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REVIEW

The role of dalbavancin for Gram positive infections in the COVID-19 era: state of the art and future perspectives

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ABSTRACT

Introduction: The COVID-19 pandemic has dramatically challenged the national health systems worldwide in the last months. Dalbavancin is a novel antibiotic with a long plasmatic half-life and simplified weekly administration regimens, thus representing a promising option for the outpatient treatment of Gram-positive infections and the early discharge of hospitalized patients. Dalbavancin is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Many preliminary data seem to support its use in other indications, such as osteomyelitis, prosthetic joint infections, and infective endocarditis.

Areas covered: A search in the literature using validated keywords (dalbavancin, Gram-positive infections, Gram-positive cocci, ABSSSI, intravenous treatment, and long-acting antibiotics) was conducted on biomedical bibliographic databases (PubMed and Embase) from 2004 to 30 September 2020. Results were analyzed during two consensus conferences with the aim to review the current evidence on dalbavancin in Gram-positive infections, mainly ABSSSI, osteomyelitis, and infective endocarditis, highlight the main limitations of available studies and suggest possible advantages of the molecule.

Expert opinion: The board identifies some specific subgroups of patients with ABSSSIs who could mostly benefit from a treatment with dalbavancin and agrees that the design of homogenous and robust studies would allow a broader use of dalbavancin even in other clinical settings.

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ABSSSIs; COVID-19; dalbavancin; endocarditis; Gram-positive; long-acting; osteomyelitis

1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has represented an enormous challenge to the national health systems worldwide. During the first months of the epidemic, the high number of COVID-19 patients requiring hospitalization and intensive care support has caused a drastic reorganization of the health-care facilities, thus allowing an appropriate response to the epidemiological emergency, but also compromising the possibility to face adequately other medical needs unrelated to the SARS-CoV-2 epidemic. Nonetheless, the spread of the infection in the population has been better kept under control in areas where a *community-based* model was promptly adopted, namely a system based on an accurate contact-tracing activity, on isolation of positive cases, on home-care for patients with mild or no symptoms and on inpatient-care for patients with a severe COVID-19 disease. On the contrary, the *hospital-based* model has shown to be mostly ineffective, leading to a premature overload of hospital facilities [1,2]. In Italy, the National Healthcare Service is regionally based, with local authorities responsible for the organization and delivery of health services, leaving the Italian Government with a weak strategic leadership. This decentralization and fragmentation of health services seems to have restricted timely interventions and effectiveness [3]. Notably, avoiding unnecessary hospitalization and delays in the discharge of patients may be an efficient long-term strategy to cope adequately with the persistent spread of the virus in the communities. However, it requires a coherent strengthening of territorial services, including general practitioners, home care and diagnostic centers. Furthermore, the decentralization of medical services imposed by the lasting pandemic could also serve as a chance to deal with some old limits of the *hospital-based* health-care systems, such as nosocomial infections from multidrug-resistant pathogens, which are often more severe in frail and old patients [4]. Within this context, the employment of long-

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Article highlights

- The COVID-19 pandemic has dramatically challenged the national health systems imposing measures for the reduction of hospitalisation and the implementation of territorial medicine to reduce the spread of in-hospital infections
- Many scientific publications are now available concerning the off-label use of dalbavancin for osteomyelitis, prosthetic joint infections, and infective endocarditis despite dalbavancin being a long-acting lipoglycopeptide approved for the treatment of ABSSSI
- The pharmacokinetic and pharmacodynamic properties of dalbavancin allow therapy schedules suitable for the treatment of subacute-chronic osteomyelitis, prosthetic joint infections, and infective endocarditis and also after clinical stabilization in acute forms as an alternative to oral treatment.
- Evidence of dalbavancin use in osteomyelitis and infective endocarditis are promising but considering the heterogeneity of the available studies and the limitations regarding inclusion criteria, administration regimens, outcome measures, and follow-up durations, more research is needed to standardize and increase the use of dalbavancin in indications other than ABSSSIs.

acting antimicrobial agents could represent a unique way to discharge patients early or to treat infections in an outpatient setting, consequently leading to a reduction of assistance costs and a reduction of nosocomial infections (as well as the possibility of acquiring COVID-19 in the hospital setting). Dalbavancin is a novel semisynthetic antimicrobial agent belonging to the second-generation lipoglycopeptides family.

By binding to the D-alanyl-D-alanine terminus of growing peptidoglycan chains, dalbavancin interferes with cross-linking and inhibits bacterial cell wall synthesis of Gram-positives. Dalbavancin has a broad range of activity, and $MIC_{50/90}$ values against *Staphylococcus aureus* ($MIC_{50/90}$ 0,03 mg/L for both MSSA and MRSA), vancomycin-susceptible *Enterococcus faecalis* ($MIC_{50/90}$, 0.03/0.06 mg/L), β-hemolytic streptococci ($MIC_{50/90}$, 0.008/0.015 mg/L), and *Streptococcus anginosus* group ($MIC_{50/90}$, ≤0.004/≤0.004 mg/L) remained stable since its clinical approval up to date [5]. Preclinical studies have shown that the pharmacodynamic determinant of dalbavancin that best correlated with antibacterial activity is the area under the concentration–time curve (AUC): MIC ratio, with the greatest net reduction in the log10 of colony forming units occurring when large doses were administered less frequently. Dalbavancin has a favorable pharmacokinetic profile with high plasma protein binding, low likelihood for drug–drug interactions and a very long elimination half-life. Overall, this unique pharmacokinetic/pharmacodynamics (PK/PD) profile makes once weekly dosing for managing severe infections feasible. After single 1500 mg dose, the free plasma concentrations of dalbavancin persisted higher than the MIC clinical breakpoints of various species of Staphylococci and Streptococci including MDR strains [6,7]. This might explain why, to our knowledge, nowadays there are only two cases describing the development of dalbavancin breakthrough resistance during, or immediately after therapy [8,9]. Although the potentially underlying mechanisms of the dalbavancin MIC increase are not yet fully understood, they could be due to a thickening of bacterial cell-wall [9].On the other hand, a topical and interesting in vitro and in vivo activity of dalbavancin toward SARS-CoV-2 was recently highlighted [8], suggesting a potential role in the treatment of COVID-19 [9]

Nevertheless, the approved indications for dalbavancin by the FDA and the EMA are for the treatment of acute bacterial skin and skin structure infections (ABSSSI), although in clinical practice smaller lesions can also be found (e.g. 8 × 8 cm cutaneous abscess or wound infection that is relatively large despite it does not meet the FDA definition).

Besides being a valid choice in the treatment of skin and soft tissue infections, there is a growing amount of evidence that dalbavancin could be useful in other invasive Gram-positive infections that need prolonged intravenous treatments, including osteomyelitis, prosthetic joint infections, infective endocarditis and catheter-related bacteremia [10]. Retrospective analyses of patients with these types of infections being treated with dalbavancin showed a favorable outcome in most cases and an excellent safety profile. The efficacy of dalbavancin was also proved in vulnerable patients with osteomyelitis or non-complicated bacteremia in whom a first-line antimicrobial therapy had been ineffective [11]. A sequential successful use of dalbavancin in patients with infective endocarditis was also reported [12]. Lastly, pharmacoeconomic analyses show that long-acting antimicrobial agents like dalbavancin are associated with a significant decrease of hospitalization days and therefore with a considerable costs reduction to the health-care services [13,14]. However, the real impact on clinical practice is nevertheless hampered by the extremely variable administration regimens reported (ranging from a single 1500 mg injection to a 7-week lasting weekly administration regimen) and the intrinsic diversity of the included Gram-positive infections, rendering them hard to be analyzed in a single retrospective study with common primary outcomes and follow-up time points [13,15].

This paper aims to review the literature and highlight the features of patients who could mostly benefit from an antimicrobial therapy with dalbavancin and to clarify the dosage and the duration of treatment which showed the most promising efficacy for each case.

2. Methods

In order to review the literature on the potential uses of dalbavancin, including on and off-label indications, like non-ABSSSI infections, and to assess the most suitable administration regimens, a group of experts was organized. Specialists belonging to different medical areas convened, namely infectious diseases (ID) specialists and a clinical pharmacologist. A total of two consensus conferences took place during which the available evidence on dalbavancin were evaluated. Specifically, a search in the literature using validated keywords filters to select articles regarding dalbavancin was performed: dalbavancin, Gram-positive infections, Gram-positive cocci, ABSSSI, intravenous treatment, and long-acting antibiotics. A literature research on biomedical bibliographic databases (PubMed and Embase) was carried out from the year 2004 up to 30 September 2020, and research papers, reviews, and

meta-analyses were considered. The manuscript draft was revised by all authors, who approved the final version before submission.

3. Results

3.1. ABSSIs

ABSSSIs have been recently defined by the FDA as bacterial infections of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema or induration). In this group, cellulitis, erysipelas, wound infections and major cutaneous abscesses are therefore included. However, it still represents an extremely heterogenous group of diseases in terms of prognosis, ranging from mild to potentially life-threatening infections [16]. ABSSSIs are generally caused by Gram-positive bacteria, particularly *Staphylococcus aureus* and *Streptococcus* spp. In the previous classification of skin and soft tissue infections (SSTIs), the infection may involve the subcutaneous tissue and is potentially attributed to a broader range of pathogens, such as Gram-positive, Gram-negative and anaerobic bacteria [17]. In order to ensure an implementation of antimicrobial stewardship programs (ASPs), etiologic diagnosis represents a milestone in the clinical approach to ABSSSIs. With this aim, biological samples should be obtained through needle aspiration, in case of systemic infection, blood culture [18]. Due to their bacterial etiology, ABSSSIs are generally treated with empiric antibiotic treatment mainly targeting Gram-positive cocci. Moreover, ABSSSIs may require surgical intervention like drainage or debridment, due to the presence of necrotic tissue [17]. Unfortunately, an increasing rate of ABSSSIs is caused by multidrug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), thus often requiring second-level antibiotic regimens [18]. Thanks to its spectrum of activity and peculiar pharmacokinetic properties, dalbavancin turned out to be effective in the treatment of ABSSSIs in two different administration regimens: a single 1500 mg dose or a two-doses (1000 mg at day 1 and 500 mg at day 8) regimen [19,20].

3.2. Osteomyelitis

Osteomyelitis are a constellation of inflammatory processes, based on different pathogenetic mechanisms, accompanied by bone destruction and caused by an infecting microorganism [21]. Based on the mechanism of infection, osteomyelitis can be classified in hematogenous and non-hematogenous, which includes iatrogenic, traumatic and contiguity osteomyelitis. Moreover, due to the duration of the illness, osteomyelitis can be further classified in acute or chronic. Hematogenous osteomyelitis are normally monomicrobial, whereas non-hematogenous cases can be monomicrobial or caused by a multitude of pathogens. In both types of osteomyelitis, the most frequently isolated bacteria are *Staphylococcus aureus*, coagulase-negative staphylococci, and streptococci [22]. Gram-negative and anaerobic bacteria are a rare cause of osteomyelitis in adults [23]. Prosthetic joint infection (PJI) is one of the most frequent complications of joint replacement surgery. Depending on the timing of the infection in relation to the surgery, PJI can be categorized as early, delayed or late onset. While early and late onset infections are often caused by *Staphylococcus aureus*, Gram-negative or anaerobic bacteria, delayed onset PJIs are generally attributed to coagulase-negative staphylococci [24]. As previously stated, osteomyelitis and PJIs are not currently approved indications for the use of dalbavancin. Nonetheless, the off-label use of this agent in these two clinical settings has been extensively reported in clinical trials and real-word observational studies (Table 1).

Dunne and coworkers realized a population pharmacokinetic model to predict the dalbavancin concentrations theoretically achievable into bone and articular tissue after the administration of two 1500 mg doses 1 week apart. The findings suggested that this administration schedule would allow the achievement of high enough drug concentrations in blood, bone and synovial fluids for up to 8 weeks, thus providing a theoretical rationale for the use of dalbavancin in the treatment of osteomyelitis and PJI [6]. Furthermore, dalbavancin showed potent in vitro activity with low MIC values against the most commonly isolated pathogens in osteomyelitis and PJI: the MIC_{50} for MRSA, MSSA, MRSE, and MSSE was 0.03 mg/L, the MIC_{90} for MRSA and MSSA was 0.06 mg/L and for MRSE and MSSE 0.12 mg/L and MSSE; the $MIC_{50/90}$ for vancomycin-susceptible (VS) *E. faecalis* and *E. faecium* were 0.03 and 0.125 µg/mL, respectively (range, ≤0.016–0.125 mg/L) [25,26]. Finally, preliminary *in vitro* and animal model data also support a potential activity of dalbavancin against bacterial biofilms, which are thought to have a significant pathogenetic role in bone and joint infections (Minimum Biofilm Bactericidal Concentration – $MBBC_{50}$ for MRSA, MSSA, MRSE and MSSE was 1 mg/L; $MBBC_{90}$ for MRSA and MSSA was 2 mg/L and for MRSE and MSSE 4 mg/L; and $MBBC_{50/90}$ for VS E. faecalis and E. faecium 0.5 and 1 mg/L, respectively) [25–27].

Currently, available clinical data on the use of dalbavancin in osteomyelitis and PJI are coworkers analyzed medical records of patients treated with dalbavancin affected by osteomyelitis ($n = 12$) and PJI ($n = 20$), mostly caused by methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA and coagulase-negative *Staphylococci* [14]. The large majority of patients included (97,1%) had already received a prior antibiotic therapy and the reasons to switch to dalbavancin were mostly related to an easier antibiotic administration or to the failure of the previous therapy. Dalbavancin was found to be effective in most of the patients with osteomyelitis (91,7%) and PJI (80%) based on the absence of clinical and microbiological evidence of infection during the follow-up period (>1 month). Another study reported similar data based on a copious cohort of 30 patients with osteomyelitis and 32 patients with PJI [28]. Included patients received a median number of 3 dalbavancin administrations and in most of cases this agent was chosen because of its pharmacokinetic properties in order to allow a treatment in an outpatient setting. In most patients, dalbavancin turned out to be safe and effective and resulted in the lack of clinical signs of infection at 90 days after last administration. Two patients with PJI experienced a treatment failure, two patients (one for each indication) had a lethal course of disease and one patient with osteomyelitis was excluded from the statistical analysis because of severe adverse effects related to the second dose of

Table 1. Dalbavancin in the treatment of bone and joint infections.

Reference	Type of study	Included patients	Dose and duration of dalbavancin treatment	% Outcome	Adverse events	Study reference
Bouza et al., 2018	Retrospective	12 OM, 20 PJI	Varying: mean of 4 doses (range 1–9), 3-week duration (range 1–24)	92% for OM, 80% for PJI	13%, Mild	[14]
Tobudic et al., 2019	Retrospective	34 OM, 8 PJI	Varying: median doses 8 weeks (range 4–32)	65% for OM, 50% for SD and 75% for PJI	Acute reactions such as exanthema or hyperglycemia, but detected no long-term negative effects.	[47]
Bryson-Cahn et al., 2019	Retrospective	7 OM	Varying: median of 1 dose (range 1–5)	71%	None	[48]
Wunsch et al., 2019	Retrospective	30 OM, 32 PJI	Varying: mean of 3 doses (range 1–32)	89% for OM, 91% for PJI	3%, Mild	[28]
Bartoletti et al., 2019	Retrospective	15 sternal OM post-cardiac surgery	Varying: median of 4 doses	93% (Follow up: 6 months)	None	[49]
Almangour et al., 2019	Retrospective	31 OM	Varying: median of 3 doses (range 1–14)	93% for OM	None	[49]
Bork et al., 2019	Retrospective	13 OM, 1 PJI	Varying: median of 3 doses (IQR 4.5)	46% for OM	10% (One secondary to acute kidney Injury and one generalized pruritus and Rash)	[11]
Morrisette et al., 2019	Retrospective	15 OM	Varying: median of 1 dose (IQR: 1–2)	92%	11%, Mild	[13]
Morata et al., 2019	Retrospective	19 OM, 45 PJI	Varying: median of 5 doses (IQR 3–8)	89.5% for OM; 69% for PJI	11%, Mild	[15]
Rappo et al., 2019	Prospective, randomized	Dalbavancin: 70 vs SOC: 10	1500 mg day 1 + 1500 mg day 8	96% Dalbavancin vs 88% SOC	None	[30]
Bai et al., 2020	Retrospective	29 OM	1500 mg, maximum number of dalbavancin administration 7 doses	89.7%	5,4%, Mild	[50]
Almangour et al., 2020	Retrospective case-control	Dalba: 11 OM vs SOC 11 OM	Range 3000 mg and 7500 mg, median 3 (IQR: 3; 500 mg	100% Dalbavancin group 82% SOC	None	[51]

OM,osteomyelitis; PJI,prosthetic joint infection; SOC,standard of care.

dalbavancin. Another group treated 64 patients with dalbavancin, including 19 patients with osteomyelitis and 45 patients with PJI [15]. In this case, the most frequently isolated pathogen was *Staphylococcus epidermidis* followed by MRSA and in most cases the reason for the switch to dalbavancin was the simplification of the antimicrobial regimen. Among the patients with osteomyelitis, 73,7% ($n = 14$) reached a clinical success and 15.8% ($n = 3$) clinically improved after a median follow-up of 164 days, while in two patients the treatment with dalbavancin was declared ineffective. Among the patients with PJI, the implant was retained in 52.3% of cases ($n = 23$) with a clinical success in 15 and an improvement in 8 patients. On the contrary, the implant was removed in 47.7% of cases ($n = 21$) with a clinical success in 16 and an improvement in 4 patients; a patient with PJI and removal of the implant experienced a clinical failure, while another patient with PJI could not be included in the efficacy analysis because of a premature loss in the follow-up [15]. Bartoletti and coworkers used dalbavancin in the treatment of 15 patients with post-surgical deep sternal wound infections, obtaining a 93% success rate after a 6-months follow-up [29]. A single randomized controlled trial (RCT) so far evaluated the efficacy of dalbavancin in the treatment of osteomyelitis: 80 adult patients with a first episode of osteomyelitis were randomized to dalbavancin ($n = 70$, 1500 mg on days 1 and 8) or standard of care ($n = 10$, the most common regimens were vancomycin for 29–30 days or vancomycin for 5–16 days and switch to linezolid or levofloxacin to complete 29 days of therapy) [30]. The most commonly isolated pathogens were *Staphylococcus aureus*, coagulase-negative *Staphylococci* and anaerobes. A clinical success was observed at follow-up in 97% of patients ($n = 65$) in the dalbavancin group and in 88% of patients ($n = 7$) in the SOC group, while five patients were not included in the statistical analysis because of a change of treatment due to isolation of only Gram-negative bacteria. Analogous success rates were reported at the 6-months and 1-year follow-up controls.

3.3. Infective endocarditis

Infective endocarditis (IE) is an infectious process involving the endocardial surface of intracardial structures, such as heart valves, both native or prosthetic, or intracardial implantable medical devices. Based on the clinical manifestations of the disease, IE can be further classified in acute or subacute. While acute endocarditis generally present with a sudden onset of fever or systemic complications, subacute endocardial infections are often misdiagnosed because of unspecific symptoms lasting over weeks or months such as fatigue, dyspnea or weight loss. The most commonly isolated pathogen in blood cultures of patients with IE is *Staphylococcus aureus*, followed by Viridians group streptococci and by enterococci which are typical for the elderly. Coagulase negative *Staphylococci* are

Table 2. Dalbavancin in the treatment of infective endocarditis.

Reference	Study type	Included patients	Prior therapy to dalbavancin treatment	Dose and duration of dalbavancin treatment	% Outcome	Adverse events	Study reference
Tobudic, 2018	Retrospective	27 IE: 59% NVE, 22% PVE, 19% PME; surgical therapy: 80% in PVE/PME.	89% Prior therapies, with dalbavancin initiated after bacteremia clearance	33%: 1000 mg load, then 500 mg/week; 66% 1500 mg load, then 1000	92%	1 Nausea; 1 increased serum creatinine	[12]
Dinh, 2019	Retrospective	9 NVE, 10 PVE	99% Prior therapies with a median duration (IQR) of 23 days	53%: 1 or 2 doses of 1500 mg weekly	73% Clinical success	2 Hypersensitivity reactions	[52]
Morrisette et al., 2019	Retrospective	5 NVE	91% Prior therapies with a mean duration of 27 dd; 30% Combination therapy	60% Dalba 1 × 1500 mg dose at end of therapy	100%	Infusion reactions, phlebitis at infusion site	[13]
Wunsch et al., 2019	Retrospective	15 NVE, 6 PVE, 4 PME; 3 cases of associated spondylodiscitis	100 Prior therapies; 64% combination therapy	9 Cases of 1 × 1500 mg dose; 8 cases of multiple weekly doses of 500 mg, preceded by a loading dose of 1000 mg. Median number of doses: 3 (range 1–32)	90% Clinical success; 1 death during therapy	1 Hypertension during infusion; 1 muscle weakness; 1 vertigo	[28]
Hidalgo-Tenorio et al., 2019	Retrospective	34 Patients with IE (41%): 32,4% NVE 44,1% PVE 23,5% PME	100% Prior therapies	Varying: median duration 14 days (range 14–21)	96,7%	4.8% mild	[53]
Spaziante et al., 2019	Case report	1 PVE MRSE and S. mitis, considered to be inoperable	Piperacillin/tazobactam and daptomycin, followed by ceftriaxone and daptomycin. Dalbavancin initiated after bacteremia clearance	1500 mg on days 1, 7, 42, 112, 189 (the frequency of infusions was guided by SBP values ≤1:8)	Net clinical and PET/CT improvement, no relapse after more than 1 year from dalbavancin discontinuation	None	[34]
Durante-Mangoni et al., 2020	Retrospective	10 Patients: 3 NVE, 5 PVE, 2 PME	Daptomycin, teicoplanin, amoxicillin-clavulanate and gentamicin were the most used antibiotics during the initial phase of IE treatment. Three patients underwent surgery prior to dalbavancin administration.	Dalbavancin treatment lasted for at least 2 weeks, and was mostly given with the intent to reduce hospital stay	70%	1 Patient experienced diffuse skin rush	[54]

IE, infective endocarditis; NVE,native valve endocarditis; NVE-rt,right-sided native valve endocarditis (unless specified, NVEs should be considered to be left-sided); PVE,prosthetic valve endocarditis; PME,pacemaker endocarditis; MSSA, methicillin-sensitive *S. aureus*; MRSA,methicillin-resistant *S. aureus*; MRSE,methicillin-resistant *S. epidermidis*; *S. mitis*;*Streptococcus mitis*.

a leading cause of infective endocarditis involving prosthetic valves or intracardiac devices. Due to frequent antibiotic resistance and difficult medication penetration into bacterial endocardial vegetations, IE often require a combined and prolonged intravenous antimicrobial therapy and debridement and valve replacement surgery [31,32]. Dalbavancin is not currently approved for the treatment of IE; nevertheless, because of its activity spectrum and pharmacokinetic properties, it may be a promising alternative in this clinical setting, reducing hospitalization duration and assistance costs.

Several retrospective studies report the use of dalbavancin in treating patients with an infective endocarditis, including both native and prosthetic valves infections (Table 2). The largest cohort has been included by an Austrian group, who administered dalbavancin to 27 patients, including 16 patients with native valve, 6 patients with prosthetic valve and 5 with intracardiac implantable device IE. In 24 cases, dalbavancin was used as a sequential treatment after negative blood cultures were achieved, whereas 3 patients received dalbavancin as primary treatment [35]. The most frequent reason for the switch to dalbavancin in the sequential group was the possibility to discharge patients and continue the treatment in an outpatient setting. Considering all patients included, the mean duration of dalbavancin treatment was 6 weeks. A clinical success was observed in 92.6% of patients ($n = 25$) based on the lack of persistence or relapse of infection at the 6-months follow-up. One patient with *Enterococcus faecalis* prosthetic valve IE died after the first dose of dalbavancin, while in another patient with a poorly surgically controlled IE, dalbavancin was discontinued because of clinical and microbiological failure. Patients with IE and treated with dalbavancin were also included in two other studies and an overall satisfactory clinical success was observed [14,28]. Another group evaluated dalbavancin efficacy in 27 patients with severe Gram-positive infections, including 8 IE, in order to facilitate earlier hospital discharge [33]. In all cases, dalbavancin was administered to complete the planned antibiotic course after an initial inpatient treatment. Among the patients with IE, six had no clinical or microbiological evidence of active infection within 90 days of the last dalbavancin dose, whereas two had no documented clinical encounters. Lastly, a recent work reports a successful long-term suppressive dalbavancin treatment in a patient with a *Staphylococcus epidermidis* and *Streptococcus mitis* infection of aortic valve and tubular ascending aorta bioprosthetic devices who was not considered eligible for valve replacement surgery and who did not tolerate oral antibiotic therapy [37]. In this case, the administration regimen was scheduled according to the serum bactericidal activity (SBA) levels which were performed immediately before each dalbavancin dose. The authors report that this long-term suppressive antimicrobial treatment was well tolerated and achieved an improvement of clinical conditions with progressive disappearance of the vegetative lesions on transesophageal echocardiography and reduction of focal uptake on PET/TC scans.

4. Expert opinion

4.1. ABSSIs

Dalbavancin should be evaluated in the treatment of moderate to severe ABSSSIs, whereas other antimicrobial agents, such as beta-lactams, should still be considered the first option in MSSA-likely mild cutaneous or subcutaneous infections, as erysipelas. Dalbavancin could be a choice in purulent infections, if adequately associated to surgical debridement. ABSSSIs can be caused by pathogens other than Gram-positive bacteria; thus, an etiologic diagnosis should be pursued before considering administration of dalbavancin. Specifically, some clinical signs may suggest Gram-negative or anaerobic etiology, thus excluding dalbavancin: infection close to the perineal region, diabetic foot infections or the presence of refractory ulcers. On the contrary, if disease or patient-related signs may suggest a MRSA etiology, dalbavancin administration should strongly be supported [43].

Some groups of patients may mostly benefit from dalbavancin, whose administration does not require long-term intravenous catheters or a prolonged hospitalization, as oncologic patients, recent or active intravenous drug users, patients with a lack of support at home, homeless, recent or active alcohol abuse, or severely burned patients [11].

Furthermore, the pharmacokinetic profile of dalbavancin may allow the administration for ABSSSIs in three logistic settings. The first is the emergency department (ER). As supported by preliminary data, a patient being evaluated in the ER for a moderate-to-severe cutaneous infection could be directly treated with dalbavancin, immediately discharged and followed up either via the outpatient clinic, by the general practitioner or through telehealth programs [36,37]. This option would avoid unnecessary hospitalization, thus reducing assistance costs and minimizing the risk of nosocomial infections. Nonetheless, physicians working in ER are rarely experienced in dealing with second-level antimicrobials and the uninterrupted presentation of patients requiring urgent care often makes the ER an inappropriate setting for long-acting medications. Therefore, dalbavancin should be administered only under the supervision of an ID specialist. Moreover, the implementation of ASPs through a multi-disciplinary network between ID specialist and ER departments may improve the prescription of long-acting antimicrobial agents. Secondly, dalbavancin could be easily administered in a dedicated outpatient clinic, where the supervision of the ID specialist is strongly recommended. Lastly, many evidences highlighted that dalbavancin can shorten the length of hospital stay through the achievement of an early discharge [38]. Indeed, in patients with comorbidities and requiring an inpatient treatment, dalbavancin could be initiated to avoid prolonged hospitalization and allow early discharge of the patients.

4.2. Osteomyelitis and PJI

The main limitation of the current evidence on the use of dalbavancin in the treatment of osteomyelitis and PJI is the retrospective nature of the data. Nonetheless, the lack of an approved indication for the drug in these contexts severely hampers the systematic evaluation of dalbavancin in clinical studies and the design of prospective RCT. Furthermore, the possibility to deduce conclusive evidence from the above-mentioned studies is hindered by some methodological limitations: inclusion criteria of patients, outcome measures and follow-up durations are extremely heterogenous among the

different studies. Many different administration regimens are reported. Moreover, the overall number of patients treated with dalbavancin is low and the only RCT on this matter is inappropriately designed (7:1 randomization). Furthermore, under the definition of osteomyelitis a broad spectrum of different entities is included, such as spondylodiscitis, hematogenous osteomyelitis or contiguity osteomyelitis. The efficacy of dalbavancin in any different subtypes should be separately considered. As for PJIs, the removal of the infected implant is a fundamental therapeutic step and data based on patients in whom the implant was retained should be separately considered. A final limitation is the lack of a systematic monitoring of plasma concentrations of dalbavancin and a correlation with the SBA levels, which may be useful in monitoring therapeutic efficacy [39]. Therapeutic drug monitoring (TDM) could also provide a helpful feedback in understanding how the active moiety vary over time. Considering the current limitations in using dalbavancin in RCTs for the treatment of osteomyelitis and PJI, the design of robust retrospective studies may increase the knowledge on the efficacy of this agent in these clinical settings. For this purpose, the definition of homogenous inclusion criteria, administration regimens, outcome measures, and follow-up durations is extremely urgent. Spondylodiscitis could represent an ideal model for the evaluation of a possible use of dalbavancin, since a microbiological diagnosis is usually achieved, and a targeted therapy could be easily administered.

Overall, on the basis of the so far available theoretical and experimental data, dalbavancin could represent, alone or in combination with beta-lactams, a valid option for the treatment of osteomyelitis and PJI and could allow, due to its unique pharmacokinetic properties, an early discharge of patients.

4.3. Infective endocarditis

The two discussed uses of dalbavancin in IE would not fully take advantage of the pharmacokinetic and pharmacodynamic properties of the molecule. Indeed, dalbavancin showed a very effective bactericidal activity against the most frequently isolated Gram-positive bacteria in IE patients and has the potentiality to become a first-line option in the therapy of IE [40,41]. Furthermore, severe subacute Gram-positive infections often require prolonged antimicrobial therapies, which are extremely expensive and rarely possible in the outpatient care (difficulty of intravenous access and limited evidence for the safety and efficacy of oral medications). The latter was addressed in a recent study, highlighting how in patients with endocarditis in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment [42]. However, these strategies do not adequately serve vulnerable populations (i.e. people who use drugs, those with difficulties to comply to unsupervised treatment or with complicating life circumstances), and dalbavancin may represent a modern alternative and its use may overcome many of the barriers that complicate traditional treatment approaches, even if some aspects should be further addressed (i.e lack of prospective data regarding efficacy in serious infections and a narrow indication) [43].

Notably, the future role of dalbavancin could become more important considering the open issues in the treatment of Gram-positive subacute infections. These include the spreading of isolates resistant to beta-lactams, vancomycin or daptomycin, the concerns on aminoglycosides toxicity in combination therapies, especially in old patients. Moreover, further studies are required in order to define specific subgroups of patients who could benefit from a first-line dalbavancin therapy alone or in combination with beta-lactams. For example, patients with an MRSA IE could be treated with surgical debridement or valve replacement followed by an extremely effective antimicrobial therapy with dalbavancin and then complete the antibiotic course with a less bactericidal agent. Nonetheless, a systematic use of dalbavancin for IE patients is feasible only if prelimin ary pharmacokinetic studies are conducted, in order to evaluate the relationship between different dosing regimens and the dalbavancin penetration rate into endocardial vegetations and the achievable bactericidal activity. Indeed, treating IE is often hard and requires high-dosed antimicrobial agents, making toxic effects more probable. Dalbavancin pharmacokinetic studies are thus urgent in order to adopt adequate administration regimens and prevent clinical failures or antimicrobial resistance development. In this clinical indication, the concomitant TDM and SBA analysis could be useful in monitoring the *in vivo* activity of the drug.

On the basis of the so far available experimental data, dalbavancin could represent a valid option for the treatment of IE as a sequential therapy to allow early discharge of patients or as a long-term suppressive treatment in patients who could not benefit from a debridement surgery or from an oral antimicrobial regimen. Notably, long-term suppressive therapy is a last option in patients with chronic infections and should be carefully used. When adopted, it can reduce the hospitalization and avoid the risk of acquiring healthcare-related infections in fragile patients [44]. Attention must be paid to the chosen antimicrobial agent in terms of safety, compliance and costs. Dalbavancin, with its unique pharmacokinetic profile, and great tolerability, as well as pharmacoeconomic advantages in terms of length of hospitalization, is an attractive option for long-term suppressive therapy, and, depending on the clinical scenario and alternative treatment options, use may be cost-effective [45,46].

5. Conclusion

As documented by RCT and real-life experience, dalbavancin showed to be highly effective in patients with ABSSSIs. Within this context, dalbavancin could be administered in an outpatient setting if a strict supervision by an ID specialist can be guaranteed and the patient can be adequately followed up. The use of dalbavancin in the ER requires an implementation of ASPs, an adequate formation of emergency physicians and a constant consultation with an ID specialist. Lastly, the possibility to administer dalbavancin to facilitate earlier hospital discharge remains a valid option.

Although not formally approved by regulatory agencies, several real-life experiences of dalbavancin use in

osteomyelitis, PJI and IE are reported. Many limitations are present in the currently available data; however, dalbavancin could unequivocally represent a valid option in these contexts due to its pharmacokinetic and pharmacodynamic properties such as the prolonged plasmatic half-life and the potent bactericidal activity against susceptible Gram-positive bacteria. Considering the current limitations in designing prospective studies, a definition of homogenous parameters to include patients in retrospective studies and to evaluate the clinical efficacy of the molecule should be carried out, leading to a more robust evidence to increase the use of dalbavancin in indications other than ABSSSIs.

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