhibiting cross-linking mechanisms (transpeptidation and transglycosylation) of the disaccharide subunits, resulting in bacterial cell death [3].

2. Target micro-organisms

Gram-positive cocci are common aetiological agents of human infections and are isolated with remarkable frequency from pathological materials in hospital microbiology laboratories. They generally grow well on conventional non-selective culture media, especially blood agar, and can be separated from concomitant Gram-negative bacilli using selective and chromogenic media. One major goal of the diagnostic microbiology laboratory is to rapidly identify Gram-positive cocci such as staphylococci, streptococci and enterococci. Next, semi-automatic or fully automatic systems will define susceptibility to antimicrobials and, most importantly, resistance to methicillin and other antibiotics in staphylococci and re-

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Table 1
Minimum inhibitory concentration (MIC) breakpoints (mg/L) for common pathogenic Gram-positive cocci (EUCAST clinical breakpoint tables) [8]

Antimicrobial	*Staphylococcus aureus*		CoNS		Enterococci		Streptococci	
	S≤	R>	S≤	R>	S≤	R>	S≤	R>
Dalbavancin	0.125	0.125	0.125	0.125	NA	NA	0.125	0.125
Teicoplanin	2	2	4	4	2	2	2	2
Vancomycin	2	2	4	4	4	4	2	2
Linezolid	4	4	4	4	4	4	2	2
Daptomycin	1	1	1	1	4	4	1	1
Oxacillin	2	2	0.25	0.25	NA	NA	NA	NA
Ampicillin	NA	NA	NA	NA	4	8	0.5	2

EUCAST, European Committee on Antimicrobial Susceptibility Testing; S, susceptible; R, resistant; CoNS, coagulase-negative staphylococci; NA, not available.

sistance to penicillin in streptococci and enterococci. Methicillin-resistant *Staphylococcus aureus* (MRSA), first described in the 1960s, continues to spread among hospitalised patients and remains a real threat worldwide [4]. Penicillin/ampicillin resistance is emerging among streptococci and enterococci and multidrug-resistant strains, with no susceptibility to daptomycin, linezolid and/or glycopeptides, may also be observed [5]. In vitro studies showed that the vast majority of MRSA, *Staphylococcus* spp., group A, B, C and G β-haemolytic streptococci, and *Streptococcus anginosus* clinical isolates are susceptible to dalbavancin [2]. Their current susceptibility breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are equal to a minimum inhibitory concentration (MIC) of ≤0.125 mg/L [6]. Non-susceptible isolates are very rare or not yet reported. Dalbavancin MICs must be determined in the presence of polysorbate 80 (0.002% in the medium for broth dilution methods; agar dilution methods have not yet been validated). However, in microbiology practice, *S. aureus*, MRSA, streptococci groups A, B, C and G, and *S. anginosus* isolates susceptible to vancomycin can be reported as also susceptible to dalbavancin [7]. In contrast, whenever the strain is resistant in vitro to vancomycin, dalbavancin should not be used. The disk diffusion method for dalbavancin on *Staphylococcus* spp. is not reliable and cannot distinguish between wild-type isolates and those with VanA-mediated glycopeptide resistance. For streptococci groups A, B, C and G, and *S. anginosus*, disk diffusion criteria have not been defined and an MIC method should be used [7].

Table 1 shows dalbavancin MIC breakpoints for the most common Gram-positive cocci pathogenic to humans compared with other anti-Gram-positive cocci agents.

3. Current indications

Dalbavancin was approved in 2014 in the USA, and 1 year later in Europe, for the treatment of adults with acute bacterial skin and skin-structure infections (ABSSSIs) caused by different bacteria including *S. aureus, S. anginosus, Streptococcus dysgalactiae, Streptococcus pyogenes, Streptococcus agalactiae* and vancomycin-susceptible *Enterococcus faecalis* [9]. Dalbavancin is not indicated to treat patients with bloodstream infections or infective endocarditis (IE), however it demonstrated an important role in treating infections due to highly resistant Gram-positive cocci [10]. For instance, a study conducted at MD Anderson Cancer Center (Houston, TX, USA) reported that in catheter-related bloodstream infections (CR-BSIs) due to coagulase-negative staphylococci (CoNS) and *S. aureus*, including MRSA, usually associated with substantial mortality, prolongation of hospital stay and increased cost of care, dalbavancin was an effective and well-tolerated treatment option [11]. In summary, indications for the use of dalbavancin included in the ABSSSI classification are as follows: skin and soft-tissue infection; cellulitis; major cutaneous abscesses after incision and drainage; and wounds such as superficial and deep surgical infections [12].

4. Mode of use

A defined protocol is used for dalbavancin administration [13]. Dalbavancin must be reconstituted and then further diluted before administration by intravenous (i.v.) infusion, which should last 30 min. Solutions containing sodium chloride must not be used for reconstitution or dilution as this may cause precipitation. Dalbavancin must be reconstituted with sterile water for injection and subsequently diluted with a 5% glucose solution for infusion as indicated in the summary of product characteristics. The content of each 500 mg vial should be reconstituted by slowly adding 25 mL of water for injection. It must not be shaken in order to avoid foaming, but gently mixed by inverting the vial until its contents are completely dissolved. Reconstitution may take up to 5 min. The reconstituted concentrate of each 500 mg vial contains 20 mg/mL dalbavancin and must be clear, colourless to yellow, with no visible floating particles; in the presence of particulate matter or colour change, the solution should be discarded. The reconstituted concentrate must be further diluted with a 5% glucose solution for infusion. To dilute the reconstituted concentrate, the appropriate volume of 20 mg/mL of concentrate must be transferred from the vial into an i.v. infusion bag or a bottle containing 5% glucose solution for infusion. After dilution, the solution for infusion must have a final concentration of between 1 mg/mL and 5 mg/mL dalbavancin. This implies that each 500 mg/25 mL of reconstituted dalbavancin should be diluted in at least 100 mL of glucose. Overall, in our clinical practice, we consider optimal diluting a 1000 mg dose in 250 mL and a full 1500 mg dose in 500 mL of 5% glucose.

Dalbavancin has received regulatory approval for the indication of ABSSSI with a dosing regimen of 1000 mg i.v. administered over 30 min, followed 1 week later by a 500 mg infusion [14]. Subsequently, Dunne et al. ran a clinical trial to compare the safety and efficacy of a single i.v. infusion of 1500 mg of dalbavancin with the standard two-dose regimen for ABSSSIs. In this randomised, double-blind trial, a single 1500 mg infusion of dalbavancin was non-inferior to a two-dose regimen and had a similar safety profile [15], therefore allowing for the single-dose regimen approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

5. Described off-label clinical uses

Dalbavancin has been shown to be an effective alternative treatment option in cases of ABSSSI caused by methicillin-susceptible *S. aureus* (MSSA) refractory to β-lactam treatment [16] and in cardiac implantable electronic device (CIED)-related soft tissue infections, with the presence of prostheses and therefore the presence of biofilm [17]. Other typical infections that harbour biofilm are diabetic foot infections, which, despite their major clinical significance, are currently excluded from treatment with dalbavancin [18].

Table 2
Use of dalbavancin in different common infectious syndromes

Current indications according to the label	ABSSSI
Described off-label uses	Osteomyelitis Spondylodiscitis Infective endocarditis Prosthetic joint infection Septic arthritis

ABSSSI, acute bacterial skin and skin-structure infection.

The long half-life of dalbavancin, its activity against MRSA, and emerging animal and human data about drug distribution with promising bone penetration suggested that it might be considered for the treatment of patients with osteomyelitis, sternal would infection after cardiac surgery, and IE [19,20]. In this review, we describe the efficacy of dalbavancin in different common infectious syndromes and its potential to resolve critical infections after prior treatment failure, allowing the patient to quickly leave the hospital, with consequent remarkable benefit for patients and savings of hospitalisation costs on the healthcare system. To better clarify the concepts, different clinical cases will be assessed reporting the challenges and resolutions adopted by using dalbavancin, envisioning a future effective therapeutic alternative compared with conventional disease management.

Table 2 summarises the current on-label indications and described off-label uses for dalbavancin.

6. Search strategy

A literature search was performed using the MEDLINE and Scopus databases. Keywords included 'antibiotics', 'dalbavancin', 'bone penetration', 'osteomyelitis', 'ABSSSI', 'endocarditis' and 'spondylodiscitis'.

7. Dalbavancin for osteomyelitis

Osteomyelitis is an infection of the bone with frequent serious consequences. It is not an uncommon disorder; infection at a distant body site may spread through the bloodstream into a bone, or an open fracture or surgery may expose the bone to infection. Rappo et al. [21] assessed the efficacy and safety of dalbavancin given as a two-dose regimen for osteomyelitis; this study represents a large randomised comparative clinical trial in adult subjects with a first episode of osteomyelitis defined by symptoms, radiological analysis and elevated C-reactive protein (CRP). Patients were randomised to dalbavancin (1500 mg i.v. on Days 1 and 8) or standard of care osteomyelitis treatment, and clinical response was assessed at 21 days, 6 months and 1 year. Clinical cure at Day 42 was seen in 65/67 (97%) and 7/8 (88%) patients, respectively, in the dalbavancin and standard of care groups in the clinically evaluable population. The clinical response was similar in the dalbavancin group at Day 21 (94%), 6 months and 1 year (96%), with the conclusion that a two-dose regimen of weekly dalbavancin (3 g overall) is effective for the treatment of the first episode of osteomyelitis in adults, with a good tolerability of this drug [21]. In a case of bacteraemic *S. aureus* vertebral osteomyelitis, a common form of haematogenous osteomyelitis, Almangour et al. showed how multiple weekly dalbavancin infusions appeared to be safe, although unable to prevent infection recurrence [22]. Spondylodiscitis (SD) commonly involves the vertebral body, the intervertebral disc and paraspinal tissues. Sometimes vertebral infections can be complicated by spinal epidural abscess and psoas muscle involvement [23]. The incidence of SD ranges from 0.4 to 2.4 cases/100 000 patient-years in Europe. Diabetes, chronic renal or liver failure, immunosuppression, malnutrition and long-term steroid use are the main predisposing factors [24]. The main route of infection is haematogenous dissemination when persistent and recurrent bacteraemia occurs. Approximately 2–20% of IE cases may be complicated by SD. Spinal surgery with implantation of prosthetic material results in SD in 0.5–18.8%. SD is a monomicrobial infection associated with bacterial, fungal and parasitic organisms, and *S. aureus* is responsible for ca. 50% of non-tuberculous spine infections [25]. Tuberculosis is the most frequent cause in developing countries, whilst brucellosis should be included in pathogen identification efforts in patients from the Mediterranean area. The diagnosis of spontaneous SD is established by the combination of clinical symptoms, laboratory tests and characteristic imaging findings, particularly on magnetic resonance imaging (MRI) and positron emission tomography–computed tomography (PET-CT) scan, and on the favourable response to antibiotics. The diagnosis is considered definitive if a micro-organism is isolated in blood cultures and spinal biopsy specimens, and probable if no bacterial organism is isolated. Our group's experience with dalbavancin for SD has been largely satisfactory, as illustrated in the case presented in Box 1.

Box 1. Case presentation 1

A 63-year-old patient with low-grade fever and deep-seated lower back pain for >30 days was admitted to the Infectious Disease Unit of Vallo della Lucania Hospital in June 2018. He had left knee pain, swelling and limited motion for 6 months and had been treated by multiple arthrocentesis and steroid infiltrations. Initial investigation revealed a white blood cell count of 2000/μL, an erythrocyte sedimentation rate (ESR) of 80 mm/h, a CRP of 149 mg/L, moderate anaemia and raised alkaline phosphatase. Procalcitonin, bacterial cultures, Wright's serology, tuberculin skin test, rheumatoid factor, antinuclear antibody and circulating immune complex were negative. Culture of left knee fluid was negative. CT scan evidenced disc changes with hypodense areas and bone abnormalities of L3–L4–L5–S1 and right psoas muscle abscess (Fig. 1).

MRI confirmed SD and psoas muscle involvement, with L3–L4 osteomyelitis and epidural and paravertebral abscesses. Blood cultures were positive at 48 h for methicillin-resistant *Staphylococcus haemolyticus* resistant to a wide variety of antibiotics. Isolation from bone biopsy confirmed *S. haemolyticus*. After neurosurgical evaluation, it was decided to treat the psoas abscess non-surgically.

The patient was started on daptomycin (8 mg/kg/day i.v.) plus rifampicin 600 mg daily intravenously for 21 days. The patient became afebrile, free from pain and with improved inflammatory markers (CRP, 50 mg/L; ESR, 40 mm/h; normal leukocyte count). The antibiotic therapy was changed to teicoplanin 12 mg/kg/day and rifampicin tablets 300 mg twice daily aiming to discharge the patient on outpatient parenteral antibiotic therapy (OPAT). However, 7 days later the patient experienced exacerbation of lumbar pain and evening chills without fever and stable CRP (44 mg/L). Blood cultures and transoesophageal echocardiography remained negative. On the basis of proven efficacy and good tolerability of dalbavancin in haematogenous vertebral osteomyelitis pyogenic infection, we started dalbavancin 1000 mg intravenously on Day 1 and Day 8 (2 weeks) followed by 500 mg i.v. weekly for an additional 6 weeks. Informed consent was obtained for off-label use of dalbavancin. The inflammatory markers began to decrease after 3 days and CRP became completely normal after 6 weeks. He responded well to conservative management and was discharged afebrile after clinical improvement. During the third week of therapy the patient suffered generalised pruritus resolved with a short course of antihistamine. No kidney impairment or anaemia occurred. The total duration of antibiotic treatment was 3 months. Follow-up MRI (October 2018) revealed significant resolution of the bi-

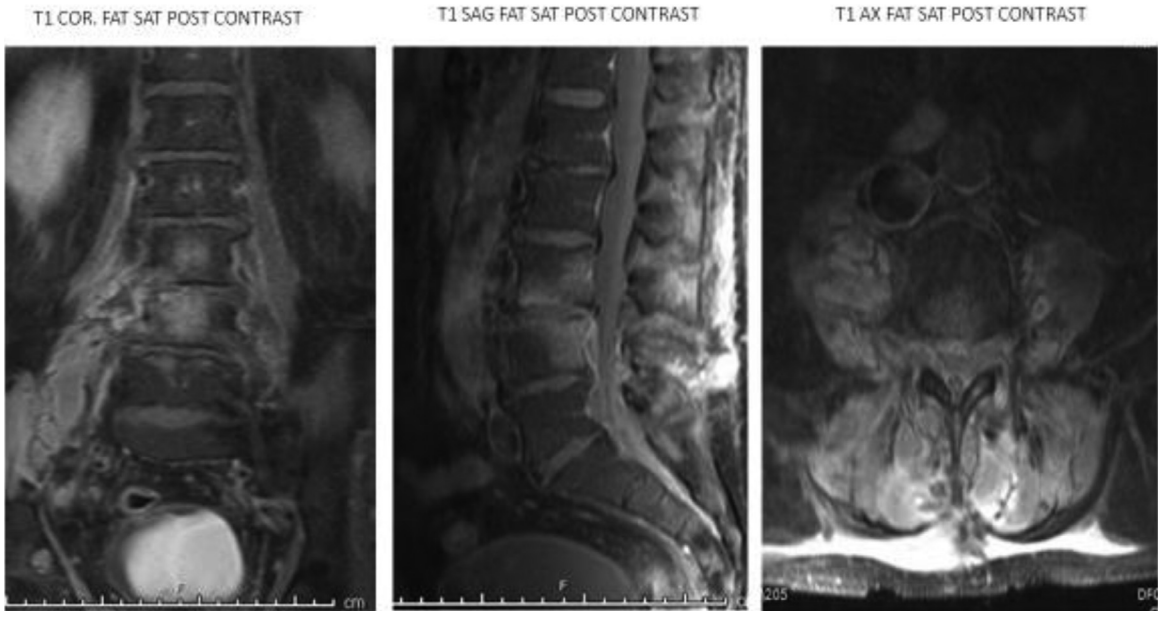

Fig. 1. Computed tomography (CT) scan with contrast. Abdomen, pelvis and lumbar spine tracts were examined. Is possible to appreciate disc changes with hypodense areas and bone abnormalities of L3–L4–L5–S1 and an increased amount of pus and multilocular right psoas muscle.

Fig. 2. Follow-up contrast-enhanced magnetic resonance imaging (MRI) of the lumbar spine after 12 weeks of antibiotics. Significant resolution of the bilateral psoas muscle abscesses with residual L3–L4 vertebral bone disease is shown.

lateral psoas muscle abscesses with residual L3–L4 vertebral bone disease (Fig. 2).

Dalbavancin has been described as a promising agent against staphylococcal SD. This lipoglycopeptide with a long half-life and mild adverse effects, including prurigo, headache or pyrexia, has strong activity against MRSA and CoNS. Dalbavancin demonstrates high concentrations in the bone (up to 7 μg/g). Once a week dosing avoids continued use of i.v. medications and facilitates patient discharge. Dalbavancin was administered as 1000 mg intravenously on Day 1 and Day 8 with i.v. infusion of 1 h, followed by 500 mg i.v. weekly for 6 additional weeks. This prolonged administration schedule likely maintained an effective control of the disease as the following MRI (March 2019) revealed near total resolution of the disease (Fig. 3).

7. Dalbavancin for infective endocarditis (IE)

IE is another infectious syndrome mostly caused by Gram-positive cocci that requires prolonged antimicrobial treatment. Extracardiac foci of infection are common and may demand therapy with antimicrobials different from those mostly active in the bloodstream. Thus, dalbavancin has been proposed as an option for the treatment of staphylococcal IE, including patients who are allergic to penicillin. IE generally occurs when bacteria from a distant body site, such as the mouth or skin, enter the bloodstream and subsequently attach to a heart valve defect or prosthesis. One of the most common causes of IE is *S. aureus* [26]. IE is considered a setting as suitable as osteomyelitis to exploit the effects of dalbavancin.

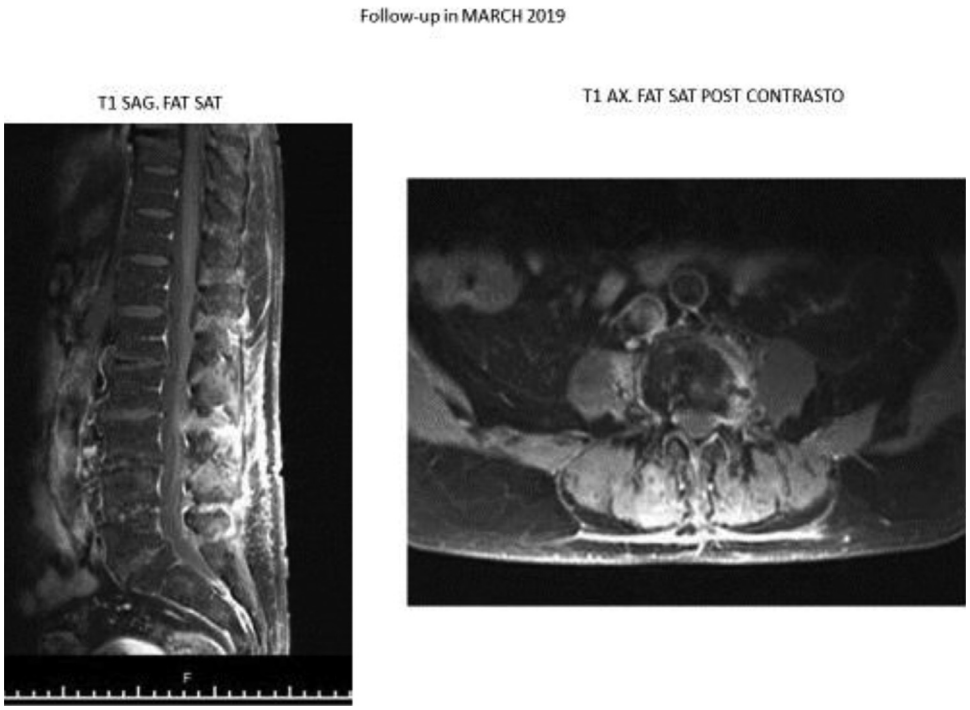

Fig. 3. Follow-up magnetic resonance imaging (MRI) of the lumbar spine region with contrast in March 2019 revealed disappearance or near total resolution of the abscess cavity.

Dalbavancin was shown to be highly active in vitro against the vast majority of 626 Gram-positive organisms causing IE collected in the SENTRY Program, 2007–2017, with very low MIC_{90} values [27]. The first report of dalbavancin use as second-line treatment in IE came from a small single-centre study of nine intravenous drug users (a vulnerable patient population with difficult intravascular access and poor treatment adherence) affected by *S. aureus* tricuspid valve IE (seven MRSA). Most patients had been treated with other molecules and had then mostly received a single 1000 mg dose of dalbavancin. Only one-third completed the predefined treatment course and clinical response was observed in five cases and was unknown in four [28].

In a subsequent report, Tobudic et al. evaluated clinical outcomes and safety of dalbavancin as either primary or sequential treatment in 27 patients with IE, including native, prosthetic and CIED infections, due to staphylococci, streptococci and enterococci [10]. In this study, dalbavancin was mostly used in an OPAT setting and was given to most patients for ≥4 weeks, with eight patients receiving >8 weeks of therapy. The clinical success rate was 92.6%, with most patients experiencing no adverse events [7,10]. In their multicentre clinical experience of real-life dalbavancin use in Gram-positive infections, Wunsch et al. [17] included 25 cases of IE reporting a cure rate of >90%. In a recent case reported by Jones et al. [29], dalbavancin was used for the treatment of *Streptococcus pneumoniae* native tricuspid valve endocarditis in a man with a history of intravenous drug use, who had a long hospital course complicated by a CR-BSI by *E. faecalis*. The subject was not a candidate for OPAT and needed 14 more days of treatment, but he could be discharged with a 3-day supply of oral levofloxacin and a single dose of dalbavancin. This report outlines the successful use of dalbavancin in the treatment of complicated streptococcal IE and *E. faecalis* bacteraemia [29]. A case of dalbavancin failure to control bacteraemia in a complex patient with MRSA IE has also been published [30]. This panel is gaining experience with dalbavancin in IE and overall believes it can be an option for selected patients, mostly to reduce hospital length of stay and costs.

Box 2. Case presentation 2

A 76-year-old woman was admitted to Monaldi Hospital (Naples, Italy) on 28 May 2019 because of fever and back pain for several weeks. She appeared unwell with co-morbid conditions consisting in grade 1 obesity, type 2 diabetes mellitus and mild cognitive impairment. A large (22 mm) vegetation was detected on the native mitral valve and her blood cultures grew over 3 days *Staphylococcus hominis* (two sets) and *E. faecalis* (two sets). Despite targeted treatment with amoxicillin/clavulanate and daptomycin, she rapidly progressed towards severe mitral valve regurgitation and underwent valve replacement with a mechanical prosthesis on 2 June 2019. PET-CT scan also found L3–L4 secondary SD. The postoperative course was uneventful and the patient returned to our medical unit after 6 days. In light of the stable clinical conditions and the concomitant SD, we opted for early discharge home on 19 June 2019 after a single 1500 mg dose of dalbavancin. Prosthesis function remained normal and inflammatory markers became negative with no further need for antimicrobial therapy. The patient was subsequently found to carry a large colonic adenomatous polyp.

8. Dalbavancin in prosthetic joint infection (PJI)

Recent studies suggest a promising role of dalbavancin in the management of patients with PJI caused by Gram-positive microorganisms thanks to its prolonged half-life, high penetration with stable concentrations in bone and periarticular tissue, and activity against bacterial biofilms [31,32]. It should be underlined that dalbavancin MICs are generally very low for *S. aureus*, CoNS, *Streptococcus* spp. and *Enterococcus* spp., the micro-organisms most frequently involved in PJI, thus suggesting a beneficial use of the drug in such infections. Currently, PJI is an off-label indication of dalbavancin. A few reports have been published on its use for this indication, and its dosage regimen is not standardised. Also, surgery,

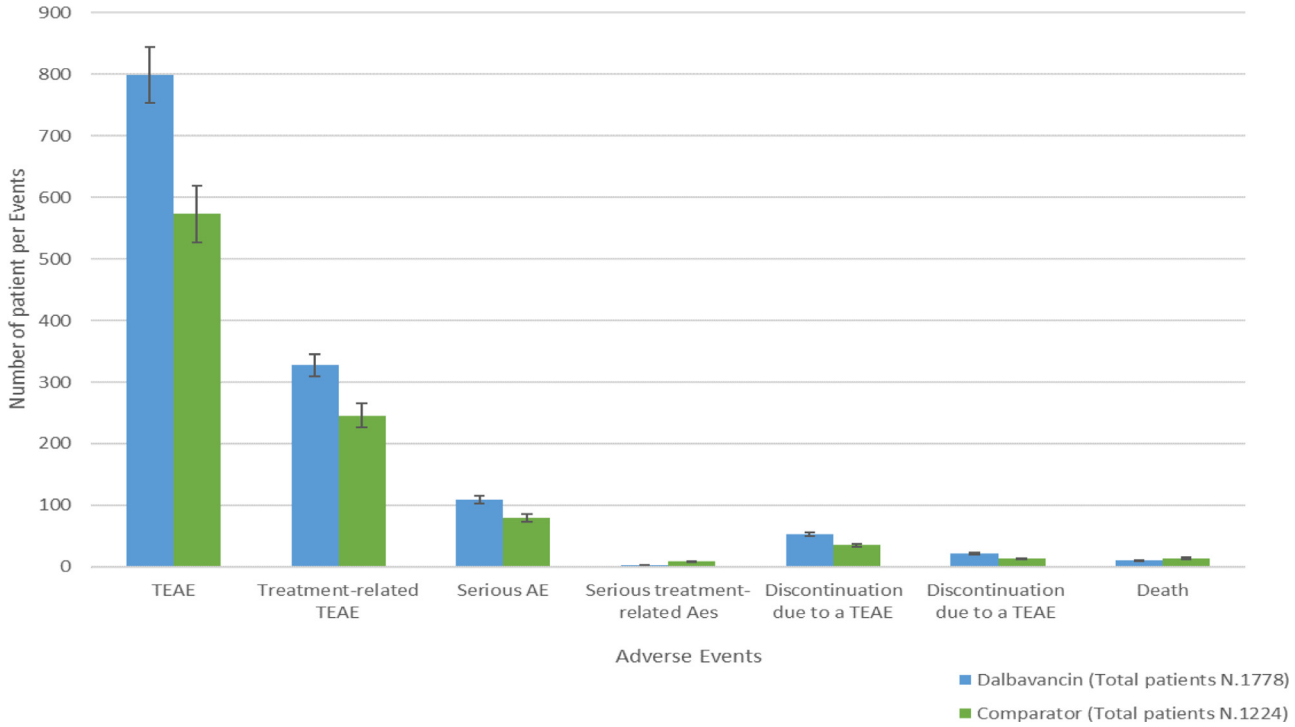

Fig. 4. Graphical representation of the adverse events (AEs) observed among patients treated with dalbavancin in clinical studies compared with patients treated with comparator antibiotics (adapted from Dunne et al. [34]). TEAE, treatment-emergent adverse event.

either as a primary approach or as revision surgery, is almost always necessary for treatment success [33]. Nevertheless, dalbavancin use in this clinical setting may allow early hospital discharge and reduce hospital stay and is therefore safe, effective and cost- saving. This is clearly emerging from our group experience.

At the Infectious Disease Unit of Potenza and Matera, 30 patients were treated with dalbavancin between 2016 and 2019. These included 12 patients with PJI. The remaining patients had osteomyelitis (4 cases), ABSSSI (8 cases), CR-BSI (4 cases) and IE (2 cases). The following aetiologies were found: 7 CoNS; 5 MSSA; 5 MRSA; 2 *E. faecalis*; 3 *Streptococcus* spp.; 2 mixed infections; and 6 negative-culture. Overall, a favourable outcome was observed for all 12 PJI cases with a combined surgical approach and medical treatment including dalbavancin. In particular, dalbavancin allowed to prolong the out-of-hospital phase of treatment, improving patient adherence and strongly limiting antibiotic-emergent adverse events, as detailed below.

9. Adverse events (AEs) and further real-life data

In the last decade, a considerable number of studies were conducted to determine the AE profile of dalbavancin in comparison with other antibiotics used for the treatment of ABSSSI. Significant work was conducted by Dunne et al. who collected data from 3002 patients enrolled in seven different randomised clinical trials receiving dalbavancin (n = 1778) or other comparator antibiotics (n = 1224) (Fig. 4). AEs were comparable or less frequent in patients receiving dalbavancin (overall treatment-emergent AEs, 799/1778; 44.9%) compared with those receiving other antibiotics (573/1224; 46.8%) (P = 0.012), the most common being nausea, constipation, skin rash, headache, diarrhoea, urinary tract infection, vomiting, pruritus and insomnia, with a similar duration. The conclusion of this study was that the use of dalbavancin is safe for treatment of ABSSSI due to Gram-positive bacteria [34].

In another retrospective study that included adult patients who received at least one dose of dalbavancin between 2016 and 2017 conducted in 29 institutions across Spain, Bouza et al. analysed the efficacy and tolerability of dalbavancin in clinical practice and the role of dalbavancin in reducing the length and, consequently, the costs of hospitalisation. Briefly, a total of 69 patients received dalbavancin during the study for a median of 21 days (range, 7–168 days) to treat CR-BSI (11.6%), osteomyelitis (17.4%), ABSSSI (21.7%) and PJI (29.0%) caused by different Gram-positive bacteria. The clinical success rate using dalbavancin was 84.1% and mild AEs were reported in nine patients only. This study further confirms the efficacy of dalbavancin to treat many serious Gram-positive infections [35].

The use of dalbavancin for osteoarticular infections was assessed in a retrospective multicentre study conducted by Morata et al. in 2019. Patients were treated with one or two 1500 mg doses of dalbavancin. In particular, a total of 64 patients were included and *Staphylococcus epidermidis* and *S. aureus* were the most frequent micro-organisms involved in the infections. In this study, the reasons for switching to dalbavancin were different, including regimen simplification (53.1%), AEs (25%) or failure (21.9%) with prior drugs. Only seven AEs were observed and no patient had to discontinue dalbavancin. In 45 cases (70%) the infection was related to an orthopaedic implant, such as PJI, and in 23 cases the implant was retained, including 15 patients (65.2%) who were classified as cured and 8 (34.8%) who presented improvement. In 21 cases the implants were removed; among these, 16 cases (76.2%) were considered a success, 4 (19%) were considered improved and 1 case (4.8%) was considered a failure. All of these results show that dalbavancin is well tolerated even when two doses only are administered [31].

In the Potenza and Matera cohort of patients, AEs occurred in 3/30 patients and were all mild to moderate. In one patient with ABSSSI and type 2 diabetes treated with 1000 mg of dalbavancin on Day 1, the therapy was continued with 500 mg on Day 8; he experienced an evanescent rash a few minutes after the first infusion that resolved spontaneously, and dizziness with negative vestibular tests. In the other two cases, one patient with hip prosthetic infec-

tion by CoNS developed fever with chills, pruritus and malaise during the 1500-mg infusion, which was therefore not repeated. The third patient, affected by CR-BSI due to MRSA in metabolic syndrome with recent revascularisation for non-ST-elevation myocardial infarction with multiple allergy history and treated with daptomycin for 1 week, presented dyspnoea and hypotension during 1500-mg infusion that was stopped and not re-started. In conclusion, overall dalbavancin treatment was safe and although in two patients the treatment was discontinued, a very likely relationship was present only in the second patient. No significant deterioration in kidney function test was observed [36]. In conclusion, in our experience, we confirm the excellent safety and tolerability as well as the high efficacy rate of dalbavancin in various clinical settings. Anyway, we recommended caution in the infusion rate (starting with a low rate and possibly prolonging infusion to 1 h for a 1500 mg dose) and clinical surveillance for 1 h after completion of drug administration.

10. Antimicrobial stewardship and pharmacoeconomic considerations

The use of dalbavancin may have major significance for antimicrobial stewardship programmes (ASPs), reducing the length of hospital stay, one of the major goals of ASPs [37–41]. Indeed, shortening hospital stay improves patient quality of life and mobility and eliminates discomfort and complications associated with intravenous catheters; specifically, it decreases the risk for non-infectious and infectious catheter-associated AEs, such as line breakage, venous thrombosis, phlebitis and CR-BSI as well as the risk of colonisation and disease by multidrug-resistant bacteria. To reduce hospitalisation length, current ASPs exploit several strategies: switching from i.v. to oral antibiotic therapy; de-escalation therapy; or reduction of the duration of antibiotic therapy [42,43]. For example, a meta-analysis of 18 studies on the effects of switching from i.v. to oral antibiotic therapy showed a non-significant modification in mortality and cure or resolution of infection among patients switched to oral therapy [44].

In light of these considerations, dalbavancin appears to be a promising option from a pharmacoeconomic point of view, allowing an early discharge of the patient owing to its long-term mode of action [45], but warranting complete adherence. A relevant cost saving may be achieved through shortening of the hospital stay [46]. A high-quality network meta-analysis that included seven randomised controlled trials focusing on complicated skin and soft-tissue infections demonstrated that the use of dalbavancin could save third-party payers from $1442 to $4803 per episode compared with standard of care [47]. Considering that dalbavancin is not an inexpensive drug, its net advantage may rely on several factors beyond its cost: type of infection and hospital ward are equally important, thereby dalbavancin's strength may be higher in case of infections requiring long courses of therapy [48] (e.g. osteomyelitis or IE).

Finally, even when infections are due to susceptible streptococci, dalbavancin could be an option whenever penicillin allergy, intolerance or poor intestinal absorption are an issue.

11. Conclusions

After reviewing the current literature and sharing our personal clinical experience, this study panel believes dalbavancin is an effective, safe and cost-effective treatment option for severe infections due to resistant Gram-positive cocci. Additional clinical studies, especially on the off-label use of this molecule, are warranted to further define its role.

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Competing interests

EDM has received research funding for his institution from MSD and Pfizer and has received speaker's honoraria, has participated in advisory boards or has been on the speaker's bureau of Roche, Pfizer, MSD, Angelini, Nordic Pharma, bioMérieux, Abbvie, Sanofi-Aventis, Medtronic and DiaSorin; VDI has received funding from EDRA and LSWR; GFDS has received funding from Janssen, Abbvie and Gilead; VE has received funding from Gilead, ViiV Healthcare, Abbvie and Merck-Sharp & Dohme; IG has served as a consultant for Abbvie, Angelini, Correvio, Merck-Sharp & Dohme, Nordic and Pfizer and has received grants from Gilead Sciences (in the framework of Fellowship program framework); NC has received grants from ViiV Healthcare, Janssen-Cilag and Gilead Science and personal fees from Gilead Sciences, Abbvie, Angelini, Bristol-Myers Squibb and Merck-Sharp & Dohme. MG and MFC declare no competing interests.

Ethical approval

Not required.

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