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REVIEW

The role of dalbavancin in the treatment of acute bacterial skin and skin structure infections (ABSSSIs)

Alex Soriano [a], Gian Maria Rossolini [b,c] and Federico Pea [d,e]

[a]Department of Infectious Diseases, University of Barcelona, IDIBAPS, Barcelona, Spain; [b]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [c]Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy; [d]Department of Medicine, University of Udine, Udine, Italy; [e]Institute of Clinical Pharmacology, Santa Maria Della Misericordia University Hospital of Udine, Udine, Italy

ABSTRACT

Introduction: Acute bacterial skin and skin-structure infections (ABSSSIs) are a subgroup of skin and soft tissue infections and are a common source of morbidity in both the community and the hospital setting. The most common cause of ABSSSIs is *Staphylococcus aureus*, which also includes methicillin-resistant *S. aureus* (MRSA), together with beta-hemolytic streptococci, enterococci, and Gram-negative bacteria. Since the emergence of MRSA, the management of ABSSSIs has become more challenging. Novel therapies alternative to teicoplanin and vancomycin, intravenous agents commonly used against MRSA and employed in hospitalized patients, and to other antibiotics which are used as standard of care for MRSA infection, with a higher efficacy and safer profile are worth evaluating.

Areas covered: This review presents and discusses current evidence on the use of dalbavancin in the treatment of ABSSSIs.

Expert opinion: Dalbavancin represents a promising therapeutic choice in patients with ABSSSIs, thanks to its favorable pharmacokinetic profile, valuable antimicrobial spectrum, and good safety profile.

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1. Introduction

Acute bacterial skin and skin-structure infections (ABSSSIs) are a subgroup of skin and soft tissue infections (SSTIs) and are a common source of morbidity in both the community and the hospital setting [1–4]. ABSSSIs have been defined in 2013 by the US Food and Drug Administration (FDA), and include cellulitis, erysipelas, major skin abscesses, and wound infections, with a minimum lesion surface area of 75 cm^2 [5]. Other skin infections are not considered as ABSSSIs. With this definition, the FDA was aiming to better characterize infections for which the advantages of a new antibiotic could be estimated through quantifiable parameters – for example, improvement of the lesion size and of systemic symptoms and signs of infection.

Worldwide, the most common cause of SSTIs – and hence of ABSSSIs – is *Staphylococcus aureus*, which also includes methicillin-resistant *Staphylococcus aureus* (MRSA) with the highest overall rate being in North America (35.9%) [6,7]. Recent epidemiological data of the European Antimicrobial Resistance Surveillance (EARS) Network and European Centre for Disease Prevention and Control (ECDC) from 30 participating countries suggested that MRSA accounts, overall, for 16.9% of all *S. aureus* isolates, with higher figures (up to 44%) in the Mediterranean and Balkan areas [8]. However, other pathogens, such as *Streptococcus pyogenes* and other streptococci, enterococci, and Gram-negative bacteria, can also be involved in ABSSSIs [1].

Before the spread of MRSA, antibiotic therapy of SSTIs was relatively straightforward [1]; however, since the emergence of MRSA, the management of ABSSSIs has become more challenging. Intravenous (iv) vancomycin has represented the mainstay of treatment against MRSA in ABSSSIs for a long time. However, alternative therapeutic options capable of reducing the number of daily administrations and the length of hospital stay (LOS) and of showing a safer profile compared to vancomycin may be more convenient and clinically attractive [2,9]. Among the novel antibiotic therapies that have a similar profile, dalbavancin may represent an interesting option.

Dalbavancin is a semisynthetic lipoglycopeptide antibiotic, which was approved by both the FDA (May 2014) and the EMA (February 2015) for the treatment of ABSSSIs in adult patients [2,10–14]. This molecule was developed as an improved alternative to teicoplanin and vancomycin, which are iv anti-MRSA agents commonly used in hospitalized patients, and to other standard-of-care anti-MRSA antibiotics whose safety profile appears less favorable (e.g. daptomycin and linezolid). This narrative review presents current evidence on the use of dalbavancin in the treatment of ABSSSIs. A special emphasis was placed on describing its broad activity against the different Gram-positive cocci, which are discussed individually here. Furthermore, given the rising number of studies evaluating the cost-effectiveness of dalbavancin in both USA and several European countries, we first discuss how dalbavancin characteristics may translate into economic value.

CONTACT Federico Pea federico.pea@uniud.it Institute of Clinical Pharmacology, Santa Maria Della Misericordia University Hospital of Udine, Piazzale Santa Maria Della Misericordia, 15, Udine UD 33100, Italy

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Article highlights

- The increase of multidrug-resistance among Gram-positive pathogens, particularly among staphylococci and enterococci, represents a major health care problem, thus resulting in significant morbidity, mortality, and health care costs.
- Unlike traditional glycopeptides, dalbavancin features structural modifications that resulted in increased antimicrobial potency, high plasma protein binding along with a prolonged elimination half-life.
- The potency advantage of dalbavancin compared with some class comparators, coupled with infrequent patient dosing, provides a unique therapeutic alternative for treating serious Gram-positive infections, including those caused by methicillin-resistant staphylococci and other species which are common causes of ABSSSIs.
- Resistance to dalbavancin among staphylococci is rare, being reported in less than 1% of isolates, and is limited to intrinsic glycopeptide-resistant species and to organisms expressing the VanA phenotype of acquired resistance.
- Dalbavancin may represent an attractive therapeutic option alternative for early hospital discharge of patients needing outpatient parenteral antimicrobial therapy.
- Treatment of ABSSSIs with dalbavacin in an outpatient setting may represent both a cost-saving and a resource-saving approach, considering that it has proved to reduce length of hospital stays and to be associated with cost-savings compared with other antimicrobial treatments.

1.1. Selection of evidence

The studies included in the present review were retrieved from a PubMed search, using different combinations of pertinent keywords (e.g. dalbavancin AND ABSSSI), with no restriction in terms of publication date and of language. Documents from Authors' personal collection of literature could also be considered. Papers were selected according to their relevance to the topic and included at the Authors' discretion.

2. Pharmacology and pharmacokinetic profile of dalbavancin

Dalbavancin is a semi-synthetic lipoglycopeptide developed from an antimicrobial compound produced by fungi of genus *Nonomuraea* [15]. This molecule is able to inhibit the synthesis of bacterial cell wall by binding to the terminal D-alanyl-D-alanine residues of peptidoglycan precursors and by inhibiting the enzymatic reactions involved in the final steps of peptidoglycan assembly [2]. The lipophilic radical chemical structure of dalbavancin enhances its binding to the bacterial cell wall compared with other similar compounds (teicoplanin and vancomycin), resulting in faster and more potent bactericidal activity [2].

Two dalbavancin treatment regimens have been approved for adults with an ABSSSI: single-shot regimen of 1500 mg on the first day of treatment and a two-infusion regimen of 1000 mg on day 1 followed by 500 mg on day 8 [10,13,16,17].

Dalbavancin has the typical volume of distribution of a hydrophilic drug (approximately 15 L) [18] and shows a good penetration into the extracellular fluid of soft tissues. In a pharmacokinetic study carried out among healthy volunteers, the penetration rate into skin blister fluid after administration of a single 1000 mg iv dose over 30 minutes was 59.6% [19]. The concentrations persisted well above the MIC_{90} values of the pathogens commonly implicated in ABSSSIs up to day 7 [19]. Noteworthy, the penetration rate of dalbavancin is of the same magnitude of those observed in similar studies with some beta-lactams (0.41 for flucloxacillin, 0.61 for ertapenem and 0.66 for meropenem), and higher compared to that of oritavancin (0.19) [20].

Dalbavancin is highly bound to plasma proteins (93%), and this contributes to the very long terminal elimination half-life of 333–405 h (equal to 15.5 days) [17,21]. This allows that even after a single-dose regimen, plasma, and tissue concentrations may broadly exceed the MICs for common ABSSSI pathogens for at least 2 weeks, that is the standard duration of ABSSSI therapy. Of note, dalbavancin concentration in skin 2 weeks after infusion of a single 1,000-mg intravenous infusion was 13.8 µg/g, providing additional support for the efficacy of dalbavancin demonstrated in clinical trials of ABSSSIs [22].

Dalbavancin shows a low potential for drug–drug interactions with other comedications. In non-clinical studies, the coadministration of dalbavancin with known CYP450 substrates, inhibitors, and inducers did not have any clinically significant effect on its pharmacokinetics [23].

Dalbavancin is eliminated both via the renal route (up to 42% of the dose) and extra-renally. No dosage adjustment is needed in patients with mild/moderate renal impairment, in those with mild hepatic impairment (Child–Pugh class A), and in those with end-stage renal disease (ESRD) who undergo intermittent hemodialysis [17,18]. Conversely, dosage reductions to 1125 mg (US label vs 1000 mg per EU label) for the single-dose regimen or to 750 mg on day 1 followed by 375 mg on day 8 for the two-dose regimen are recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) who do not undergo hemodialysis [17,24,25]. Caution in using dalbavancin is recommended in Child-Pugh class B and/or class C hepatic impairment, as pharmacokinetic data in these settings are currently lacking [17].

3. Microbiological profile of dalbavancin

A susceptibility breakpoint of ≤0.25 mg/L is stated by the CLSI M100 standard and recognized by FDA for dalbavancin with *S. aureus* (including MRSA), β-hemolytic streptococci, *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible strains) [25]. On the other hand, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) stated a susceptibility breakpoint of ≤0.125 mg/L for dalbavancin with staphylococci, β-hemolytic streptococci of groups A, B, C, and the *Streptococcus anginosus* group, while does not provide breakpoints for enterococci [26]. Considering that the number of clinical isolates with dalbavancin MICs >0.12 mg/L is exceedingly rare [22], the difference in breakpoints between US and EUCAST is probably irrelevant from the clinical standpoint.

3.1. Activity against staphylococci

Dalbavancin presents potent *in vitro* activity against *Staphylococcus* spp., including MRSA isolates Table 1 [16]. In all studies, dalbavancin consistently showed MIC_{90} values against *S. aureus* isolates at 0.06 mg/L [2].

Table 1. Summarizes available data on *in vitro* activity of dalbavancin against different pathogens.

Organisms	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range	CLSI % S	CLSI % R	References
Staphylococci						
Staphylococcus aureus						[27]
• Dalbavancin	0.03	0.03	≤0.002–0.25	100.0		
• Daptomycin	0.25	0.5	≤0.12–2	100.0		
• Vancomycin	0.5	1	≤0.12–2	100.0		
• Oxacillin	0.5	>2	≤0.25–>2	63.6	36.4	
• Linezolid	1	1	≤0.12–>8	>99.9		
MSSA						[27]
• Dalbavancin	0.03	0.03	≤0.002–0.25	100.0		
• Oxacillin	0.5	1	≤0.25–2	100.0		
• Daptomycin	0.25	0.5	≤0.12–1	100.0		
• Linezolid	1	1	≤0.12–2	100.0		
• Teicoplanin	≤0.5	≤0.5	≤0.5–8	100.0		
• Vancomycin	0.5	1	≤0.12–2	100.0		
MRSA						[27]
• Dalbavancin	0.03	0.03	≤0.002–0.12	100.0		
• Oxacillin	>2	>2	>2–>2	0.0	100.0	
• Daptomycin	0.5	0.5	≤0.12–2	>99.9		
• Linezolid	1	1	≤0.12–>8	>99.9		
• Teicoplanin	≤0.5	≤0.5	≤0.5–8	100.0		
Coagulase-negative staphylococci						[27]
• Dalbavancin	≤0.03	0.06	≤0.002–0.12	99.6[a]	0.4[a]	
• Daptmocyin	0.5	0.5	≤0.12–2	99.9		
• Vancomycin	1	2	≤0.12–4	100.0		
• Oxacillin	2	>2	≤0.25–>2	37.8	62.2	
• Teicoplanin	2	4	≤0.5–>16	99.3	0.2	
S. aureus with decreased susceptibility to:						[32]
• *Daptomycin*	0.06	0.12	≤0.03–0.5	95.8		
• *Vancomycin*	0.06	0.12	≤0.03–0.5	99.3		
• *Telavancin*	0.06	0.25	≤0.03–0.5	90.4		
Enterococci						
All E. faecalis						[27]
• Dalbavancin	0.03	0.06	≤0.015–>2	97.8		
• Daptomycin	1	1	≤0.25–4	100.0		
• Linezolid	1	2	≤0.25–8	99.9		
• Teicoplanin	≤2	≤2	≤2–>16	97.9	2	
• Vancomycin	1	2	≤0.5–>16	97.6	2.4	
Vancomycin-susceptible E. faecalis						[27]
• Dalbavancin	0.03	0.06	≤0.015–0.25	100.0		
• Daptomycin	1	1	≤0.25–4	100.0		
• Linezolid	1	2	≤0.25–8	99.9		
• Teicoplanin	≤2	≤2	≤2–4	100.0		
• Vancomycin	1	2	≤0.5–4	100.0		
Vancomycin-susceptible E. faecium						[27]
• Dalbavancin	0.06	0.12	≤0.015–0.25	Not available		
• Daptomycin	1	2	≤0.25–>8	99.8		
• Linezolid	1	2	≤0.25–8	14.5	77.5	
• Teicoplanin	≤2	≤2	≤2–4	100.0		
• Vancomy*cin*	≤0.5	1	≤0.5–4	100.0		
Streptococci						
S. pneumoniae	0.015	0.015	≤0.002–0.06	Not available		[27]
• Dalbavancin	0.03	1	≤0.015–>2	87.6	2.9	
• Ceftriaxone	1	2	0.25–2	100.0		
• Linezolid	≤0.25	>1	≤0.25–>1	84.8	14.7	
• Clindamycin	0.25	0.25	≤0.06–0.5	100.0		
• Vancomycin						
β-Hemolytic streptococci						[60]
• Dalbavancin	≤0.03	≤0.03		100.0		
• Daptomycin	0.12	0.25		100.0		
• Linezolid	1	1		100.0		
• Vancomycin	0.25	0.5		100.0		
Viridans group streptococci						[27]
• Dalbavancin	0.008	0.03	≤0.002–0.12	100.0		
• Daptomycin	0.25	1	≤0.06–>2	99.9		
• Vancomycin	0.5	0.5	≤0.06–1	99.9		
• Linezolid	0.5	1	≤0.06–>4	100.0		

% S, percentage susceptible; % R, percentage resistant; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus.
[a]According to EUCAST.

In a recent study, dalbavancin was shown to be 16-fold more potent than daptomycin and 32-fold more potent than vancomycin and linezolid against MRSA [27]. Similar results were reported in a previous study, in which dalbavancin was 16-fold more active than vancomycin against *S. aureus* [28]. Similarly, among clinical isolates from the Canadian Ward Surveillance Study (CANWARD), dalbavancin showed a potency higher than vancomycin and telavancin against *S. aureus* and *S. epidermidis* [29].

Dalbavancin has a higher activity than vancomycin against *S. aureus* strains with decreased susceptibility to vancomycin (MIC_{90} 2 mg/L *vs*. MIC_{90} 4 mg/L), while comparable high MIC values were observed against VRSA strains (MIC >16 mg/L) [30]. In a recent study on 1141 *S. aureus* isolates with decreased susceptibility to vancomycin (i.e. MIC ≥2 mg/L), dalbavancin retained activity against 99.3% or 94.5% of isolates considering CLSI or EUCAST breakpoints, respectively, being also active against most isolates resistant to teicoplanin, telavancin, or linezolid [31].

Interestingly, dalbavancin also exhibited notable activity against biofilms of *S. aureus* (including MRSA) and coagulase-negative staphylococci, thus representing a promising drug for the treatment of biofilm-associated infections [32–34].

In support of these *in vitro* findings, studies conducted in animal models confirmed that dalbavancin has potent *in vivo* activity against *S. aureus* strains, including those with decreased susceptibility to vancomycin [35]. Moreover, the activity of dalbavancin against clinical isolates of *S. aureus* has been demonstrated also in the pivotal clinical trials (DISCOVER 1 and DISCOVER 2), in which the MIC_{90} of dalbavancin was 0.06 mg/L for the 511 *S. aureus* isolates [10].

3.2. Activity against enterococcal isolates

Dalbavancin exhibits a good *in vitro* antibacterial activity also against vancomycin-susceptible enterococci (VSE) [16]. Dalbavancin has been indicated only for infections caused by vancomycin-susceptible *E. faecalis* isolates, although a relevant antibacterial activity has also been observed *in vitro* against vancomycin-susceptible *E. faecium* isolates [16].

Among vancomycin-resistant enterococci (VRE), dalbavancin has in vitro activity against VanB resistant strains, but not against the VanA ones [12,36–38]. In the studies in which a distinction between Van phenotypes was performed, 50% of VanB isolates were inhibited at 0.03 mg/L, while VanA isolates exhibited high-level MICs (i.e. >4 mg/L) [36,37]. In the study conducted by Jones et al., only 6/54 VanB isolates showed dalbavancin MIC ≥1 mg/L [36]. Biedenbach and coauthors reported dalbavancin MIC values >0.25 mg/L among 29.8% of *E. faecalis* and 22.4% of *E. faecium* isolates with a VanB phenotype [38], while, in the study of Neudorfer et al., all VRE isolates, including all *vanA, vanB1* and *vanB2/3* positive, had MIC values >16 mg/L [37].

Interestingly, dalbavancin exhibited notable in vitro activity also against susceptible *E. faecalis* isolates grown in biofilms [37], further supporting a potential role for treatment of biofilm-associated infections.

3.3. Activity against streptococci

Dalbavancin has marked activity against streptococci. Penicillin and ceftriaxone-resistant *S. pneumoniae* strains were inhibited at MIC_{90} values ranging from 0.016 to 0.03 mg/L [16]. Dalbavancin is also active against viridans group streptococci (VGS) and β-hemolytic streptococci (MICs consistently <0.12 mg/L), regardless of their resistance phenotype [16]. Moreover, dalbavancin MIC_{90} values were at least 16-fold lower than those obtained for any comparator against VGS, both MDR and non-MDR isolates [39]. Dalbavancin is also active against less common isolates of β-hemolytic streptococci, such as those of serogroups C, F, and G, or of VGS (e.g. *S. anginosus, S. milleri dysgalactiae, S. mitis, S. mutans, S. salivarius/S. vestibularis* group), with *S. anginosus* and *S. milleri* being among the most susceptible species (MIC_{90} ≤0.03 mg/L) [40].

3.4. Activity against other species

Dalbavancin is also very active against *Corynebacterium* spp. ($MIC_{50}/_{90}$ 0.06/0.12 mg/L), *Listeria monocytogenes* ($MIC_{50}/_{90}$ 0.06/0.12 mg/L), and *Micrococcus* spp. ($MIC_{50}/_{90}$ ≤0.03/≤0.03 mg/L) [40].

To date, resistance to dalbavancin is rare among staphylococci, being reported in less than 1% of isolates [12]. It is limited mainly to intrinsic glycopeptide-resistant species and to organisms with the acquired VanA phenotype of resistance [41]. Furthermore, data from global surveillance programs published post-approval revealed that dalbavancin has sustained activity against the vast majority of *S. aureus* isolates that are resistant to other currently available antimicrobials, including MRSA isolates with MDR phenotypes [41].

4. Clinical efficacy

The pivotal studies of dalbavancin for the treatment of ABSSSIs come from the DISCOVER 1 and DISCOVER 2 trials [10]. These were identically designed, double-blind, double-dummy, non-inferiority trials of dalbavancin (given i.v. on days 1 and 8, 1000 mg and 500 mg, respectively) versus vancomycin (given i.v. for ≥3 days with the option to switch to oral linezolid for 10–14 days of therapy). Early clinical response (*i.e.* cessation of spread of infection-related erythema and the absence of fever at 48–72 h; primary endpoint) was similar in the two groups in both trials. Moreover, at the pooled analysis, 525/659 patients (79.7%) in the dalbavancin group and 521/653 (79.8%) in the vancomycin-linezolid group had an early clinical response. These figures were 90.6% and 93.8% for patients infected with *S. aureus* (including MRSA), respectively.

Secondary analysis did identify that a significantly higher rate of patients in the vancomycin/linezolid treatment group received 14 days of blinded treatment compared to the dalbavancin arm (38.4% and 31.0% of the patients received 14 days of therapy, respectively; $p = 0.008$) [2,10]. Significantly fewer patients in the dalbavancin group experienced diarrhea (0.8% vs 2.5%; $p = 0.02$) or pruritus (0.6% vs 2.3%, $p = 0.01$) compared to the vancomycin/linezolid group.

Dunne et al. reported the results of another phase III, randomized, double-blind study, in which patients received dalbavancin 1500 mg either as a single infusion or 1000 mg i.v. on day 1 followed 1 week later by 500 mg [42]. The primary endpoint was a ≥ 20% reduction in the area of erythema at 48–72 h, with non-inferiority set if the lower limit of the 95%

confidence interval (CI) on the difference in the outcomes was greater than −10%. Overall, dalbavancin as a single dose was non-inferior to a two-dose regimen (81.4% vs 84.2%; difference, −2.9%; 95% CI: −8.5–2.8%]). Secondary endpoints also demonstrated similar clinical success rates at 14 and 28 days. Adverse events were similar between treatment groups with only 1.7% vs 1.4% of treatment-related adverse events resulting in discontinuation of the study medication. In a *post hoc* analysis of this study, outpatients reported greater convenience and satisfaction with antibiotic treatment and care setting compared with inpatients [43]. In another *post-hoc* analysis specific on persons who inject drugs (PWID; n = 212), dalbavancin efficacy was similar between the single- and two-dose therapy groups in the PWID and non-PWID populations at all timepoints [44]. However, the convenience of a single dose may contribute to optimize treatment adherence in this population.

A network meta-analysis compared the efficacy and safety between different i.v. antibiotics used in the management of ABSSSIs, namely vancomycin (comparator in all studies), daptomycin, dalbavancin, linezolid, and tigecycline [45]. Overall, the likelihood of clinical and microbiological success with dalbavancin was similar to what reported with all other therapies, but with the advantage of a simple way of administering the treatment.

5. Safety profile

Dalbavancin has been well tolerated during investigational trials, with the majority of adverse events being of mild-to-moderate severity, and in most cases not directly attributable to the study drugs [2,46].

In the DISCOVER trials, only 2.1% of the patients assigned to dalbavancin discontinued therapy for an adverse event compared with 2.0% of those in the vancomycin/linezolid comparator group [10]. The overall rate of adverse events in the dalbavancin group was significantly lower than in the vancomycin/linezolid arm (32.8% vs 37.9%, respectively; p = 0.05), although the proportion of treatment-related adverse events was similar in the two groups. The most common medication-related adverse event was nausea in both groups, and fewer patients on dalbavancin experienced diarrhea (0.8% vs 2.5%; p = 0.02) or pruritus (0.6% vs 2.3%; p = 0.01). Importantly for safety, the duration of any adverse event in the dalbavancin group was similar to that observed in the comparator group, irrespective of the fact that exposure to dalbavancin lasted much longer [2].

In the study by Dunne et al. on escalating dosages of dalbavancin, the incidence of adverse events was similar between treatment groups, and less than 2.0% of the events in either group resulted in treatment discontinuation [42].

In a pooled analysis of seven randomized clinical trials, Dunne et al. compared the safety profile of dalbavancin with that of the comparator agents in the SSTIs/ABSSSIs [47]. Overall, adverse event rates for patients on dalbavancin were similar or lower (799/1778; 44.9%) compared with those receiving other agents (573/1224; 46.8%, p = 0.012). Duration and timing of onset of adverse events in patients on dalbavancin were similar to those in the comparator group. In the network-meta-analysis by Guest et al., no differences in the discontinuation rate due to adverse events were observed between dalbavancin and any of the comparators [45]. However, dalbavancin was associated with a significantly lower incidence of adverse events than linezolid, with a significantly lower incidence of severe adverse events than vancomycin and daptomycin, and with a lower risk of all-cause mortality than vancomycin, linezolid, and tigecycline [45].

In a real-world experience on patients with Gram-positive infections, the incidence of adverse events potentially associated with dalbavancin was 13%, with rash (n = 2; 2.9%), tachycardia (n = 2; 2.9%) and impaired renal function (n = 2; 2.9%) being the most common; the majority of adverse events were of mild severity [48].

Lastly, a recent report described the case of a patient with severe hypersensitivity reaction to vancomycin who successfully tolerated a dalbavancin-graded challenge [49].

6. Pharmacoeconomic and organizational considerations

Well-designed phase IV post-marketing surveillance studies may enrich our understanding of the effectiveness of new health care approaches and may better inform patients and health care providers alike. These studies should be carried out for determining the real benefits deriving from long-term dalbavancin use, and for quantifying how early hospital discharge may translate into economic value for the health care system. Given the potential organizational advantages of dalbavancin over other antibiotics used in the treatment of ABSSSIs, it is interesting to report pharmacoeconomic experiences on this drug and other similar ones.

Keyloun et al. modeled the implementation of a new treatment pathway leveraging long-acting antibiotics (LAs) for the treatment of ABSSSIs in the ED setting, using standard of care (vancomycin i.v.) as a comparator [50]. Outcomes included patient throughput rate, LOS, and cost (from the US perspective). Overall, the implementation of an LA pathway improved ABSSSI patient throughput rate by 350% and reduced LOS by 68% (−7.2 h/patient). These improvements were driven by the reduced infusion time required for LA antibiotics and were greater for dalbavancin over oritavancin owing to the shorter infusion time (30 min vs 3 h). In a retrospective study, conducted in the US and pooling data on dalbavancin or oritavancin, the median hospital LOS reduction was 20 days (interquartile range [IQR]: 10–30 days) in PWUD (n = 17) vs 11 days (IQR: 9–14 days) in non-PWUD patients (n = 39). Estimated savings were 40,455 USD (IQR: 20,900–62,700 USD) in PWUD and 19,555 USD (IQR: 15,375–23,735 USD) in non-PWUD [51]. In a similar study by the same group, long-acting antibiotics for Gram-positive infections resulted in a reduction of hospital LOS of 9.2 days/person and a cost saving of 17,204 USD/person [52]. Collectively, these data suggest that long-acting lipoglycopeptides, such as dalbavancin, can allow earlier discharge of patients and significant cost savings compared with traditional agents.

A recent retrospective analysis conducted in US has provided further confirmation that dalbavancin may stand as a valuable option able to minimize health care expenditures with a total of 617 days saved and a mean cost avoidance of 40,414 USD per patient [53].

Last, the very recently published ENHANCE ABSSSI pre- vs. post-period pragmatic trial evaluated the impact on LOS and work productivity in consecutive patients on dalbavancin (n = 43; post period) versus standard of care (n = 48; pre-period) at an urban tertiary-care center in the US [54]. Over a 44-day period, mean infection-related LOS was reduced by 2 days with dalbavancin as compared with standard of care (3.2 days vs 4.8 days; p = 0.003). Work productivity and activity impairment outcomes significantly were also improved in the post-period. Complete response rates were 57% with dalbavancin and 50% with standard of care.

In the Italian scenario, Barbieri et al. retrospectively reviewed 35 patients with ABSSSIs after cardiac surgery [55]. The use of dalbavancin was associated with cost savings versus the other antibiotics evaluated (linezolid, vancomycin, daptomycin, tigecycline, and teicoplanin), ranging from approximately €3,200 versus vancomycin to €4,700 versus daptomycin. These savings were mainly due to a reduction in LOS (–2.3 days). In another pharmacoeconomic study, from the national health care provider's perspective of Italy, Romania and Spain, a decision–analytic model was developed to evaluate the diagnostic and clinical pathways of hospitalized ABSSSI patients [56]. The model estimated an average annual number of patients with ABSSSIs of approximately 50,000 patients. The introduction of dalbavancin reduced the hospital LOS by 3.3 days per ABSSSI patient, compared with standard of care, without any additional cost for the National Healthcare System.

7. Expert opinion

The increase of multidrug resistance among Gram-positive pathogens, particularly among staphylococci and enterococci, represents a major health care problem, since it results in significant morbidity, mortality, and health care costs [57,58]. The emergence of such resistant bacterial strains highlights the need for further research to optimize treatment approaches and to develop new agents capable of dealing with drug-resistant ABSSSIs [59]. In this view, antimicrobial agents endowed with long-term activity allowing single-shot administration would be extremely useful [3].

Dalbavancin belongs to the lipoglycopeptide class of antimicrobial agents that cause bacterial death by inhibiting the bacterial cell wall synthesis. Unlike traditional glycopeptides, dalbavancin features structural modifications that resulted in increased antimicrobial potency, and in high plasma protein binding with a prolonged elimination half-life.

The favorable pharmacokinetic profile, the broad antimicrobial spectrum covering the MDR Gram-positive causative pathogens most frequently involved in ABSSSIs (such as MRSA), the lack of known drug–drug interactions (dalbavancin being neither a substrate, nor an inhibitor or inducer of CYP450 enzymes) [3], and the good tolerability profile, all make dalbavancin suitable for the treatment of drug-resistant ABSSSIs [60].

Overall, the very long elimination half-life enables that free plasma concentrations of dalbavancin may still persist 16-fold above the MIC_{90} of pathogens commonly involved in ABSSSIs even after 3 weeks from the last administration. One of the main advantages of this prolonged antimicrobial activity is the convenient schedule of administration of dalbavancin in humans. The single-shot (1500 mg on day 1) or the two-shot regimen 1 week apart (1000 mg on day 1 and 500 mg on day 8) may increase the patient's compliance and prevent the need for long-term iv access. Consistently, dalbavancin may represent an attractive therapeutic option alternative for rapid hospital discharge of patients needing outpatient parenteral antimicrobial therapy. This approach may offer improved quality of life for patients, considering benefits, such as no need for a central line for daily infusions, fast hospital discharge, and less need for laboratory monitoring. Noteworthy, avoidance of a central line is helpful in preventing line-related complication and self-administration of drugs in drug abusers with ABSSSIs [61]. Remarkably, dalbavancin may represent even a suitable alternative to conventional antibiotics for the treatment of surgical site infections, which remain one of the most common postsurgical complications [62,63]. In this regard, dalbavancin may couple the advantage of early hospital discharge with that of health care cost-saving [63,64].

Long-term intravenous antibiotic therapy poses a particular challenge for treating patients classified as vulnerable or at high-risk for complications, such as PWUD or those lacking social support, including frail elderly and/or those who are homeless, and those with an underlying psychiatric illness [65].

Pivotal clinical trials demonstrated the efficacy and safety of dalbavancin for the treatment of ABSSSIs [10,44,66]. Moreover, a survey showed that among patients receiving dalbavancin treatment as outpatients the degree of satisfaction with the treatment and the care setting was really very high compared with that perceived as inpatients [43].

Collectively, a large body of evidence suggests that dalbavancin has proven to be a successful and less toxic alternative to vancomycin in the treatment of ABSSSIs caused by MDR Gram-positive pathogens.

Overall, it may be concluded that, on these bases, dalbavancin may represent a suitable effective and safe therapeutic option that is very promising in the management of patients with ABSSSI [67,68].

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ORCID

Alex Soriano http://orcid.org/0000-0002-9374-0811
Gian Maria Rossolini http://orcid.org/0000-0002-9386-0434
Federico Pea http://orcid.org/0000-0002-6966-7167

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