Official journal of the Spanish Society of Chemotherapy

Update on antimicrobial pharmacotherapy

José Barberán
Alicia de la Cuerda
Lourdes Cristina Barberán

Dalbavancin

Servicio de Medicina Interna – Enfermedades Infecciosas, Hospital Universitario HM Montepríncipe, Universidad San Pablo CEU, Madrid, Spain.

Revista Española de Quimioterapia
doi:10.37201/req/s01.07.2021

ABSTRACT

Dalbavancin is a long-acting antimicrobial agent with an excellent *in vitro* activity against Gram-positive pathogens, including staphylococcal biofilms. The unusually long terminal half-life ranging from 149 to 250 hours in human subjects, allows a weekly dose. Currently is indicated in acute bacterial skin and skin structure infections (ABSSSIs), but in real-life clinical practice it has already been used successfully and safely in other infections, especially as consolidation therapy.

Key words: Dalbavancin, Gram-positive pathogens, ABSSSIs, bone and joint infections, endocarditis, bacteremia

INTRODUCTION

Dalbavancin is a semisynthetic lipoglycopeptide with a long lipophilic side chain that confers it two new determining properties: 1) a faster and more potent bactericidal activity than vancomycin or teicoplanin, and 2) a long terminal half-life ranging from 149 to 250 hours in human subjects, allowing for a weekly dose. Dalbavancin also possesses an amidated carboxyl side group that increases the agent's anti-staphylococcal activity (Figure 1). It was approved by both the FDA in May 2014 and the EMA in February 2015 for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs). Recently, dalbavancin has also received the FDA approval to treat ABSSSIs in pediatric patient (July 2021) [1].

MICROBIOLOGICAL PROFILE

Dalbavancin has a similar microbiological profile to the other available glycopeptides. Against MRSA, dalbavancin has demonstrated to be 16-fold more potent than daptomycin, and 32-fold more potent than vancomycin and linezolid. Dalbavancin is also the most potent agent against coagulase-negative staphylococci (CoNS) (MIC_{90} 0.06 mg/L).

Overall, dalbavancin is 16-fold more potent against β-hemolytic streptococci ($MICs_{90}$ 0.03-0.047 mg/L) than vancomycin (MIC_{90} of 0.75 mg/L). All vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium* isolates are inhibited by dalbavancin at ≤ 0.25mg/L, but is not active against enterococci with VanA-mediated glycopeptide resistance and only partially active against VanB isolates [2].

PHARMACODYNAMIC AND PHARMACOKINETIC PROFILE

In staphylococcal animal models the clinical efficacy of dalbavancin has been related to AUC/MIC values ≥ 1000. The main pharmacokinetic properties of dalbavancin are as follows: approximately 93% is binding to serum albumin after an intravenous dose; excretion is through non-microsomal metabolism with inactive metabolites and up to 42% of the dose through the kidneys by glomerular filtration; and a terminal elimination half-life can exceed 200 hours. Dose adjustment is required in patients with severe renal impairment (creatinine clearance <30 mL/min) who do not undergo hemodialysis, and caution is recommended in Child-Pugh class B and/or class C hepatic impairment [3].

CLINICAL EFFICACY

Current indications for the use of dalbavancin in the ABSSSIs come from the pivotal studies DISCOVER 1 and DISCOVER 2 trials (dalbavancin vs vancomycin/linezolid 1:1, double-blind, double dummy, non-inferiority trials), that showed noninferiority of dalbavancin in both DISCOVER 1 and DIS-

Correspondence:
José Barberán
Servicio de Medicina Interna – Enfermedades Infecciosas
Hospital Universitario HM Montepríncipe
Universidad San Pablo CEU
Madrid, Spain
E-mail: jbarberan@ceu.es

Lipophilic side chain:

- **Enhancement binding to bacterial cell membrane**
- **Faster and more potent bactericidal activity**
- **Increase in half-life**

Amidated carboxyl side group:

- **Increase anti-staphylococcal activity**

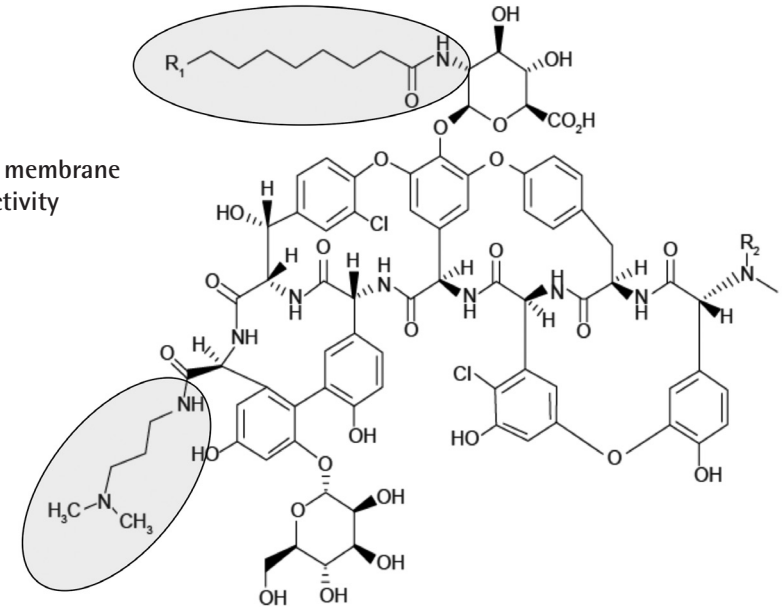

Figure 1 | **Structure of dalbavancin**

Table 1 | **Potential indications of dalbavancin in real-life clinical practice**

Treatment	Prophylaxis
Consolidation therapy in acute infections[a]	Recurrent processed
Catheter-related staphylococcal bacteremia	Recurrent cellulitis
Infective endocarditis	Recurrent enterococcal cholangitis
Osteomyelitis	Recurrent enterococcal urinary tract infection
Spondylodiscitis	Vascular implants at risk of staphylococcal bacteremia
Acute septic arthritis	
Diabetic foot infections	
Prosthetic joint infections	
Suppressive treatment of chronic infections	
Chronic osteomyelitis	
Chronic prosthetic joint infections	

[a]Particularly in infections with prolonged treatment (≥ 14 days)

COVER 2. Dalbavancin was better tolerated than vancomycin/linezolid and significantly fewer patients in the dalbavancin group experienced diarrhea (0.8% vs 2.5%; *P*=0.02) or pruritis (0.6% vs 2.3%, *P*=0.01) compared to the vancomycin/linezolid group. A secondary analysis did identify significantly longer duration of therapy in the vancomycin/linezolid treatment group as compared to the dalbavancin arm (38.0% vs 31.0%; *P*=0.008) [4].

The long terminal half-life of dalbavancin allows its use as consolidation therapy in acute infections that require prolonged treatment, suppressive treatment of chronic infections and prophylaxis of some recurrent processes caused by Gram-positive cocci (Table 1). The use of dalbavancin for bone and joint infections (BJIs), including prosthetic joint infections (PJIs) has also been assessed in several retrospective studies and one randomized clinical trial. In osteomyelitis the cure rates ranged from 65% to 100%. The worst results have

been observed in postoperative, chronic and diabetic foot osteomyelitis and when dalbavancin was mainly used as a first or rescue regimen after failure of a previous treatment. The experience of dalbavancin in PJIs is smaller. The cure rate ranged from 33% to 93%. The lack of information in many cases about surgical management and the heterogeneity of PJIs included make it difficult to draw conclusions on the efficacy of dalbavancin in these processes. The use of dalbavancin in BJIs is supported by the activity of dalbavancin against staphylococcal biofilms and its bone and articular tissue penetration that exceeds the MIC_{90} of *S. aureus* for extended periods of time after a significantly shortened dosing regimen [4].

In catheter-related bloodstream infection (CR-BSIs) caused by gram-positive pathogens (included *S. aureus* and CoNS), a phase 2, open-label, randomized, controlled, multicentre study has shown a superior efficacy of dalbavancin compared with vancomycin [5]. In infective endocarditis treated with dalbavancin, clinical cure rates range from 50% to 100%. The best results have been observed when dalbavancin was used as a consolidation therapy after blood culture clearance rather than as a rescue strategy. As in BJIs, the diversity of the therapeutic regimens used and the fact that most patients have previously received other antibiotics, are two important limitations to knowing the efficacy of dalbavancin. In some of the published studies of dalbavancin in BJIs and IE, a reduction in the length of hospital stay (LOS) and economic cost has been observed [6].

SAFETY PROFILE

Dalbavancin, in all published evidence, has been shown to be safe and less nephrotoxic than other glycopeptides. Drug-drug interactions are uncommon with other comedications.

CONCLUSIONS

Dalbavancin, in addition to its indication in ABSSSIs, represents an effective and safe therapeutic alternative in clinically stable patients with other infections requiring prolonged treatment to shorten the LOS.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

REFERENCES

1. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Break- point tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http: //www.eucast.org [accessed 28 July 2021].
2. Pfaller MA, Mendes RE, Duncan LR, Flamm RK, Sader HS. Activity of dalbavancin and comparator agents against Gram-positive cocci from clinical infections in the USA and Europe 2015–16. J Antimicrob Chemother 2018; 73:2748–2756. doi:10.1093/jac/dky235.
3. Azanza JR, Sádaba B, Reis J. Dalbavancina: parámetros farmacocinéticos y farmacodinámicos. Enferm Infecc Microbiol Clin. 2017; 35(Supl 1):22-7. doi: 10.1016/S0213-005X(17)30031-9
4. Durante-Mangoni E, Gambardella M, Lula VD, De Stefano GF, Corrado MF, Esposito V et al. Current trends in the real-life use of dalbavancin: report of a study panel. Int J Antimicrob Agents 2020; 56:106107. doi: 10.1016/j.ijantimicag.2020.106107.
5. Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H et al. Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens. Clin Infect Dis 2005; 40:374–80. doi: 10.1086/427283.
6. Lampejo T. Dalbavancin and Telavancin in the treatment of infective endocarditis: a literature review. Int J Antimicrob Agents 2020; 56:106072. doi: 10.1016/j.ijantimicag.2020.106072.