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The current and future off-label uses of dalbavancin: a narrative review

A. DE VITO[1], V. FIORE[1], A. COLPANI[1], B. ZAULI[1], C. FANELLI[1], G. TISEO[2], S. OCCHINERI[2], S. BABUDIERI[1], M. FALCONE[2], G. MADEDDU[1]

[1]Department of Medicine, Surgery and Pharmacy, Unit of Infectious Diseases, University of Sassari, Sassari, Italy
[2]Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Abstract. – Dalbavancin is a novel long-acting semi-synthetic lipoglycopeptide. It is licensed for acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Many studies on dalbavancin alternative use in clinical practice have been published recently, including osteomyelitis, prosthetic joint infections (PJIs), and infective endocarditis (IE). Thus, we conducted a narrative review on dalbavancin efficacy in difficult-to-treat infections, such as osteomyelitis, PJIs, and IE.

We performed a comprehensive literature search through electronic databases (PubMed-MEDLINE) and search engines (Google Scholar). We included peer-reviewed publications (articles and reviews), and grey literature on dalbavancin use in osteomyelitis, PJIs, and IE. No time or language restrictions have been established.

Despite the great interest in clinical practice, only observational studies and case series on the use of dalbavancin in infections other than ABSSSI are available. The reported success rate was extremely variable between studies, ranging from 44% to 100%. A low success rate has been reported for osteomyelitis and joint infections, while in endocarditis, the success rate was higher than 70% in all studies. However, there is no literature agreement about the correct regimen of dalbavancin for this type of infection heretofore.

Dalbavancin showed great efficacy and a good safety profile, not only in patients with ABSSSI but also in those with osteomyelitis, PJIs, and endocarditis. Further randomized clinical trials are needed to assess the optimal dosing schedule depending on the site of infection. Implementing therapeutic drug monitoring for dalbavancin may represent the future step to achieving optimal pharmacokinetic/pharmacodynamic target attainment.

Key Words:
Dalbavancin, Off-label treatment, Long-acting, Endocarditis, Osteomyelitis, Prosthetic joint infection.

Introduction

Dalbavancin is a novel long-acting semi-synthetic lipoglycopeptide[1,2]. It is licensed for acute bacterial skin and skin structure infections (ABSSSI), caused by susceptible Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (vanB and vanC)[3]. Furthermore, higher dalbavancin efficacy in preventing biofilm formation than vancomycin has been demonstrated[4].

The recommended dosage of dalbavancin in ABSSSI is 1,500 mg, which could be administered as a single intravenous infusion of 1,500 mg or 1,000 mg followed by 500 mg one week later[5]. This regimen significantly reduces hospitalization time when compared with other intravenous antibiotics[6]. Therefore, compared to old drugs, it represents a clear advantage regarding costs and nosocomial infection risk related to prolonged hospitalization[7]. Furthermore, shorter hospitalization is becoming more important nowadays since many ordinary wards have been converted into COVID-19 wards, several SARS-CoV-2 foci have started in hospital, and healthcare-related settings, and people who acquired SARS-CoV-2 during hospitalization have a worst outcome[8,9].

Studies on dalbavancin alternative use in clinical practice have been published recently, including osteomyelitis, prosthetic joint infections (PJIs), and infective endocarditis (IE)[5-9].

Corresponding Author: Andrea De Vito, MD; e-mail: andreadevitoaho@gmail.com

Osteomyelitis in adults is a major clinical challenge due to the long antibiotic course required (up to 6 weeks). In addition, the administration can be both parenteral and oral. Often, surgical debridement or resection is needed. An annual incidence of approximately 90 per 100,000 individuals has been reported among adults[10].

Osteomyelitis is commonly caused by *Staphylococcus aureus* (*S. aureus*) and coagulase-negative staphylococci (CoNS)[11-13].

PJIs are one of the most severe complications related to joint replacement procedures, with an estimated incidence between 0.5 and 2.2%, with a significant impact on the healthcare system and patient's quality of life[14-16]. Due to the ageing population and improved prosthetic techniques, the number of indications for total joint arthroplasty is growing continuously. It is estimated that more than 600,000 arthroplasty interventions are performed yearly in the U.S.[17].

Previous studies[18] highlighted that more than half of all prosthetic infections (50-60%) are caused by *S. aureus* and CoNS. Polymicrobial infections represent less than 20% of cases, and isolated strains are most commonly aerobic gram-negative bacteria, Enterococci and *S. aureus*.

IE is an infection of the hearts' endocardial surface. The overall incidence of IE ranges from 2 to 6 cases per 100,000 individuals in the general population[19,20]. Depending on etiology, mortality rates between 10 and 30% have been reported[21]. The most common strains in IE are oral streptococci in the general population[20,22]. At the same time, S. *aureus* and CoNS are more common among people who inject drugs (PWIDs), prosthetic-valve carriers, and in health-care-associated IE[23].

We conducted a narrative review on dalbavancin efficacy in difficult-to-treat infections, such as osteomyelitis, PJIs, and IE.

Methods

We performed a comprehensive literature search through electronic databases (PubMed-MEDLINE) and search engines (Google Scholar). We included peer-reviewed publications (articles and reviews), and grey literature on dalbavancin use in osteomyelitis, PJIs, and IE.

The search strategy had no time limits or language restrictions. We screened the articles by title and abstract in full text if relevant. To complement the evidence from the peer-reviewed literature, we searched for papers, abstracts, research reports, and case studies on the web. Conference abstracts were checked to avoid duplication of peer-reviewed literature. In that case, the full-text article was preferred. Three reviewers (AC, BZ, CF) independently searched and reviewed the studies. Any discrepancies were resolved by the other two reviewers (ADV, VF). After an initial screening of titles and abstracts of published articles, the reviewers evaluated full articles to assess eligibility for each study's inclusion in this narrative review. A study was included if it was likely to provide valid and valuable information according to the review's objective.

Bone and Joint Infections

Bone and joint infections are considered among the most important difficult-to-treat infectious diseases[24]. The most common isolated pathogen is *Staphylococcus aureus* (*S. aureus*) in adults and children, with an increased incidence of MRSA infections[25]. Standard treatment requires long-term use of antibiotics with surgical debridement[24,25]. Vancomycin is considered the first line of treatment for MRSA strains. Instead, nafcillin or oxacillin are indicated when methicillin-sensitive *Staphylococcus aureus* (MSSA) is isolated[25]. However, these treatments showed several problems. First, they require prolonged hospitalizations, with an increased risk of nosocomial infections[26,27]. Second, intravenous (IV) treatments could cause venous thrombosis and central line-associated infections. In addition, several drug allergies or intolerance have been reported regarding vancomycin, and the vancomycin trough levels need to be strictly monitored[6,28].

Dalbavancin showed promising results in osteomyelitis management. *In vitro* studies[3,29,30] supported the use of dalbavancin for Gram-positive related osteomyelitis. No minimum inhibitory concentration (MIC) change has been shown in more than ten years. Only anecdotal cases of dalbavancin resistance have been reported[31,32]. Animal models showed high bone and joint penetration[33] and action against MRSA-related infections[34,35]. Despite lacking uniform criteria and dosages for dalbavancin clinical application for osteomyelitis treatment, a recently published article by Cojutti et al[36] provides evidence that the two doses of 1,500 mg one week apart could be the best option for osteomyelitis caused by MSSA

and MRSA. The same was reported by De Nicolò et al[37]. This study provides long-term pharmacokinetics (PK) parameters, reporting a median T > MIC (0.125 mg/L) of 11.9 and 13.7 weeks for single and dual doses, respectively, and a median AUC0-2w/MIC ratios of 20,590 and 31,366 for single and dual dose regimens, respectively[37]. These data suggest the better performance of the two-dose regimen, even if the difference is not statistically significant. Moreover, another paper by Cojutti et al[38] suggests that therapeutic drug monitoring (TDM) should guide the optimal treatment duration. Published literature on dalbavancin use in bone and joint infections has been reported in Table I and Table II.

Few clinical trials are available in this field[39-43]. Dunne et al[39] conducted two phase-1 trials, investigating dalbavancin bone penetration and extended duration dosing. A regimen of two 1,500 mg intravenous infusions one week apart resulted in dalbavancin exposure at or above the *S. aureus* MIC of dalbavancin for the whole treatment duration. This study also provided evidence of penetration of dalbavancin into bone, while it did not provide evidence of its PK activity in the bone[39]. The same study suggested the high tolerability and safety of dalbavancin. Rappo et al[40] conducted one phase-2 randomized clinical trial to assess the efficacy of dalbavancin for treating osteomyelitis. Only patients who reported first episodes of osteomyelitis were included. This trial confirmed dalbavancins' efficacy, safety, and tolerability in osteomyelitis[40]. Two trials aiming to assess the efficacy of dalbavancin in the treatment of osteomyelitis have been terminated or withdrawn[41,42], while one phase-4 trial is still ongoing[43].

Numerous retrospective studies[44-57] on dalbavancin in osteomyelitis have been published. The success rate in treating osteomyelitis ranged from 40 to 90% of cases, depending on the study. Almangour et al[55] compared 11 patients who received at least two doses of dalbavancin to those who received standard care (SOC). The study showed no significant differences between the two groups regarding clinical outcome. In another retrospective case-control study, Veve et al[44] considered 215 patients. Among them, 70 received dalbavancin. Overall, 102 osteoarticular infections were included. The study showed a significantly lower readmission rate, shorter hospital stays, and lower adverse events among patients treated with dalbavancin[44].

Other retrospective studies lack of a comparator group[52,53,58]. Inclusion criteria differ for dosing regimen, primary outcome, length of follow-up, diseases, and patients' clinical history. Another aspect that needs to be pointed out is that dalbavancin was used as a second-line treatment and combined with other antibiotics in some cases. Considering all this, it is difficult to compare these studies. Moreover, the retrospective nature of data makes them susceptible to bias.

Almangour et al[53] reported a case of recurrent MRSA bloodstream infection complicated by discal infection and osteomyelitis of the lumbar spine. The treatment schedule was dalbavancin 1,000 mg weekly for two weeks, followed by 500 mg weekly for six additional weeks. In this case, treatment with dalbavancin was well tolerated, but it is not clear if it effectively prevented recurrences[53]. Vates et al[58] described the use of dalbavancin in treating spondylodiscitis. As a result, a >80% paravertebral abscess reduction and improvement of the infection were described. Loupa et al[52] reported a case of osteomyelitis in diabetic foot treated with a 14 days dalbavancin schedule combined with other antibiotics, which resulted in imaging and clinical improvement.

In conclusion, according to available literature, dalbavancin showed good effectiveness, safety, and tolerability profile in bone and joint infections, both acute and chronic[39,40,52-55,44-51]. However, since most studies used different regimens and did not provide a control group, further clinical data about the use of dalbavancin in bone infections is needed.

Prosthetic Joint Infections

PJIs represent difficult-to-treat infections, and in most cases, they require surgery to remove the artificial and infected part[16]. PJIs could be classified into three different groups according to Tsukayama's scheme: early postoperative infections (EPI), occurring within the first month from the surgery; late chronic infections (LCI), which generally have chronic indolent clinical course; acute hematogenous infections (AHI)[59,60]. Regarding the AHIs, the most common underlying pathogens are *S. aureus* and streptococci; EPIs are due to virulent and often MDR microorganisms such as *S. aureus*, CoNS, Enterococcus faecalis, and Enterobacteriaceae. LCIs are caused by CoNS, *S. aureus*, and low virulent or slow-growing small-colony-variant (SCV) bacterial strains[61,62].

Duration of antibiotic treatment varies according to the surgical strategy [two-stage, one-stage

Table I. List of studies including bone or joint infection treated with dalbavancin.

Design of the study	Authors	Sample size	Site of infection	Organism isolated	Prior antibiotic therapy	Dalbavancin regimens	Follow-up	Rate of success
Retrospective	Ajaka et al[67]	18	Bacteriemia = 78%; Endocarditis = 22%	MRSA = 39%; MSSA = 17%; polymicrobial GRAM-P and GRAM-N = 17%; polymicrobial GRAM-P = 11%; others = 16%	100.00%	SR1 = 72.2%; SR2 = 5.6%; OR1 = 11.1%; 1500 mg + 1000 mg = 11.1%;	90 days	44.44%
Retrospective	Arrieta-Loitegui et al[84]	102	ABSSSI = 30.4%; Bacteriemia = 31.4%; Endocarditis: 13.7%; Osteomyelitis = 10.8%; PJI = 10.8%; Others = 2.9%.	Enterococcus spp 9.7%; *Staphylococcus* spp 70.6%; Streptococcus spp 4%; Others 6%; No microbiological isolations 10.7%	100%	SR1 = 58.8%; SR2 = 7.8%; OR1 × 2 = 13.7%; OR1 × 3 = 2.9%; OR1 × 6 = 1.9%. 1000 mg = 2.9%; SR2 + 500 mg × 4w = 1.9%; Others = 1 0%	90 days since the end of treatment	93.7%
Retrostective	Bai et al[54]	206	ABSSSI = 60.2%; Endocarditis = 2.9%; Osteomyeitis = 16% PJI = 8.3%; others = 12,6%	CoNS = 11.2%; MRSA = 12.1%; MSSA = 6.8%; No microbiological isolations = 2.9%; DNP = 59.2%	77.8%	SR1 = 60.2%; Others = 39,8%	30-180 days	75.00%
Retrospective	Bork et al[47]	45	ABSSI = 37.8% Osteomyelitis = 46%, Others = 39%	CoNS = 14%; MRSA = 29% MSSA = 21%; Mixed GRAM positive = 29%; DNP = 18%	68.00%	Not provided	30 and 90 days	71.00%

Continued

Table I *(Continued)*. List of studies including bone or joint infection treated with dalbavancin.

Design of the study	Authors	Sample size	Site of infection	Organism isolated	Prior antibiotic therapy	Dalbavancin regimens	Follow-up	Rate of success
Retrospective	Bouza et al[46]	69	ABBSI = 21.7%, Endocarditi s = 10.1%, Osteomyelitis = 18.5%, PJI = 29.0%; Others: 17,3%	CoNS = 34.8%; *Enterococcus* spp.= 15.9%; MRSA = 23.2%; MSSA = 15.9%; *Streptococcus* spp. = 2.9%; Others = 5.8% No microbiological isolations = 5.8%	97.1%	Not provided	≥ 1 month	84.1%
Retrospective	Brescini et al[74]	55	ABSSSI = 51%; Endocarditis = 2%; Osteomyelitis = 14%; PJI = 24%; Others = 11%	*E. faecalis* 4%; MRSA 16%; MSSA 2%; MRSE 2%; MSSE = 5%; Polimicrobial infection 11%; Others 15%; No microbiological isolations = 45%	96.00%	SR1 = 54%; OR1 = 18%; Others = 24%	30-90 days	91% (96% of ABSSSI; 69% of PJIs)
Retrospective	Bryson-Cahn et al[50]	32	ABSSSI = 18.8% Endocarditis = 28,1% Osteomyelitis = 25% Others = 28.1%	MRSA = 88%; DNP=12% 1 × 500 mg = 3.1%, SR2 = 18.9%, Others: 12,4%	100.00%	1 × 1000 mg = 65,6%,	30-365 days	56.00%
Retrospective	Dinh et al[56]	75	ABSSI = 17.3%; Endocarditis = 25.3%; Osteomyelitis = 64.0%	CoNS = 44.4%; *Corynebacterium* spp.= 6.9%; *E. faecalis* = 6.9%; MRSA = 18.6%; MSSA = 30.7%. OR1 + OR1 = 3; SR2 + 500 for 2 w = 3%; Others: 19.5%;	98.7%	OR1 = 50,6%; 1000 mg = 3%, SR1 = 17.08%, SR2 = 1.5%, 1000 mg × 2 = 1.5%, OR1 + 1500 mg = 1.5;	87.8 ± 86.9	79.4%
Retrospective	Morrisette et al[57]	56	ABSSIs = 36%; Endocarditis = 9%; Osteomyelitis = 27%; Others = 30%	CoNS = 11%; *E. faecalis* = 11%; MRSA = 19%; MSSA = 25%; VRE = 8% No microbiological isolations = 14%	91.00%	Not provided	180 days (median)	80.00%

Continued

Table I *(Continued)*. List of studies including bone or joint infection treated with dalbavancin.

Design of the study	Authors	Sample size	Site of infection	Organism isolated	Prior antibiotic therapy	Dalbavancin regimens	Follow-up	Rate of success
Retrospective	Poliseno et al[95]	50	ABSSSI = 40%; Osteomyelitis = 36%; Others = 24%	CoNS = 34%; MSSA = 34%; Others = 10%; No microrganism isolated = 22%;	100%	OR1 = 100%	30-180 days	98.00%
Retrospective	Streifel et al[70]	37	ABSSSI 22%, Endocarditis 5%; Osteomyelitis 30%, PJI 11%, Others 33% 9%,	CoNS 11%, Corynebacterium jeikeium 3%; MRSA 38%; MSSA 24%; Polymicrobial 19%; DNP = 5%	3%	SR1 = 27%, OR1: 16%, 1000 mg × 1= 27%, SR2 = 24%; Others: 6%	30 days	95.00%
Retrospective	Tobudic et al51	72	ABSSI = 36.1%; Osteomyelitis = 33,3%; PJI = 11,1%; Others = 19,5	MRSA = 8%; MRSE = 4%; MSSA = 38%; MSSE = 7%; DNP = 14%	81.00%	Not provided	180 days	64.00%
Retrospective case-control	Veve et al[44]	215 (1:2)	Endocarditis = 27%; Osteomyelitis = 44%; PJI = 3; Others = 26%.	CoNS=4%; Enterococcusfaecalis = 3%; MRSA = 82% MSSA = 8% *Streptococcus* spp.= 3%	100.00%	OR1 = 55%; SR1 = 26%; Others: 19	90 days	Dalbavancin use was independently associated with lower IRR
Retrospective	Wunsch et al[45]	101	ABSSI = 10.9%; Endocarditis = 24.8%; Osteomyelitis = 29.7%; PJI = 31.7%; Others = 2.9%	CoNS = 33%; *Enterococcus* spp.= 8%; MRSA= 9%; MSSA= 16%; *Streptococcus*. spp.= 6%; Others = 5%; No microbiological isolations = 14%	Unknown	SR1 = 23.8%; OR1 = 16.9%; SR2 = 42.6%; 1000 mg +1000 mg = 3%; Other = 13.9%	90 days	89.00%

ABSSSI: Acute Bacterial Skin and Skin Structure Infections; PJI: Prosthetic Joint Infection; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; CoNS: Coagulase-Negative Staphylococci; DNP: data not present; MRSE: Methicillin-Resistant *Staphylococcus epidermidis*; MSSE: Methicillin-sensitive *Staphylococcus epidermidis*; SR1: 1500 mg; SR2: 1000 mg + 500 mg after 1 week; OR1: 1500 mg + 1500 mg; w: week; IQR: interquartile range; IRR: incident rate ratio.

Table II. List of studies including only Osteomyelitis and/or prosthetic joint infection treated with dalbavancin.

Design of the study	Authors	Sample size	Site of infection	Organism isolated	Prior antibiotic therapy	Dalbavancin regimens	Follow-up	Rate of success
Retrospective	Almangour et al[48]	31	Osteomyelitis	MRSA = 48%; MSSA = 39; Mixed GRAM-P = 6%; Others = 1 3%	84,00% No	Not provided OR1 = 45,5%;	≥ 90 days 90 days	90.00% 100.00%
Case-Control	Almangour et al[55]	22 (1:1)	Osteomyelitis	MSSA = 45.5% MRSA = 54.5%		SR1 + 500 mg × 3w = 9,1%; SR2 + 500 × 3w = 18,2%; Others = 27,3%.		
Retrospective	Buzón Martín et al[72]	16	PJI	*E. faecalis* = 6.25%; *E. faecium* = 25%; CoNS = 43.7%; MRSA = 25%	Unknown	SR2 + 500 every 2 wks for 2-3 mths = 56%; SR2 + 500 weekly × 5 = 12.5%; others = 31.5%	434.5-567 days	75.00%
Retrospective case-control	Fiore et al[73]	67 (1:2)	PJI	MRSA = 38.1%; MSSA = 47.6%; *S. hominis* =1 4.3%	No	OR1 = 100%	90 days	81%
Retrospective	Matt et al[71]	17	PJI=100%	CoNS = 58.8%; MRSA = 5.9%; MSSA = 52.9%	94.1%	OR1 = 5 2.9%; SR1 = 17.6%; others = 29.5%	97-476 days	47.1%
Retrospective	Morata et al[49]	64	Osteomyelitis = 59.4% PJI = 40.6%	MRSA = 14%; MSSA = 8%; *S. epidermidis* = 47%; Polimicrobial = 11%	100,00%	Not provided	164 days IQR = (93-262.5 days)	70.3%

ABSSSI: Acute Bacterial Skin and Skin Structure Infections; PJI: Prosthetic Joint Infection; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; CoNS: Coagulase-Negative Staphylococci; DNP: data not present; MRSE: Methicillin-Resistant *Staphylococcus epidermidis*; MSSE: Methicillin-sensitive *Staphylococcus epidermidis*; SR1: 1500 mg; SR2: 1000 mg + 500 mg after 1 week; OR1: 1500 mg + 1500 mg; w: week; IQR: interquartile range; IRR: incident rate ratio.

exchange, or "debridement, antibiotics and implant retention" (DAIR)], ranging from some weeks to chronic suppressive antibiotic therapy[63]. In case of a two-stage exchange, which represents the most effective strategy, 4-6 weeks of antibiotic directed against the causative organism is recommended. At the same time, a more prolonged period and chronic suppressive therapy may be necessary for patients treated with a one-stage exchange or DAIR[64]. Oral antibiotic treatments could represent an alternative, but the long duration could cause adverse drug events (ADEs) and discontinuation; furthermore, oral treatment could not be available for MDR microorganisms[64]. In this setting, dalbavancin was proposed as a possible alternative by several authors.

The biofilm penetration and the pharmacokinetics make dalbavancin a useful option for Gram-positive related PJIs. Dunne et al[39] thoroughly analyzed dalbavancin PK and pharmacodynamics (PD) in 2015, providing accurate data on MICs depending on the target tissue. Moreover, the limited need TDM has been described as another useful aspect for other infection sites[65]. Decreasing outpatient parenteral antimicrobial therapy (OPAT) was one advantage highlighted in studies[55-57,66]. Another raised issue by Veve et al[44] was the usefulness of lipoglycopeptides in PJIs among people who inject drugs (PWIDs) to improve patient outcomes[44]. Many PWIDs need outpatient parenteral antimicrobial therapy (OPAT), but it could be unsafe or unwarranted among these patients because of catheter manipulation and, in hospitalized ones, voluntary discharge against medical advice without receiving adequate treatment[47,67]. Furthermore, PWIDs tend to develop OPAT-related complications[68,69].

Currently, there is a lack of data on dalbavancin use in PJIs. Available studies have been summarized in Table I and Table II. Since no trial has been published yet, retrospective observational cohort studies represent the only evidence of the efficacy of dalbavancin[45-47,49-51,54,55,70]. There is one ongoing trial, but the results will not be available until December 2022[43]. The major limitation of these retrospective studies is that PJIs cases are considered in mixed groups of off-label dalbavancin use, making it difficult to establish therapeutical success rates among PJIs apart from osteomyelitis, endocarditis, and ABSSSI. A few examples of dalbavancin studies[71-73] focused only on PJIs are present: two retrospective cohort and one case-control studies.

Fiore et al[73] conducted a case-control study enrolling 21 people treated with dalbavancin and 46 with SOC. People treated with dalbavancin showed a similar success rate to SOC group (81% *vs.* 82.6%, *p*-value 0.87), with lower ADEs (0 *vs.* 17.4%, *p*-value 0.04), and a shorter hospitalization time (13.5±5.6 *vs.* 24.3±8.2 days, *p*-value <0.001).

Matt et al[71] conducted a retrospective study including 17 patients with PJI treated with dalbavancin. Of notice, only in one case dalbavancin was administered as the first-line therapy. The clinical cure was achieved in only 8 (47%) patients. Buzón-Martín et al[72] also conducted a retrospective study on 16 patients, reporting clinical success in 12 (75%) cases.

Bouza et al[46] included 20 PJIs in a retrospective observational study conducted in 2017, with a success rate of 80%. The biggest study on dalbavancin as a treatment option was conducted by Morata et al[49] in 2019, evaluating 26 patients with PJIs, 19 with infection of other implants (spine, long bone), and 19 with bones infection. Regarding prosthetic infections, treatment success was reported in 31 (68.9%) patients. Tobudic et al[51] conducted a retrospective cohort study including 72 patients treated with dalbavancin; only 8 had a PJI, and a clinic cure was reported in 6 cases. The two failures occurred in people with previous long-term antibiotic treatment and without surgical treatment.

Bai et al[54] conducted a multicenter retrospective cohort study in 2020, in Italy, analyzing records from 206 patients treated with dalbavancin. Of these, only 17 (8.3%) were PJIs, and 13 (76.5%) patients reported a positive outcome. Also, Wunsch et al[45] conducted a multicenter retrospective study in Austria, including 101 patients; of these, 32 (31.7%) had PJIs, with a 94% of clinical success, which was higher than other infection sites reported in the study. Finally, Brescini et al[74], in their monocentric study, included 50 patients treated with dalbavancin, including 13 (24%) PJIs, with a clinical cure in 9 (69%) cases.

Tobudic et al[51] reported that failures were mainly due to the presence of *Streptococcus anginosus,* while Bouza et al[46] identified *Corynebacterium striatum* as the main cause of treatment failure. Other causes were ADEs[44] with treatment interruption and loss to follow-up[47,49].

In all studies, dalbavancin was used as a second-line option for almost all subjects. The dosing regimen and therapy duration varied case by case. The most used ones were an initial dose of 1,500 mg followed by 1,000 mg 14 days after, or 1,500 mg in a single dose. Every study highlighted dalbavancin's tolerance and excellent safety

profile, confirmed by the low numbers and mild characteristics (i.e., rash) of ADEs presented, especially when compared to SOC[44,45,54,56,73].

Infective Endocarditis

IE is a common infection of the cardiac valves or the endocardium, with a poor prognosis and high mortality[75]. The incidence is about 3-10 episodes/100,000 person-years, and it is most common in older people (>70 years old)[75]. Prosthetic valve endocarditis (PVE) accounts for 10-30% of all cases of IE (mechanical and bioprosthetic valves are affected equally). Staphylococci, streptococci, and enterococci cause IE in 36.6%, 36.2%, 10.5%, respectively[76-77]. The SOC in IE depends on bacterial strain. However, empirical treatments are well known, depending on infection localization, and valve nature[23].

Over the past few years, the incidence of infections caused by MRSA has increased, including IE. In this case, the recommended treatment is represented by vancomycin or daptomycin[78,79]. Furthermore, some vancomycin-intermediate *S. aureus* and hetero-vancomycin-intermediate *S. aureus* have been isolated from infected patients, which are associated with IE treatment failures[23,80,81]. Moreover, some intravascular infections including infections of foreign bodies (prosthetic valves, vascular grafts, transcatheter aortic valve implants, pacemakers, implantable cardiac defibrillators, or left ventricular assist devices) may present a chronic indolent course and may be difficult to treat[82]. In some cases, the foreign body cannot be removed and the retention of the device complicates the choice of treatment and the duration of antibiotic therapy. In these cases, long-term suppressive therapy may be the last option. In this scenario, it is crucial to find new therapeutical strategies[80]; hence, our interest in off-label dalbavancin use in IE. In this regard, most of the data come from retrospective observational studies[45,46,84-86,47,50,54,56,66,67,70,83], and case reports[87-91]; Veve et al[44] conducted a retrospective case-control study on dalbavancin *vs.* SOC in different settings, including IE. As a result, patients treated with dalbavancin had both a shorter median length of stay (p-value = 0.021) and lower infection-related readmission (p-value = 0.033). One phase-2 randomized controlled trial (RTC) was stopped for business reasons, and no results were available[92].

Studies from Lefort et al[93] and Candiani et al[94] demonstrated the efficacy of dalbavancin in rats and rabbits on *S. aureus*-related IE. In addition, dalbavancin was as effective as vancomycin and teicoplanin in reducing the bacterial load in the heart, but with a lower dose and less frequent dosing intervals than the SOC[93,94].

In humans, numerous retrospective studies highlighted a successful IE treatment[45,46,54,66,83,85,86] when using dalbavancin, with a success rate above 78%.

Bryson-Cahn et al[50] treated 5 cases of IE with dalbavancin. Among them, only 60% had a clinical cure. However, data on the remaining two patients are missing because they were lost to follow-up (LTFU). Dinh et al[56], Ajaka et al[67], and Guleri et al[86] collected case series, with 68.0%, 25.0%, and 90.9% success rates, respectively. Also in these cases, data were limited by the LTFU.

NVE, PVE, and CDE have been included in some studies[45,56,66,83,85,95], unfortunately, data on specific clinical outcomes are not provided, except for an Italian study[95]. Thus, assessing the efficacy of dalbavancin adjusted for infection origin is impossible. Poliseno et al[95] studied the effect of dalbavancin in 11 patients with cardiac implantable electronic device (CIED) infection and in one patient with aortic vascular graft infection, documenting 100% of clinical success. Despite this success, further studies need to demonstrate dalbavancin efficacy for infective endocarditis caused by device or prosthetic valve infections[95].

Regarding etiology, few data about success rate depending on each causative agent were provided[67,83,85]. When coming to MRSA IE, data are scarce and not concordant: three cases of dalbavancin failure in MRSA have been reported[67,88,91], while two patients with MRSA-related IE have been cured in 2019[66].

Some authors[57,66,84,95] underly that dalbavancin is cost-effective, weighting the reduction of hospitalization days and the cost of a dose of dalbavancin.

Most of studies on dalbavancin in IE are retrospective and lack of a control group, thus it is impossible to compare the use of dalbavancin to the SOC and they are susceptible to biases. A comparison between SOC and dalbavancin was performed by Veve et al[44] through a case-control study, which highlighted a lower 90-days infection-related readmission (IRR), and a longer time to IRR in the group treated with dalbavancin. Of notice, the unique randomized clinical trial (RCT) was interrupted for business reasons after enrolling only two patients[92,96].

In addition, each study differs for dosing regimen. In all studies a loading dose of dalbavancin

corresponding to 1,000 mg, or 1,500 mg[45,46,86,87,89-91,95,50,54,56,66,67,70,83,85] was administered. It is already known that a substantial variability characterizes daptomycin PK in septic patients[97]. Thus, in patients with intravascular infections, including IE, a deeper knowledge of PK parameters of dalbavancin is necessary. The implementation of TDM should be encouraged in patients with IE receiving dalbavancin[65]. Dalbavancin has usually been used after and/or in association with other antibiotics, and enrolled patients showed different comorbidities, making data even more difficult to compare. Available studies on dalbavancin use for IE have been summarized in Table I and Table III.

In conclusion, available data showing its efficacy and safety support the use of dalbavancin in the treatment of IE. However, limited data are available because of LTFU, variable schedules, patients' compliance, and not homogeneous diagnostics. Therefore, further studies, including RCTs, are necessary to better assess dalbavancin's efficacy in treating IE and standardize a proper dosing regimen.

Future Perspectives

As previously discussed, the major off-label studies on dalbavancin investigate bone and joint infections, PJIs, endocarditis, and bacteriemia. However, pneumonia was also considered in some cases.

Rappo et al[98] conducted a phase-1 trial on dalbavancin levels in epithelial lining fluid (ELF) among 35 healthy adults after administering a single 1,500 mg dose. The authors found that dalbavancin's ELF levels exceeded the MIC90s for both *S. pneumoniae* and *S. aureus* for more than seven days.

Very few data are available in the literature regarding the use of dalbavancin among people with pneumonia. Barber et al[99] described in 2017 a case of a young man living with HIV, with MRSA-related pneumonia. After multiple treatment failures, he was successfully treated with a single 1,500 mg dalbavancin dose. Sader et al[100] also suggest a possible role of dalbavancin in the treatment of pneumonia in people with cystic fibrosis, but no clinical study is present in this particular population.

Given the limited available evidence regarding MRSA pneumonia, we suggest that dalbavancin should be used in selected cases when other treatments, such as vancomycin or linezolid, are not indicated.

Van Matre et al[101] conducted a clinical trial to investigate dalbavancin's possible use in peritoneal dialysis's peritonitis. They evaluated the PK/PD in 10 end-stage renal disease (ESRD) patients who received peritoneal dialysis. They administered 1,500 mg of dalbavancin and evaluated the dalbavancin level in plasma and peritoneal fluid after 1, 2, 3, 4, and 6 h and 7 and 14 days. The plasmatic PK parameters in peritoneal dialysis-treated patients were similar to those previously reported in healthy subjects, with only a slight increase in drug exposure described over a 14-day treatment period. No adverse events were reported. The dalbavancin penetration into the peritoneal space after IV administration was approximately 5% of the overall plasma exposure. However, the achieved concentrations remained above the designated MIC breakpoints throughout the treatment period. Furthermore, the authors had planned to administer dalbavancin intraperitoneally, but this arm of the study was interrupted because all three participants complained about abdominal discomfort and severe bloating[101].

After the results of this trial, Kiser et al.[102] started a new trial to evaluate the efficacy of dalbavancin intraperitoneal infusion to treat Gram-positive peritonitis among patients requiring peritoneal dialysis. However, the trial is still recruiting the participants, and the results are not yet available.

Another interesting field would be the dalbavancin use for central nervous system infections. Actually, only *in vitro* time-kill kinetics have been studied with very promising preliminary data on MRSA susceptibility profile on this site[103].

Finally, PK/PD of dalbavancin in special patient populations, such as elderly patients, should be implemented since it may represent an interesting therapeutic option associated with reduced length of hospital stay and hospitalization-related complications in frail patients[104].

Conclusions

Dalbavancin showed a great efficacy and a good safety profile, not only in patients with ABSSSI, but also in those with osteomyelitis, PJIs and endocarditis. Despite the great interest in clinical practice, only observational studies, and case series on the use of dalbavancin in infections

Table III. List of studies including only infective endocarditis treated with dalbavancin.

Design of the study	Authors	Sample size	Site of infection	Organism isolated	Prior antibiotic therapy	Dalbavancin regimens	Follow-up	Rate of success
Retrospective	Durante-Mangoni et al[85]	10	Endocarditis	CoNS = 20%; *E. faecium* = 20%; *E. faecalis* = 20%; MRSE = 20%; MSSA = 10%; *S. gallolyticus* = 20%; *S. hominis* 10%; *S. mitis* 10%	100%	SR1 = 40%; SR2 = 20%; SR2 + 500 mg = 10%; SR2 + 500 × 2 = 10%; SR2 + 500 × 4 = 10%; OR 1 = 10%	Different for each patient and microorganism isolated. Not defined (every 2 months from the end of treatment)	70.00%
Case series	Guleri et al[86]	11	Endocarditis	*S. gallolyticus* 9.1%; *S. mitis* = 9.1%; *S. oralis* = 18.2%; MSSA = 27,3%; *E. faecalis* = 36.4%	100%	OR1 = 54.6%; SR1 = 46.4%	12 months	90.9%
Retrospective	Hidalgo Tenorio et al[66]	34	Endocarditis = 100%	MSSA = 20%, MRSA = 8.6%, CoNS 42.9%, *E. faecalis* 8.6%, *Streptococcus* spp. 20%	100%	SR1 = 35.3%; SR2 = 29.4%, 1000 mg = 14.7%; 1500 mg + 1000 mg = 8.8%; Other: 11,6%	12 months	100.00%
Retrospective	Tobudic et al[83]	27	Endocarditis	CoNS = 25.9%; E. faecalis = 14.8%; MSSA = 33.3%; *Streptococcus* spp = 29.6%; Others = 3.7%	88.9%	SR2 = 3.7%; SR2 + 500 mg = 7,4%; SR2 + 500 × 5w = 11,1%; 1500 + 1000 = 7.4%; 1500 mg + 1000 mg × 2 = 14.8%; 1500 mg + 1000 mg × 3 = 25.9%; Others = 29.6%	6 months	92.6%

ABSSSI: Acute Bacterial Skin and Skin Structure Infections; PJI: Prosthetic Joint Infection; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; CoNS: Coagulase-Negative Staphylococci; DNP: data not present ; MRSE: Methicillin-Resistant *Staphylococcus epidermidis*; MSSE: Methicillin-sensitive *Staphylococcus epidermidis*; SR1: 1500 mg; SR2: 1000 mg + 500 mg after 1 week; OR1: 1500 mg + 1500 mg; w: week; IQR: interquartile range; IRR: incident rate ratio.

other than ABSSSI are available. Further RCTs are needed to assess the optimal dosing schedule depending on the site of infection. Implementing TDM for dalbavancin may represent the future step to monitor serum levels and achieve optimal PK-PD target attainment.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Authors' Contribution
Conceptualization: Andra De Vito, Vito Fiore, Marco Falcone and Giordano Madeddu. Investigation: Agnese Colpani, Beatrice Zauli, Chiara Fanelli, Giusy Tiseo, Sara Occhineri. Methodology: Andrea De Vito, Vito Fiore, Sergio Babudieri, and Giordano Madeddu. Validation: Marco Falcone, Sergio Babudieri and Giordano Madeddu. Resources: Agnese Colpani, Beatrice Zauli, Chiara Fanelli, Gisy Tiseo, Sara Occhineri. Writing-original draft: Andrea De Vito, Vito Fiore, Agnese Colpani, Beatrice Zauli, Chiara Fanelli and Giordano Madeddu. Writing-review and editing: Giusy Tiseo, Sara Occhineri, Sergio Babudieri, Marco Falcone.

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ORCID ID
Andrea De Vito: 0000-0002-8265-5400; Beatrice Zauli: 0000-0002-3358-5936; Sergio Babudieri: 0000-0001-7291-8687; Giordano Madeddu: 0000-0001-6099-2273; Marco Falcone: 0000-0003-3813-8796; Giusi Tiseo: 0000-0002-3884-4933; Sara Occhineri: 0000-0002-3866-1627; Agnese Colpani: 0000-0002-8959-1403.

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