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SOMMARIO

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Scientific evidences on microbiological efficacy, pharmacokinetic/ pharmacodynamic (PK/PD) and clinical profile of dalbavancin

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ABSTRACT

Dalbavancin, a novel second-generation semi-synthetic lipoglycopeptide, has recently been approved for the treatment of severe skin infections sustained by Gram-positive multi-drug resistant (MDR) pathogens. More specifically, it is indicated for the treatment of adult patients with ABSSSIs, caused by Gram-positive pathogens: *S. aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*) and *Enterococcus faecalis* (vancomycin susceptible strains). To reduce the development of drug-resistant bacteria and maintain the effectiveness of dalbavancin, FDA recommends this drug only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. In Europe, dalbavancin is indicated for the treatment of ABSSSIs in adults.
Two dalbavancin treatment regimens have been approved for adults with ABSSSI: single-dose regimen (1500 mg) in patients with normal renal function, shows to be equally effective and well tolerated with respect to the two-dose regimen (1000 mg followed by 500 mg), in terms of prompt clinical response (48-72 h) and low rates of adverse outcome.
This paper will review the scientific evidence of the microbiological efficacy of dalbavancin against Gram-positive and rare isolates, its synergistic activity in combination with other drugs, and the pharmacokinetic/pharmacodynamic (PK/PD) and clinical profile.

INTRODUCTION

Acute bacterial skin and skin structure infections (ABSSSIs), previously named skin and soft-tissue infections (SSTIs), are among the most common bacterial infections and can occur with variable clinical presentation, from mild to serious life-threatening infections. Since SSTIs represent a heterogeneous array of disorders, recently, the Food and Drug Administration (FDA) introduced the definition of ABSSSIs, which allowed a standardization and the introduction of more comparable endpoints in registration phase II-III clinical trials [1, 2].
The common source of pathogens is the endogenous flora of the patient skin or mucous membranes. Consequently, the etiological agents are frequently Gram-positive cocci, generally residents on the skin, or anaerobic bacteria and Gram-negative aerobes when incisions are made near the perineum or groin [3].

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According to the National Nosocomial Infection Surveillance system reports, Gram-positive cocci (particularly *Staphylococcus aureus*, coagulase-negative staphylococci and *Enterococcus* spp.), followed by *Escherichia coli, Pseudomonas aeruginosa* and *Enterobacter* spp., are the most commonly encountered pathogens in ABSSSIs [4].

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a major public health problem, causing significant morbidity and mortality and elevated health care costs [5]. MRSA is the most important pathogen involved in ABSSSIs, and several new drugs with anti-MRSA activity have been developed in the last years for their use in the setting of ABSSSIs [2], to increase the efficacy against resistant isolates, but also to overcome the main disadvantages of old drugs and to open the way to modern approach to clinical management of patients, including the early discharge or outpatient management [6].

Dalbavancin is a second-generation semisynthetic lipoglycopeptide, belonging to the same class of vancomycin, that binds to the C terminal D-alanyl-D-alanine subgroup of the stem pentapeptide in nascent cell wall peptidoglycan and inhibits the late stages of bacterial cell wall synthesis by preventing transglycosylation and transpeptidation of the peptidoglycan chain. In addition, the lipid radical allows dalbavancin to form a long lipophilic side chain that firmly anchors the compound to the cellular membrane, increasing its antimicrobial activity against Gram-positive cocci by improving its affinity for the terminal D-Ala-D-Ala, and prolongs its half-life, allowing for once-weekly dosing. In fact, two treatment regimens have been approved for dalbavancin: in patients with normal renal function dalbavancin should be administrated at the dosage of 1500 mg (single dose regimen) or 1000 mg followed one week later by 500 mg (two-dose regimen). This dosage is also approved for patients on regular hemodialysis. In patients with glomerular renal function < 30 mL/min or in those not on regular hemodialysis the single dose regimen expects the administration of 1125 mg of the drug, while the two-dose regimen the administration of 750 mg followed one week later by 375 mg [7, 8].

Long-acting antibiotics such as dalbavancin may represent a significant innovation, that improves the process of care of complex or frail patients admitted to acute-care hospitals. Elderly or frail patients nowadays constitute a large proportion of hospital population. Frail patients have usually multiple comorbidities, need frequent hospitalization due to exacerbation of underlying diseases, and receive multiple medications [2]. In these cases, the presence of an infection like ABSSSI could result in a worsening of a baseline condition, because of infection itself, side effects of antimicrobials, risk of drug-to-drug interactions, prolonged hospitalization, and subsequent risk of clinical failure or death. Under these circumstances, the availability of easy to deliver single dose drugs, with minimal drug interactions and possibly promoting a fast discharge of the patient from the hospital is crucial to optimize the process of care.

IN VITRO ACTIVITY OF DALBAVANCIN AGAINST GRAM-POSITIVE COCCI

Food and Drug Administration (FDA) suggested an interpretative susceptible breakpoint of ≤0.25 µg/mL for dalbavancin against *S. aureus* [including MRSA and methicillin-susceptible *S. aureus* (MSSA)], *Streptococcus pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus* group [including *S. anginosus, S. intermedius and S. constellatus*], and *Enterococcus faecalis* [vancomycin-susceptible strains only] [7]. The European Committee on An-

timicrobial Susceptibility Testing (EUCAST) susceptible breakpoint against *Staphylococcus* spp., β-haemolytic streptococci of Groups A, B, C and G, and *S. anginosus* group is ≤0.125 µg/mL, with the specification that *S. aureus* isolates susceptible to vancomycin can be reported susceptible to dalbavancin [9].
The reference method suggested by all international guidelines is the broth microdilution method (BMD) according to ISO standard 20776-1, although a study comparing dalbavancin MIC values determined by gradient test and reference BMD validated the former as an accurate procedure [10].

In vitro activity of dalbavancin against staphylococci isolates

Dalbavancin demonstrated potent *in vitro* activity against *Staphylococcus* spp. (including methicillin-resistant isolates). *In vitro* activity has also been demonstrated against heterogeneous vancomycin-intermediate *S. aureus* (hVISA), vancomycin intermediate *S. aureus* (VISA; 0.5-2 mg/L) and other MDR-MRSA isolates, including those with decreased susceptibility to daptomycin.
Table 1 and Table 2 show the microbiological activity of dalbavancin against *S. aureus* and coagulase-negative staphylococci (CoNS) iso-

Table 1 - Microbiological activity of dalbavancin against *Staphylococcus aureus* isolates.

Study	*N. of isolates*	*MSSA MIC (mg/L)*			*MRSA MIC (mg/L)*		
		Range	MIC_{50}	MIC_{90}	*Range*	MIC_{50}	MIC_{90}
Streit JM et al., 2004 [11]	2992 (1815 MSSA, 1177 MRSA)	≤0.015-0.25	0.06	0.06	≤0.015–0.5	0.06	0.06
Gales AC et al., 2004 [23]	536 (393 MSSA, 143 MRSA)	≤ 0.008-0.25	0.06	0.06	0.016–0.12	0.06	0.06
Lin G et al., 2005 [48]	72 (43 MSSA, 29 MRSA)	≤0.015-0.125	0.06	0.06	≤0.015–0.125	0.03	0.06
Jones RN et al., 2005 [20]	3417 (2441 MSSA, 976 MRSA)	-	0.03	0.06	-	0.03	0.06
Jones RN et al., 2006 [24]	2102 (1041 MSSA, 1061 MRSA)	-	0.06	0.06	-	0.06	0.06
* Biedenbach DJ et al., 2007 [13]	1771 (1009 MSSA, 762 MRSA)	-	0.064	0.125	-	0.064	0.19
Biedenbach DJ et al., 2009 [22]	46773 (27052 MSSA, 19721 MRSA)	≤0.03-0.25	0.06	0.06	≤0.03–0.5	0.06	0.06
Karlowsky JA, 2011 [14]	2611 (1980 MSSA, 631 MRSA)	≤0.03-0.25	0.06	0.06	≤0.03–0.12	0.06	0.06
Jones RN et al., 2013 [30]	1036 (514 MSSA, 522 MRSA)	≤0.03-0.25	0.06	0.06	≤0.03–0.12	0.06	0.06
McCurdy et al., 2015 [47]	62195 (35220 MSSA, 26975 MRSA)	≤0.008- 0.5	0.06	0.06	≤0.008- 0.5	0.06	0.06
Huband M et al., 2016 [26]	9303 (6832 MSSA, 2471 MRSA)	-	0.06	0.06	≤0.03–0.25	0.06	0.06
Pfaller MA et al., 2018 [12]	14319 (9111 MSSA, 5208 MRSA)	≤0.002-0.25	0.03	0.03	≤0.002–0.12	0.03	0.03
Pfaller MA et al., 2018 [27]	801 (534 MSSA, 267 MRSA)	-	≤0.03	0.06	-	0.06	0.06

*Dalbavancin MIC values were obtained by reference BMD method in all studies, except for Biedenbach DJ et al, 2007 [13], where MICs were obtained by gradient test (AB BIODISK).

Table 2 - Microbiological activity of dalbavancin against coagulase-negative staphylococci.

Study	*N. of isolates*	*Methicillin-S MIC (mg/L)*			*Methicillin-R MIC (mg/L)*		
		Range	MIC_{50}	MIC_{90}	*Range*	MIC_{50}	MIC_{90}
Streit JM et al., 2004 [11]	774 (157 MS, 617 MR)	≤0.015-0.25	0.03	0.06	≤0.015-0.5	0.03	0.06
Gales AC et al., 2004 [23]	251 (58 MS, 192 MR)	≤0.008-0.12	0.03	0.06	≤0.008-1	0.03	0.12
Lin G et al., 2005 [48]	74 (38 MS, 36 MR)	≤0.015-0.06	0.03	0.06	≤0.015-0.25	0.03	0.06
Jones RN et al., 2005 [20]	1231 (295 MS, 936 MR)	-	0.03	0.06	-	0.03	0.06
Jones RN et al., 2006 [24]	255 (46 MS, 209 MR)	-	0.03	0.12	-	0.03	0.06
*Biedenbach DJ et al., 2007 [13]	240 (58 MS, 182 MR)	-	0.047	0.125	-	0.064	0.19
Biedenbach DJ et al., 2009 [22]	12308 (2836 MS, 9472 MR)	≤0.03-1	≤0.03	0.06	≤0.03-2	≤0.03	0.12
Karlowsky JA, 2011 [14]	236 (202 MS, 34 MR)	≤0.03-1	≤0.03	0.06	≤0.03-0.06	≤0.03	0.06
Jones RN et al., 2013 [30]	115‖	≤0.03–0.25‖	≤0.03‖	0.06‖	-	-	-
Pfaller MA et al., 2018 [12]	1992‖	≤0.002 to >.0.25‖	0.03‖	0.06‖	-	-	-
Pfaller MA et al., 2018 [27]	160‖	-	≤0.03‖	0.06‖	-	-	-

*Dalbavancin MIC values were obtained by reference BMD method in all studies, except for Biedenbach DJ et al, 2007 [13], where MICs were obtained by gradient test (AB BIODISK).
‖all strains, not distinguished based on methicillin-susceptibility

lates, respectively [11, 12]. MIC values have been distinguished based on resistance profiles, when the categorization was provided.
In all studies, dalbavancin exerted its activity against 90% of *S. aureus* isolates at 0.06 mg/L, regardless of the presence or methicillin-resistance. The unique exception was reported in the study of Biedenbach DJ, in which MICs were evaluated by gradient test [13].
Compared with the most frequently used anti-Gram-positive drugs, dalbavancin showed a potent *in vitro* antibacterial efficacy. The most recent study of Pfaller et al, evaluating antimicrobial activity of dalbavancin against clinical isolates from USA and Europe showed that against MRSA, dalbavancin was 16-fold more potent than daptomycin and 32-fold more potent than vancomycin and linezolid [12]. In a large collection of staphylococcal isolates, dalbavancin was 16-fold and from 16 to 32-fold more active than vancomycin against *S. aureus* and CoNS, respectively [13]. Similarly, among clinical isolates from the Canadian Ward Surveillance Study (CANWARD), dalbavancin showed a potency higher than that of vancomycin and telavancin, both among *S. aureus* and *S. epidermidis* [14].
Further considerations are needed for vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA). Against VISA isolates, dalbavancin showed a higher *in vitro* activity than vancomycin (dalbavancin MIC_{90} 2 mg/L *versus* vancomycin MIC_{90} 4 mg/L), and comparable MIC values against VRSA strains (MIC >16 mg/L) [15]. Recently, Sader and coauthors tested dalbavancin against a large collection of *S. aureus* isolates, including isolates with decreased susceptibility to the most antimi-

crobial agents used to treat severe *S. aureus* infections [16]. Overall, 1141 isolates showed decreased susceptibility to vancomycin (MIC ≥2 mg/L), 143 isolates to teicoplanin (MIC ≥4 mg/L) and 52 isolates to telavancin (MIC ≥0.12 mg/L); 48 isolates were non-susceptible to daptomycin (MIC ≥2 mg/L), and 25 isolates were resistant to linezolid (MIC ≥8 mg/L). Dalbavancin retained its *in vitro* antibacterial activity against 99.3% of isolates with vancomycin MIC ≥2 mg/L and was active against isolates with decreased susceptibility to the other drugs; only 8 strains (0.01%) were found dalbavancin non-susceptible (MIC ≥0.25 mg/L) [16]. As part of a multicenter Italian study, the *in vitro* antibacterial and bactericidal activity of dalbavancin was also demonstrated against clinically relevant *S. aureus* isolates, including heterogeneous vancomycin-intermediate (hVISA), daptomycin non-susceptible (DNS) and rifampicin resistant (RIF-R). In this study, the RIF-R strains showed the highest percentage of isolates with reduced susceptibility (n. 11, 22%), considering that some *rpo*B mutations have been already associated with the emergence of vancomycin intermediate-resistance [17].
In support of these *in vitro* findings, studies conducted in murine thigh infection models showed that dalbavancin has potent *in vivo* activity against *S. aureus* strains, including those exhibiting a VISA phenotype [18].
Finally, the activity of dalbavancin against clinical isolates of *S. aureus* has been demonstrated also in the randomized clinical trial (DISCOVER 1 and DISCOVER 2), in which the MIC_{90} of dalbavancin was 0.06 mg/L for the 511 *S. aureus* isolates [19].

In vitro activity of dalbavancin against enterococcal isolates

Dalbavancin has been indicated only for infections sustained by vancomycin susceptible *E. faecalis* isolates [7], although it exhibits a good *in vitro* antibacterial activity also against vancomycin-susceptible *E. faecium* isolates. Vancomycin-susceptible enterococci (VSE) showed dalbavancin MIC values lower than the susceptibility breakpoint established by FDA (MIC ≤0.25 mg/L) [7]. In all studies, dalbavancin was also analyzed among vancomycin-resistant enterococci (VRE) strains, showing expected higher MIC values (MIC_{50} >4 mg/L) (Table 3). Among VRE isolates, variable MIC values were observed, with respect to the Van phenotype expressed by the VRE isolates. Dalbavancin was found to be inactive against VanA enterococci. 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 from >4 to 32 mg/L [20, 21]. In the study conducted by Jones *et al*, only 6/54 VanB isolates showed dalbavancin MIC ≥1 mg/L [20]. 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 [22]. While, in the study of Neudorfer et al., all VRE isolates, including all *vanA, vanB1* and *vanB2/3* positive, had MIC values >16 μg/mL [21].
In conclusion, dalbavancin is considered active against VSE isolates, but only partially against VRE. In particular, it did not exert any activity against isolates showing VanA phenotype and only partially against VanB isolates. This characteristic limits its use in infections sustained by VRE isolates.

In vitro activity of dalbavancin against streptococci isolates

Dalbavancin is broadly active against streptococci. Penicillin and ceftriaxone-resistant *S. pneumoniae* strains were inhibited at very low concentrations of dalbavancin with MIC_{90} values ranging from 0.016 to 0.03 mg/L [11-14, 20, 22-27].
Dalbavancin was also active against viridans group streptococci (VGS) and β-hemolytic

Table 3 - Microbiological activity of dalbavancin against *Enterococcus* spp isolates.

Study	*Type of isolates*	*N. of isolates*	*VSE MIC (mg/L)*			*VRE MIC (mg/L)*		
			Range	MIC_{50}	MIC_{90}	*Range*	MIC_{50}	MIC_{90}
Streit JM et al., 2004 [11]	*E. faecalis*	606 (586 VSE, 20 VRE)	≤0.015-4	0.03	0.06	≤0.015->32	4	32
	E. faecium	128 (77 VSE, 51 VRE)	≤0.015-4	0.06	0.12	≤0.03->32	8	32
Gales AC et al., 2004 [23]	*Enterococcus* spp	157 (148 VSE, 9 VRE)	≤0.008-0.25	0.03	0.06	0.06 to >16	16	-
Streit JM et al., 2004 [11]	*E. faecalis*	14 (All VRE)[1]	-	-	-	0.12->32	32	32
	E. faecium	73 (29 VSE, 44 VRE)	≤0.016- 0.12	0.06	0.12	0.03->32	16	32
Jones RN et al., 2005 [24]	*Enterococcus* spp	1905 (1424 VSE, 481 VRE)[2]	-	0.03	0.06	-	4⌈	>16
Biedenbach DJ et al., 2009 [22]	*E. faecalis*	10374 (10025 VSE, 374 VRE)[3]	≤0.03-0.5	≤0.03	0.06	≤0.03->4	>4	>4
	E. faecium	4754 (2578 VSE, 2176 VRE)[3]	≤0.03-2	0.06	0.12	≤0.03–>4	>4	>4
Jones RN et al., 2013 [30]	*Enterococcus* spp	54 (30 VSE, 24 VRE)[4]	≤0.03-0.12	≤0.03	0.06	0.25->4	>4	>4
Neudorfer K et al., 2018 [21]	*E. faecalis*	58 (52 VSE, 8 VRE)[5]	≤0.016-0.125	0.03	0.125	>16	>16	>16
	E. faecium	25 (4 VSE, 21 VRE)[5]	≤0.016-0.125	0.03	0.125	>16	>16	>16
Pfaller MA et al., 2018 [12]	*E. faecalis*	2022 (all VSE)	≤0.015-0.25	0.03	0.06	-	-	-
	E. faecium	531 (all VSE)	≤0.015-0.25	0.06	0.12	-	-	-
Pfaller MA et al., 2018, [27]	*E. faecalis*‖	82‖	-	0.06‖	0.12‖	-	-	-

[1]Referred only to *van*A positive enterococci. 11 isolates of *van*B positive *Enterococcus* spp had MIC_{50} 0.03 mg/L and MIC_{90} 0.12 mg/L; [2]Referred to *van*A, *van*B and *van*C VRE. Forty-eight (889%) of the 54 VanB isolates had MIC values ≤0.25 mg/L, while 317 (94.6%) of the 335 *van*A isolates had MIC values ≥1 mg/L; [3]Referred to all VRE isolates, including *van*A and *van*B. Overall, 230 VanA and 84 VanB *E. faecalis*, 1744 VanA and 134 VanB *E. faecium* have been included in the study. Among these, 70.2% of 84 *E. faecalis* isolates with a VanB phenotype and 77.6% of 134 *E. faecium* isolates with a VanB phenotype had dalbavancin MIC values ≤0.25 mg/L; [4]Referred only to VanA enterococci, 2 VanB *E. faecium* isolates had MIC_{50} ≤0.03 mg/L; [5]all VRE isolates, including all *van*A, *van*B1 and *van*B2/3 isolates tested.
⌈MIC_{50} 8 µg/mL for VRE isolates from North America; ‖all strains, not distinguished based on vancomycin-susceptibility.

streptococci with all MICs <0.12 mg/L. With regards to VGS, they were very susceptible to dalbavancin that inhibits all strains at ≤0.12 mg/L, regardless of resistance phenotype. Moreover, dalbavancin MIC_{90} values were at least 16-fold lower than those obtained for comparator agents against VGS, both MDR and non-MDR isolates [28]. The MIC_{90} value for *S. agalactiae* (0.12 mg/L) was somewhat higher when compared to *S. pyogenes* data (MIC_{90} ≤0.03 µg/mL) (Table 4) [25, 29].

In vitro activity of dalbavancin against uncommon isolates

Dalbavancin has been tested against uncommon isolates of streptococci, such as serogroup C, F and G of β- hemolytic streptococci, uncommon VGS (*S. anginosus*, *S. milleri*,

Table 4 - Microbiological activity of dalbavancin against streptococci.

Study	*Type of isolates*	*N. of isolates*	*Penicillin-S MIC (mg/L)*			*Penicillin-R MIC (mg/L)*		
			Range	*MIC_{50}*	*MIC_{90}*	*Range*	*MIC_{50}*	*MIC_{90}*
Streit JM et al., 2004 [11]	*S. pneumoniae*	1396 (996 PS, 400 PR)	≤0.015-0.06	≤0.015	0.03	≤0.015–0.25	≤0.015	0.03
	Viridans streptoocci	134 (104 PS, 30 PR)	≤0.015-0.06	≤0.015	0.03	≤0.015–0.03	≤0.015	0.03
	β-haemolytic streptococci	234	≤0.015-0.25	≤0.015	0.06	-	-	-
Gales AC et al., 2004 [23]	*S. pneumoniae*	208 (152 PS, 27PI, 29PR)	≤0.008-0.06	0.016	0.016	≤0.008–0.06	0.016	0.016
	Viridans streptoocci	13	≤ 0.008-0.03	0.016	0.016	-	-	-
	β-haemolytic streptococci	53	≤ 0.008-0.06	≤0.008	0.06	-	-	-
Jones RN et al., 2005 [20]	*S. pneumoniae*	682 (452 PS, 107 PI, 123 PR)	-	0.016	0.03	-	0.016	0.016
	Viridans streptoocci	140‖	-	0.016 ∫	0.03	-	-	-
	β-haemolytic streptococci	342	-	≤0.008	0.016 ∫∫	-	-	-
Jones RN et al., 2006 [24]	*S. pneumoniae*	678 (416 PS, 135 PI, 127 PR)	-	0.016	0.03	-	0.016	0.016
	Viridans streptoocci	46	-	≤0.008	0.03	-	-	-
	β-haemolytic streptococci	241	-	0.016	0.03	-	-	-
*Biedenbach DJ et al., 2007 [13]	β-haemolytic streptococci	479	-	0.016	0.047	-	-	-
Biedenbach DJ et al., 2009 [22]	Viridans streptoocci	2148	≤0.03-0.12	≤0.03	≤ 0.03	-	-	-
	β-haemolytic streptococci	5316	≤0.03-0.25	≤0.03	≤0.03	-	-	-
Karlowsky JA, 2011 [14]	*S. pneumoniae*	893 (739 PS, 120 PI, 34 PR)	≤0.03-0.12	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	S. pyogenes	220	≤0.03-0.06	≤0.03	≤0.03	-	-	-
Jones RN et al., 2013 [30]	Viridans streptoocci	40	≤0.03-0.12	≤0.03	0.06	-	-	-
	S. pyogenes	155	≤0.03-0.12	≤0.03	≤0.03	-	-	-
	S. agalactiae	153	≤0.03-0.25	≤0.03	0.12	-	-	-
Huband M et al., 2016 [26]	Viridans streptoocci	135‖	≤0.03-0.12	0.03	0.06	-	-	-
	β-haemolytic streptococci	125‖	≤0.03-0.12	≤0.03	0.06	-	-	-
Pfaller MA et al., 2018 [12]	*S. pneumoniae*	3487‖	≤0.002-0.06	0.015	0.015	-	-	-
	Viridans streptoocci	1063‖	≤0.002-0.25	0.08	0.03	-	-	-
	β-haemolytic streptococci	3269	≤0.002-0.12	0.015	0.03	-	-	-
Pfaller MA et al., 2018 [27]	Viridans streptoocci	45	-	≤0.03	≤0.03	-	-	-
	β-haemolytic streptococci	164	-	≤0.03	≤0.03	-	-	-

∫MIC_{50} ≤0.08 μg/mL for isolates from North America.
*Dalbavancin MIC values were obtained by reference BMD method in all studies, except for Biedenbach DJ et al, 2007 [13], where MICs were obtained by gradient test (AB BIODISK).
‖all strains, not distinguished based on penicillin-susceptibility; ∫∫ MIC_{90} 0.03 μg/mL for isolates from North America.

S. dysgalactiae, *S. mitis*, *S. mutans*, *S. salivarius/S. vestibularis* group) and, finally, against *Corynebacterium* spp, *L. monocytogenes*, *Micrococcus* spp [30]. *S. anginosus* and so-called *S. milleri* were the most susceptible streptococci (MIC_{90} ≤0.03 mg/L), while *S. mitis* group and *S. salivarius/vestibularis* group isolates had higher recorded results ($MIC_{50/90}$, ≤0.03/0.06 mg/L) [30]. Dalbavancin was very active against *Corynebacterium* spp. ($MIC_{50/90}$, 0.06/0.12 mg/L), *L. monocytogenes* ($MIC_{50/90}$, 0.06/0.12µg/mL), and *Micrococcus* spp. ($MIC_{50/90}$, ≤0.03/≤0.03 mg/L) [30].

In vitro activity of dalbavancin against different pathogens isolates

Dalbavancin has been tested *in vitro* against isolates responsible for DFIs, both aerobes (MSSA, MRSA, CoNS, *S. agalactiae*, β-hemolytic streptococci, *Corynebacterium* spp. *C. amycolatum*), and anaerobes (*Clostridium* spp, *Peptoniphilus asaccharolyticus*, *Finegoldia magna, Anaerococcus prevotii*) [31]. As expected, dalbavancin was at least two-fold more active than vancomycin and daptomycin and fourfold more active than linezolid against MRSA, MSSA, and CoNS isolates [31]. However, the MIC values of dalbavancin for one of three strains of *S. haemolyticus* was 2 mg/L. Moreover, dalbavancin results active against *C. perfringens*, other clostridia, *P. asaccharolyticus*, *F. magna*, and *A. prevotii*, with MIC_{90} of ≤0.125 mg/L [31]. These *in vitro* data demonstrated that dalbavancin could be active against isolates from patients with DFIs and could be a basis for further evaluation in some specific populations of patients. As a matter of fact, for DFIs, who often were managed as outpatients, an antimicrobial agent with a long half-life, especially one administered once weekly, could be advantageous.

Dalbavancin has been evaluated against clinical isolates from patients with bone and joint infections (BJI), an infection for which this drug has not yet obtained the approval from regulatory authorities. Dalbavancin has been evaluated against a total of 801 *S. aureus*, 160 CoNS, 164 β-haemolytic streptococci, 82 *E. faecalis* and 45 VGS causing BJI from different sites in Europe and US from 2011 and 2016 [27]. Dalbavancin showed lower MIC_{90} values of 0.06 mg/L against *S. aureus* from the US and European countries, irrespective of the methicillin susceptibility and resulted 8-fold more potent than daptomycin and 16-fold more potent than vancomycin and linezolid [27]. Similar results have been obtained against CoNS (S. *epidermidis* and *S. lugdunensis*) with MIC_{50} and MIC_{90} values of <0.03 and 0.06 mg/L respectively, β-haemolytic streptococci and VGS (100.0% susceptible). As expected, all *E. faecalis* with the exception of *van*A carrying strains, were susceptible to dalbavancin [27].

SYNERGISTIC EFFECT OF DALBAVANCIN WITH OTHER ANTIMICROBIAL AGENTS

Combination therapy has a distinct advantage over monotherapies because the related synergistic effect and the prevention of the emergence of drug resistance. In a study in which dalbavancin was tested in combination with other 9 drugs (clindamycin, daptomycin, gentamicin, levofloxacin, linezolid, oxacillin, quinupristin/dalfopristin, rifampicin, vancomycin) synergistic effect was found only with oxacillin, and no antagonist effect was observed [32]. However, several studies recently highlighted the synergistic activity of dalbavancin in combination with other antimicrobials. More specifically, dalbavancin seems to have a good synergistic effect when used in combination with β-lactams (cefazolin, cefepime, ceftaroline, ertapenem and oxacillin) [33], linezolid and daptomycin [43]. Finally, in an *in vivo* model of foreign-body infection, the use of dalbavancin in combination with rifampicin

was shown to prevent the emergence of rifampicin resistance [34].
Even if combination therapies could mitigate the main advantage of dalbavancin, which is the possibility of once weekly or single administration, involving the use of some drugs available as oral formulation, could strengthen its efficacy in patients with infections sustained by resistant microorganisms. Further clinical research involving dalbavancin combinations is warranted.

MICROBIOLOGICAL ACTIVITY OF DALBAVANCIN AGAINST BIOFILM

Biofilms can potentially form on any foreign object inserted into the human body, such as implants or catheters, and the number of infections in which biofilms are involved is growing each year. For clinicians, the ability of biofilm bacteria to withstand the actions of antibiotics and the host defense represents a substantial challenge. Thus, the assessment of the activity of a drug against biofilms is a crucial point in the evaluation process of the new antibiotics. Moreover, in the setting of antibiotics acting against Gram-positive cocci, the activity against biofilm appears to be an essential property because *S. aureus* and *S. epidermidis* are among the most common pathogens involved with surface-associated infections, as a result of the capability of producing biofilm [2, 35]. The open-label study design and the small sample size did not allow the generalizability of these results, but these findings suggested a potential role of dalbavancin in the eradication of biofilms.
Several preclinical studies specifically evaluated the activity of dalbavancin against biofilms. *In vitro* data showed promising anti-biofilm activity of dalbavancin against Gram-positive isolates belonging to different species. Dalbavancin successfully reduced biofilms obtained from 10 MRSA and 10 methicillin-resistant *S. epidermidis* (MRSE) bloodstream isolates, collected from patients in the General Hospital of Vienna between 2012 and 2015 [36]. Recently, Fernández J and coworkers demonstrated the activity of dalbavancin against staphylococcal biofilms associated with prosthetic joint infections, in both planktonic and biofilm states [37]. The minimum biofilm bactericidal concentrations ($MBBC_{50}$) for *S. aureus* and *S. epidermidis* was 1 mg/L independently from methicillin-susceptibility, while the $MBBC_{90}$ was 2 µg/mL for MRSA and MSSA and 4 mg/L for MRSE and methicillin susceptible *S. epidermidis* (MSSE). If compared with data about vancomycin ($MBBC_{50}$ and $MBBC_{90}$ ≥128 mg/L) and tedizolid ($MBBC_{50}$ and $MBBC_{90}$ were both >32 mg/L) [37], these findings appear very promising for the use of dalbavancin in infections sustained by biofilm. Similar results have been obtained when dalbavancin was tested against biofilm of VSE isolates, but not for VRE strains [21]. For *E. faecalis* and *E. faecium*, dalbavancin MBBCs (both $MBBC_{50}$ and $MBBC_{90}$) were ≤4 mg/L for vancomycin-susceptible, but >16 mg/L for VRE isolates [38]. However, it has to be considered that vancomycin MBBCs were >128 mg/L for all isolates, and daptomycin $MBBC_{90}$ values for both species were 128 mg/L [21]. These findings are in line with *in vitro* studies of dalbavancin activity against enterococcal isolates.
In an *in vivo* study, 12 rabbits underwent a subcutaneous implantation of catheter segments in their back, inoculated with *S. aureus* [38]. Animals were randomized in three groups, in relation of having received a pre-implantation, itravenous injections of dalbavancin, vancomycin or normal saline (control). There was a trend toward a lower rate of device colonization in the rabbits pre-treated with dalbavancin compared with the vancomycin and control groups. However, probably due to the low number of animals used in this study, no statistically significant differences among the 3 groups were observed [38].

The activity of dalbavancin, alone and in combination with rifampicin, was investigated in a MRSA foreign-body infection model in guinea pigs [34]. More specifically, 4 sterile polytetrafluoroethylene cylindrical cages were subcutaneously implanted in the flanks of the guinea pigs under aseptic conditions. Cages were infected by percutaneous injection of MRSA strains (Day 0). Antimicrobial treatment with dalbavancin, alone or in combination with rifampicin, was initiated 3 days after infection. Two weeks after surgery, the sterility of the cages was checked by culture of aspirated cage fluid. Dalbavancin at high dose (60 mg/kg and 80 mg/kg) reduced planktonic MRSA in cage fluid, but failed to eradicate biofilm MRSA from cages. At 80 mg/kg (corresponding to 1000 mg in humans) and in combination with rifampicin, dalbavancin eradicated only one-third of cage-associated MRSA infections [34].

The discrepancies of *in vitro* and *in vivo* studies could have different explanation. First of all, *in vitro* studies evaluated the specific microbiological activity of dalbavancin against different isolates in a highly controlled artificial environment but independently from the host response to the infection. Moreover, pharmacokinetic and pharmacodynamic factors could influence the success in animal models.

In conclusion, although dalbavancin demonstrated to possess a potent *in vitro* activity against biofilm, future studies are needed to evaluate the *in vivo* efficacy of dalbavancin alone and in combinations with other antimicrobials, in biofilm-related infections.

PK/PD AND CLINICAL PROFILE OF DALBAVANCIN

Dalbavancin requires intravenous administration, has a high protein binding and long half-life (up to 8.5 days) [39]. This latter feature confers to this antibiotic a unique characteristic: the possibility of once-a-week dosage.

In healthy adult volunteers, dalbavancin exhibits linear, dose-proportional PK [40]: following administration of multiple 30-min intravenous infusion doses, mean dalbavancin concentrations in plasma increase proportionally with dose and decline in a log-linear manner [39]. Conversely, the $T_{1/2}$, clearance and volume of distribution at steady state remain essentially unchanged. Similar systemic exposures (expressed as Area Under Curve [AUC] values) of dalbavancin were seen between subjects with normal renal function and those with mild renal impairment, while slightly higher AUC values were observed in those with moderate renal impairment [40]. Instead, patients with severe renal impairment had a marked increase in exposure that would require dose adjustment. Dalbavancin exposure is not affected by hepatic insufficiency [40].

The penetration of dalbavancin in specific tissues has been also investigated. A phase I study evaluated dalbavancin distribution in the bone, skin, and articular tissue [41]. Dalbavancin concentration in cortical bone was 6.3 µg/g, 12 h after infusion of a single 1000-mg intravenous and 4.1 µg/g 2 weeks later [17]. In skin, dalbavancin concentrations after 12 h and 2 weeks were 19.4 µg/g and 13.8 µg/g, respectively [41]. In synovial tissue, they were 25.0 µg/g and 15.9 µg/g [41]. Thus, in these compartments dalbavancin distributes at concentrations that are expected to exceed the MIC for *S. aureus* for extended periods.

Excretion of the drug is very slow; with the majority of drug excreted in the urine (33% unchanged, 12% metabolite) in 42 days and, to a lesser degree, in feces (20%) in 70 days [42]. PK parameters of dalbavancin in children are slightly different from those observed in adult patients. In pediatric subjects

(12-17 years) who received 1000 mg of dalbavancin, median values of $T_{1/2}$ were 216 hours and in those who received dalbavancin at the dose of 15 mg/kg, median $T_{1/2}$ was 219 hours. Of note, 9 of the 10 subjects still had detectable dalbavancin in plasma samples (>0.5 µg/mL) 1320 hours (55 days) after dosing [43]. Moreover, the AUC exposures were approximately 30% less than those documented in adults. It can be due to the enhanced renal and/or hepatic elimination usually documented in healthy adolescents compared with adults [43].

Table 5 summarizes phase III clinical trials of dalbavancin in patients with ABSSSIs. The first clinical study evaluating the efficacy of dalbavancin in infected patients goes back to 2005. A total of 854 patients with complicated SSTIs, including infections known or suspected to involve MRSA, were randomized 2:1 to receive dalbavancin (1000 mg given intravenously on day 1, followed by 500 mg on day 8) or linezolid (600 mg given intravenously or intravenously/orally every 12 h for 14 days) [44]. MRSA was identified in 51% of patients from whom it was possible to isolate a pathogen at baseline. Among patients who were clinically evaluable at the TOC visit, 88.9% in the dalbavancin arm and 91.2% in the linezolid arm achieved clinical success, defined as improvement of signs and symptoms of infection. Moreover, both treatments yielded successful microbiological response in excess of 85% among microbiologically evaluable patients at end of therapy [44].

Safety and efficacy of dalbavancin in clinical setting have been further demonstrated in two double blind, non-inferiority phase III clinical trials, DISCOVER 1 and DISCOVER 2, conducted from 2011 to 2012 [19]. Patients with ABSSSIs, defined accordingly with the FDA definitions [1], having one or more systemic signs of infection within 24 hours and

Table 5 - Phase 3 clinical trials on efficacy of dalbavancin in patients with ABSSSIs.

Study	*Inclusion criteria*	*Intervention*	*Comparator*	*N. of patients*	*Clinical efficacy*	*Related adverse events*
Jauregui LE et al., 2005 [44]	Suspected or confirmed SSSI due to gram-positive pathogens	Dalbavancin 2-dose regimen	Linezolid 600 mg q12h	Total: 854 pts Pts clinically evaluable at the TOC visit: 660	88.9% (dalbavancin) versus 91.2% (comparator)	25.4% (dalbavancin) versus 32.2% (linezolid) Most frequent: nausea, diarrhea
Boucher H et al., 2014 [19] DISCOVER 1 and 2	Patients with ABSSSIs needed iv therapy	Dalbavancin 2-dose regimen	Vancomycin 1 g (or 15 mg/kg) q12h, eventually de-escalated to linezolid 600 mg q12h	Total: 1312 pts (659 versus 653 comparator)	79.7% (dalbavancin) versus 79.8% (comparator), Weighted difference - 0.1% (95% CI, -4.5 to 4.2	32.8% (dalbavancin) versus 37.9% comparator, p=0.05 Most frequent: nausea, diarrhea
Dunne MW et al., 2016 [45]	Patients with ABSSSIs needed iv therapy	Dalbavancin 2-dose regimen	Dalbavancin single-dose regimen	Total: 698 pts (349 2-dose regimen versus 349 single dose regimen)	84.2% (2-dose regimen) versus 81.4% (single dose regimen) Absolute difference - 2.9% (95% CI -8.5, 2.8)	19.9 (2-dose regimen) versus 20.1% (single dose regimen) Most frequent: nausea

ABSSSI: Acute bacterial skin and skin structure infections; Pts: patients.

requiring at least 3 days of intravenous therapy were included in the study [19]. Patients who received previous antibiotic therapy within the immediate 14 days were excluded. They were randomized 1:1 to receive dalbavancin at a dose of 1 g intravenously followed by 500 mg on day 8 (two-dose regimen) or vancomycin 1 g (or 15 mg per kilogram of body weight) every 12 hours for at least 3 days, with an option to switch to oral linezolid, at a dose of 600 mg every 12 hours, to complete a course of 10 to 14 days of therapy [19]. A total of 1312 adults with ABSSSI were finally included in the studies. Of note, approximately 15% of the patients had a history of recent or current intravenous drug use, and 13% had diabetes mellitus. DISCOVER 1 included more patients with major abscesses, while DISCOVER 2 included more with patients affected by cellulitis. Analysis of the primary endpoint (early clinical response, requiring the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours) showed non-inferiority of dalbavancin compared to vancomycin in both DISCOVER 1 and DISCOVER 2 [19]. In the pooled analysis 79.7% in the dalbavancin group and 79.8% in the vancomycin-linezolid group had cessation of spread of infection-related erythema and absence of fever at 48 to 72 h (weighted difference, -0.1 percentage point; 95% CI, -4.5 to 4.2). Moreover, similar rates of reduction in the size of the infected area of at least 20% at 48 to 72 hours were detected [19].

Dunne and coworkers, conducted a randomized, double-blind trial in patients with ABSSSIs to assess the safety and efficacy of a single intravenous infusion of 1500 mg of dalbavancin compared to the standard 2-dose regimen [45]. Patients with catheter infection, infected devices, diabetic foot ulceration, perirectal abscess, or decubitus ulcer were excluded. They were randomized 1:1 to receive dalbavancin as either a single intravenous infusion of 1500 mg of dalbavancin over 30 minutes or in 2 doses as 1000 mg intravenously over 30 minutes, followed by 500 mg intravenously one week later. For patients with a creatinine clearance of <30 mL/minute the single-dose regimen was 1000 mg as a single infusion while the 2-dose regimen 750 mg intravenously followed 1 week later by 375 mg intravenously. To maintain the blinding, patients randomized to the single dose received a placebo infusion on day 8. Metronidazole and aztreonam were allowed in both treatment groups for infection with suspected anaerobic gram-negative pathogens, respectively. Clinical response (defines as the achievement of a ≥20% reduction in the size of the erythema and no need of rescue antibacterial therapy in the 48-72 hours from the start of therapy) was observed in 81.4% of those randomized to the single-dose regimen *vs* 84.2% in the 2-dose regimen (absolute difference -2.9 [95% CI, -8.5%, 2.8%]), demonstrating the non-inferiority of the single-dose compared to the 2-dose regimen. Moreover, no differences in terms of adverse events were observed between the two study groups [45].

Dalbavancin is usually well tolerated. In a pooled analysis of patients, participating in phase 2 and 3 clinical trials, the 85% of patients completed the course of therapy. The most commonly identified reasons for discontinuation are similarly distributed among worsening clinical *status*, lost to follow-up, occur of an adverse event, and withdrawal of consent [46]. The most common adverse events during dalbavancin course were gastrointestinal disturbances, while serious adverse events were progression of cellulitis, leukopenia and an anaphylactoid reaction. The rate of adverse events and ~~the~~ its time of onset were similar between dalbavancin and comparators group used in the whole clinical development [46].

CONCLUSIONS

In conclusion, dalbavancin represents an effective choice, alternative to established therapies with the conventional anti-Gram-positive drugs commonly used for the treatment of ABSSSIs in adults.
Its broad antimicrobial spectrum of activity against MDR Gram-positive pathogens, advantageous pharmacokinetic benefits, long half-life and excellent tissue penetration make this drug a suitable treatment option for clinicians. Moreover, the single-dose administration, effective as conventional therapies, without requiring prolonged hospital stay, could be significantly advantageous for patients and the overall health care system.

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