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REVIEW

New developments in the treatment of acute bacterial skin and skin structure infections: considerations for the effective use of dalbavancin

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Abstract: Dalbavancin, an intravenous glycopeptide, was approved by the US Food and Drug Administration in May 2014 for use in adult patients with acute bacterial skin and skin structure infections. The recommended dosing regimen for effective use of dalbavancin is 1,000 mg followed by a 500 mg dose after 1 week. Two multinational, identically designed, non-inferiority trials, DISCOVER 1 and 2, demonstrated similar early clinical success with dalbavancin compared to vancomycin with an option to switch to oral linezolid. In a recently published non-inferiority trial, a single-dose regimen of dalbavancin was compared to the traditional two-dose administration and was found to have a non-inferior clinical response. In the aforementioned trials, dalbavancin was well tolerated, with patients experiencing transient adverse events of mild to moderate severity. The prolonged half-life, excellent skin and soft tissue penetration, bactericidal activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, and convenient dosing make dalbavancin a reasonable option for the treatment of acute bacterial skin and skin structure infections in adult patients who have tried and failed other therapies.

Keywords: acute bacterial skin and skin structure infections, skin and soft tissue infections, dalbavancin, glycopeptide

Introduction

Acute bacterial skin and skin structure infections (ABSSSIs) are infections of the skin and accompanying tissues, fascia and muscle layers, with severity ranging from mild to severe. Gram-positive organisms are the most common causes of ABSSSIs and are difficult to treat as a result of increasing prevalence of drug resistance, especially in *Staphylococcus* spp. and *Enterococcus* spp.[1–4]

Vancomycin, a glycopeptide antibacterial that was first approved for use in 1958, has been the mainstay of antibacterial therapy for severe infections caused by resistant Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA).[1–3,5] The use of vancomycin does not come without risk. In addition to the risk of nephrotoxicity and the need for therapeutic drug monitoring, reduced vancomycin susceptibility due to the development of vancomycin-intermediate *S. aureus* (VISA; minimum inhibitory concentration [MIC] 4–8 μg/mL) and vancomycin-resistant *S. aureus* (VRSA; MIC ≥16 μg/mL) and enterococci strains is further limiting its use.[1,6–8]

Though the overall prevalence of these isolates remains low in the US, infections caused by vancomycin-resistant strains are concerning due to high rates of treatment failure and poor clinical outcomes.[6–10] Therefore, novel antimicrobial agents are needed for the treatment of ABSSSIs.

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The Infectious Diseases Society of America practice guidelines for the management of skin and soft tissue infections were recently updated in 2014. According to the guideline recommendations, empiric intravenous (IV) antimicrobial agents for the treatment of suspected severe MRSA ABSSSIs include vancomycin, daptomycin, linezolid, telavancin, or ceftaroline. For mild to moderate purulent infections where community-acquired MRSA should be considered, oral sulfamethoxazole/trimethoprim and doxycycline are recommended, whereas for mild to moderate non-purulent ABSSSIs, oral clindamycin is an option for treatment.[6]

When developing new antibiotics for ABSSSIs, several important variables warrant consideration, including the ability of the drug to concentrate at the site of the infection, enhanced affinity to binding sites, a novel mechanism of action or multiple mechanisms of action to circumvent current resistance patterns, a favorable pharmacokinetic profile allowing for convenient dosing regimens and enhanced feasibility in the community or outpatient setting, and a minimal adverse effect profile. Thus, several new second-generation lipoglycopeptides have been developed including dalbavancin (Dalvance™, Xydalba™), oritavancin (Orbactiv®), and telavancin (Vibativ®). Each of these agents possesses lipophilic side chains that result in increased activity against Gram-positive bacteria with a low potential for resistance. IV dalbavancin was recently approved by the US Food and Drug Administration (FDA) and represents a convenient treatment option for adult patients with ABSSSIs.[2,3,11]

This article reviews the mechanism of action, in vitro antibacterial activity, pharmacokinetics, pharmacodynamics, and clinical use of dalbavancin in adult patients with ABSSSIs.

Pharmacology of dalbavancin

Dalbavancin is a parenteral second-generation semisynthetic lipoglycopeptide member of the glycopeptide antimicrobial family.[12] Other antibiotics included in this class are vancomycin, teicoplanin, oritavancin, and telavancin.[13] Structurally, each member of the glycopeptide family contains a heptapeptide core, which leads to the inhibition of cell wall synthesis and cross-linking by binding to the C-terminal of the D-alanyl-D-alanine peptidoglycan chain in Gram-positive organisms.[3] Dalbavancin was created through modifications of various functional groups of the naturally produced teicoplanin-like antibiotic A-40926 (synthesized from a fermentation product of the *Nonomuraea* sp.), without altering the peptide backbone required for its antimicrobial activity.[3,14] In addition to changes in the chemical structure from its parent compound, dalbavancin has a lipid side chain that enhances binding to the D-alanyl-D-alanine site through dimerization. This complex acts as a membrane anchor, which increases the concentration of dalbavancin at its site of action and therefore its potency compared to other glycopeptides.[3]

Pharmacokinetics of dalbavancin

Dalbavancin possesses unique and favorable pharmacokinetic properties, and exhibits a three-compartment model of distribution. Similar to all glycopeptides, dalbavancin has poor oral absorption and therefore requires IV administration.[6] The pharmacokinetics of dalbavancin, including tissue distribution, was initially studied in rat models. Findings included a terminal half-life of 187.4 hours due to extensive protein binding (93%–98%), a volume of distribution of 0.52 L/kg, and increased penetration of dalbavancin into skin and other peripheral compartments.[15] These data suggested that extended interval dosing may be effective, and that a once-weekly dosing regimen is conceivable in human trials.[16]

Data from a Phase I dose-ranging study found that dalbavancin undergoes an initial distribution phase followed by a longer elimination phase, with the maximum serum concentration (C_{max}) increasing proportionately with the administered dose. Activity against MRSA was preserved for at least 7 days in all strains tested following the administration of a single dose of ≥500 mg. These data support a once-weekly dosing regimen.[17]

Further studies in healthy volunteers and patients with ABSSSIs have shown excellent skin and soft tissue penetration of dalbavancin. Dalbavancin levels were well above the MICs for pathogens associated with ABSSSIs.[18,19]

Dalbavancin is not a substrate, inducer, or inhibitor of CYP450 isoenzymes. It is not metabolized in vitro by hepatic microsomes or hepatocytes. It has two metabolites, which have been observed in humans, OH-dalbavancin and mannosylaglycone (MAG) metabolite. However, neither of these metabolites is detected in human plasma, and has a minor contribution to the in vivo activity of dalbavancin.[20] Dalbavancin exhibits dual mechanisms of elimination including renal and non-renal (fecal) routes; however, the majority of the drug is eliminated unchanged in the urine.[6,20]

In adults with moderate (creatinine clearance [CR_{CL}] 30–49 mL/min) and severe (CR_{CL} <30 mL/min) renal impairment, mean plasma clearance was reduced by 35% and 45%, respectively. Therefore, in patients with a CR_{CL} <30 mL/min

and not on hemodialysis, the dose of dalbavancin should be reduced to 750 mg followed by a dose of 375 mg after 1 week. No dosage adjustments are required for patients with CR_{CL} >30 mL/min or patients receiving regularly scheduled hemodialysis. Experience in patients with moderate or severe hepatic impairment is limited; therefore, dalbavancin should be used with caution in this specific population.

In vitro activity

Similar to other glycopeptides, dalbavancin exhibits bactericidal activity against numerous Gram-positive organisms associated with ABSSSIs; however, it displays no activity against Gram-negative organisms.[2] Dalbavancin has potent activity against *S. aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus milleri* group (including *S. anginosus, S. intermedius,* and *S. constellatus*). The susceptibility of these *Streptococcus spp.* is based on the FDA-approved breakpoint of <0.12 µg/mL.[13,20] However, for *Streptococcus pneumoniae*, the acceptable MIC range is 0.008–0.03 µg/mL.[20] Dalbavancin also demonstrates in vitro activity against vancomycin-susceptible *Enterococcus* spp. (VanB and VanC phenotypes, lacking activity against VanA phenotypes) and against several anaerobic Gram-positive bacteria, including *Clostridium* spp., *Peptostreptococcus* spp., and *Actinomyces* spp. and Gram-positive aerobes including *Corynebacterium* sp. and *Bacillus subtilis*.[2,13,20]

Staphylococcus

In vitro susceptibility studies have demonstrated significantly lower MICs with dalbavancin compared to vancomycin for the treatment of MRSA. Susceptibility of *Staphylococcus aureus* (including MRSA isolates) is based on the FDA-approved breakpoint of <0.12 µg/mL.[20] A worldwide surveillance study evaluated in vitro activity of dalbavancin against 27,052 MSSA and 19,721 MRSA isolates from 33 countries in ABSSSIs. Both the MSSA and MRSA isolates had an MIC_{90} of 0.06 µg/mL, with no isolates deemed to be resistant to dalbavancin.[21] Manufacturer data (SENTRY) collected from 2002 to 2012 evaluated ~40,000 isolates of *S. aureus*, with 52% identified as MRSA. MIC_{90} of dalbavancin for MSSA and MRSA ranged from 0.06 to 0.12 µg/mL throughout the 10 years of surveillance, illustrating sustained potency and susceptibility.[20]

Additionally, the Phase III DISCOVER trials revealed MIC_{90} values of 0.06 µg/mL against *S. aureus* (MSSA =361; MRSA =135), which is consistent with the aforementioned surveillance studies.[2,22] Other smaller studies have corroborated these findings (Table 1). Dalbavancin also exhibits activity against VISA. In a study of 25 VISA and heteroresistant VISA isolates, all MIC values of dalbavancin were ≤1 µg/mL. In other studies, dalbavancin MICs for 36 heteroresistant VISA strains were 0.03–0.12 µg/mL.[23] Dalbavancin displays poor activity against VRSA; however, it was shown to be active against one of the VRSA strains isolated in the US (MIC 0.5 µg/mL).[24]

Dalbavancin also demonstrates activity against *Staphylococcus epidermidis* and *Staphylococcus lugdunensis*. In vitro activity against *S. epidermidis* was evaluated in 33 prosthetic joint isolates in Sweden. Ninety-one percent of isolates were considered multi-drug resistant (defined as being resistant to more than three classes of antibiotics), with 85% of isolates harboring the *mecA* gene. MIC_{50} and MIC_{90} were determined to be 0.032 and 0.047 mg/L, respectively.[25]

Additionally, 59 strains of *S. epidermidis* were evaluated from multiple sources including ABSSSIs, and 100% of isolates, both oxacillin-sensitive and -resistant, were susceptible to dalbavancin. Dalbavancin was susceptible to all the four strains of *S. lugdunensis* evaluated in the study.[26]

Streptococcus

Dalbavancin demonstrates high in vitro susceptibility against many *Streptococcus* spp. Candiani et al[29] initially demonstrated susceptibility of dalbavancin against penicillin-sensitive and -resistant *S. pneumoniae* and *S. pyogenes* isolates, and determined the MIC_{50} to be 0.03 and ≤0.002, respectively. Worldwide surveillance studies have shown excellent in vitro activity against viridians group streptococci and β-hemolytic streptococci, with *S. agalactiae* having slightly elevated MICs compared to isolates from Groups A, C, F, and G. *S. pyogenes* and *S. agalactiae* isolates from the US were found to be highly susceptible to dalbavancin in surveillance studies. The dalbavancin MIC_{50} was consistently ≤0.03 µg/mL for both the species, and MIC_{90} was ≤0.03 and 0.06 µg/mL, respectively.[21] Smaller studies have also corroborated these findings (Table 2).

Enterococcus

Dalbavancin is active against vancomycin-susceptible *Enterococcus* spp. and non-VanA vancomycin-resistant *Enterococcus* (VRE), including *Enterococcus faecium* and *Enterococcus faecalis* (Table 3). However, the clinical significance from in vitro data remains to be determined as there are no outcome data for the use of dalbavancin in this population.[13] There are also currently no FDA-established breakpoints for dalbavancin against *Enterococcus* spp.

Table 1 In vitro activity of dalbavancin against *Staphylococcus* collected in the US, Canada, Latin America, and globally[a]

Author	Study	Year	Isolate	No of isolates	Source of isolates	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Gales et al[15]	Isolates from Latin America medical centers	2003	MSSA	393	NR	0.06	0.06
			MRSA	143		0.06	0.06
Biedenbach et al[26]	Isolates from United States medical centers	2005–2006	MSSA	762	Skin/skin structure, bloodstream, respiratory tract	0.064	0.125
			MRSA	1,009		0.064	0.19
Zhanel et al[27]	Canadian surveillance studies	2005–2006	MSSA	687	Blood, urine, wound/tissue, respiratory tract	0.06	0.06
			MRSA	197		0.06	0.06
			Staphylococcus epidermidis	111		≤0.03	0.06
Biedenbach et al[21]	Worldwide resistance studies	2002–2007	MSSA	27,052	NR	0.06	0.06
			MRSA	19,721		0.06	0.06
Karlowsky et al[28]	CANWARD cross-Canada surveillance study	2007–2009	MSSA	1,980	Blood, respiratory tract, skin, urine	0.06	0.06
			MRSA	631		0.06	0.06
Jones et al[31]	SENTRY Antibacterial Surveillance study	2002–2012	MSSA	18,934	Blood, respiratory tract, skin, urine, other	0.06	0.06–0.12
			MRSA	20,890		0.06	0.06–0.12
Boucher et al[22]	DISCOVER 1 and 2 trials	2011–2012	MSSA	361	NR	0.06	0.06
			MRSA	135		0.06	0.06
Canidani et al[29]	Experimental animal models	NR	MSSA	10		0.06	0.13
			MRSA	23		0.13	0.25
			Methicillin-sensitive *Staphylococcus epidermidis*	13		0.06	0.25
			Methicillin-resistant *Staphylococcus epidermidis*	12		0.06	0.25

Note: [a]The methodology in each study was through the use of broth microdilution.
Abbreviations: MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates; NR, not reported.

From 2006 to 2009, 4,457 vancomycin-susceptible and 525 VRE spp. were collected in Euorpe.[20] In the vancomycin-susceptible group, at least 90% of *E. faecium* and *E. faecalis* isolates had an MIC of ≤0.12 μg/mL. However, in the VRE group, 90% of isolates had an MIC of >4 μg/mL. MICs for dalbavancin against VanA enterococci are considerably higher, confirming lack of activity against VanA-containing vancomycin-resistant enterococci.[13]

Table 2 In vitro activity of dalbavancin against *Streptococcus* collected in the US, Canada, Latin America, and globally[a]

Author	Study	Year	Isolate	No of isolates	Source of isolates	MIC_{90} (μg/mL)
Candiani et al[29]	Experimental animal models	NR	*S. pneumoniae* (Pen S)	12	Various	0.06
			S. pneumoniae (Pen R)	5		–
			S. pyogenes	5		–
Zhanel et al[27]	Canadian surveillance studies	2005–2006	*S. pneumoniae*	244	Blood, urine, wound/tissue, respiratory tract	≤0.03
			S. pyogenes	49		≤0.03
			S. agalactiae	39		≤0.03
Biedenbach et al[21]	Worldwide resistance studies	2002–2007	β-Hemolytic Strep	5,316	NR	≤0.03
			Viridans group Strep	2,148		≤0.03
Karlowsky et al[28]	CANWARD cross-Canada surveillance study	2007–2009	*S. pneumoniae* (Pen S)	739	Blood, respiratory tract, skin, urine	≤0.03
			S. pneumoniae (Pen I)	120		≤0.03
			S. pneumoniae (Pen R)	34		≤0.03
			S. pyogenes	200		≤0.03
Jones et al[31]	SENTRY Antibacterial Surveillance study	2002–2012	*S. pyogenes*	2,051	Blood, respiratory tract, skin, urine, other	≤0.03
			S. agalactiae	2,000		≤0.03–0.12

Note: [a]The methodology in each study was through the use of broth microdilution.
Abbreviations: NR, not reported; *S. pneumoniae*, *Streptococcus pneumoniae*; Pen S, penicillin sensitive; Pen R, penicillin resistant; *S. pyogenes*, *Streptococcus pyogenes*; *S. agalactiae*, *Streptococcus agalactiae*; Strep, streptococci; Pen I, penicillin intermediate; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates.

Table 3 In vitro activity of dalbavancin against *Enterococcus* collected in the US, Europe, and globally[a]

Author	Study	Year	Isolate	No of isolates	Source of isolates	MIC_{90} (μg/mL)
Candiani et al[29]	Experimental animal models	NR	*Enterococcus* spp. non-VRE	6	Various	–
			Enterococcus spp. (VanA)[b]	21		>128
			Enterococcus spp. (VanB)[b]	10		1
Streit et al[30]	Gram-positive worldwide collection	2001–2003	*E. faecium* non-VRE	29	Various	0.12
			E. faecium VRE (VanA)	44		32
			E. faecalis VRE (VanA)	14		32
			Enterococci VRE (VanB)	11		0.12
Jones et al[34]	Isolates from European hospitals	2006–2009	All *Enterococcus*	4,982	Various	0.12
			VRE			>4
Jones et al[31]	Comparison of US and European susceptibility data	2002–2010	United States:		NR	
			– *E. faecium*	3,990		>4
			– *E. faecalis*	7,456		0.06
			Europe:			
			– *E. faecium*	851		>4
			– *E. faecalis*	653		0.06

Note: [a]The methodology in each study was through the use of broth microdilution. [b]VanA and VanB are phenotypes of Enterococcus spp. that confer vancomycin resistance.

Abbreviations: NR, not reported; VRE, vancomycin-resistant *Enterococcus*; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates.

Efficacy of dalbavancin

The efficacy of dalbavancin was evaluated in two Phase III, double-blind, double-dummy, international, multicenter, non-inferiority registration trials. These two trials, DISCOVER 1 and DISCOVER 2, were identically designed to assess the use of dalbavancin in the treatment of adult patients with ABSSSIs, which allowed for the pooling of data.[22]

Adult patients thought to require at least 3 days of IV therapy who had one or more systemic signs of infection were eligible for inclusion. Patients were excluded if they had received antibiotic treatment 1 day prior to randomization. Patients received either two doses of dalbavancin, 1 g initially followed by 500 mg on day 8 of treatment, or vancomycin 1 g every 12 hours for ≥3 days, with the option of transitioning to oral linezolid to complete 10–14 days of therapy. The primary endpoint was early clinical response defined as both cessation of spread of erythema and a temperature of ≤37.6°C at 48- to 72-hour duration of therapy.

In the DISCOVER 1 trial, 288 patients were randomized to receive dalbavancin, and 285 patients were assigned to the vancomycin–linezolid group. In DISCOVER 2, 371 patients were assigned to the dalbavancin treatment group and 368 patients to the vancomycin–linezolid group.[22]

In DISCOVER 1, the primary endpoint was recorded in 83.3% of patients in the dalbavancin group and 81.8% in the vancomycin–linezolid group (95% confidence interval [CI] 4.6–7.9). In DISCOVER 2, an early clinical response occurred in 76.8% of patients in the dalbavancin group and 78.3% in the vancomycin–linezolid group (95% CI −7.4 to 4.6). Outcomes were similar with the pooled analysis of data, with 79.7% having achieved treatment success in the dalbavancin group and 79.8% in the vancomycin–linezolid group (95% CI −4.5 to 4.2).[22]

There are several points to note when evaluating the DISCOVER trials that may limit the applicability of results. First, vancomycin trough levels were not reported to ensure adequate dosing. If vancomycin was inappropriately dosed for the treatment of ABSSSIs, it could be considered an unfair comparator. Additionally, only a small portion of the total number of enrolled patients (n=124) had a documented MRSA ABSSSI, as it is likely that cultures were not obtained from many patients. Therefore, the actual rate of MRSA ABSSSIs is unknown. Given the broad spectrum of activity of dalbavancin, this antibiotic should be reserved for MRSA ABSSSIs. In the DISCOVER trials, a large majority of patients may not have required dalbavancin, but were committed to IV antibiotic therapy for at least 8 days.

In a recently published randomized, double-blind, non-inferiority trial, dalbavancin was evaluated as a single IV infusion of 1,500 mg compared to the traditional two-dose regimen that was studied in the DISCOVER trials.[32] Inclusion criteria for this study were identical to the DISCOVER trials, and included patients with erythema >75 cm^2 with a diagnosis of either a major abscess, cellulitis, or a traumatic wound or surgical site infection. Patients were allowed to receive metronidazole and aztreonam for anaerobic and Gram-negative coverage, respectively. The primary endpoint compared the proportion of patients that achieved ≥20% reduction in the size of erythema 48–72 hours after the administration of dalbavancin in both the groups. Clinical

response at 48–72 hours was demonstrated in 81.4% in the single-dose administration arm compared to 84.2% in the two-dose regimen arm. Documented MRSA infections were more common in the two-dose regimen arm (27.7%) compared to the single-dose administration arm (17.1%).[32] Based on published results, the single-dose regimen was considered non-inferior to the two-dose regimen.[32] Despite good clinical outcomes, there is a lack of pharmacokinetic data surrounding the single-dose regimen. Further studies are warranted to demonstrate whether pharmacokinetics of the single-dose regimen is non-inferior to that of the two-dose regimen, and to further define the clinical utility of single-dose administration. Similarly to the DISCOVER trials, documented MRSA infection rates were low in both the arms.

Safety and tolerability of dalbavancin

Safety outcomes were measured throughout both the DISCOVER 1 and DISCOVER 2 trials. Adverse and serious adverse events that occurred throughout the study period were recorded on or after the first administered dose of the study drug through the long-term follow up visit at day 70.[22] There were fewer adverse events in patients treated with dalbavancin than in those treated with vancomycin–linezolid. The most common adverse events in the dalbavancin and vancomycin–linezolid groups were nausea (2.5% and 2.9%; P=0.62), diarrhea (0.8% and 2.5%; P=0.02), and pruritus (0.6% and 2.3%; P=0.01). Infusion site reactions were also reported and occurred at a similar frequency in both the groups (1.4% and 1.7%). Serious adverse events occurred in 2.6% of patients treated in the dalbavancin group and 4.0% in the vancomycin–linezolid group. One patient in each group experienced cellulitis, anaphylactic reaction, gastrointestinal disorder, toxic nephropathy, and acute renal failure. Death occurred in one patient in the dalbavancin group compared with 7 patients in the vancomycin–linezolid group (P=0.03).[22] The safety and tolerability of dalbavancin as a single-dose regimen were similar to the two-dose regimen.[32]

Considerations of dalbavancin usage

Two important benefits of the once-weekly dosing of dalbavancin are worth noting. The first is the potential prevention of inpatient admission for IV antimicrobial therapy. As dalbavancin can be given on an outpatient basis in an infusion center or the emergency department, this eliminates the need for inpatient admission, thus reducing the overall financial burden on health care costs. Secondly, once-weekly dosing on an outpatient basis removes the need for long-term central venous catheter placement, which has significant implications on the cost, quality of life, and prevention of central line-associated bloodstream infections and complications.

However, the use of dalbavancin does not come without disadvantages. There are potential consequences of administration of only a single dose of dalbavancin in non-compliant patients who do not return for their second dose. The FDA-approved dosing regimen of dalbavancin was selected based on the results of a Phase II dose-response trial, in which there were three treatment arms.[20] A one-time dalbavancin dose of 1,100 mg IV (arm one) was compared to 1,000 mg IV dalbavancin on day 1, followed by 500 mg IV on day 8 (arm two). The third arm (arm three) comprised investigator-designated comparative antimicrobial agents at standard doses. Over a period of 1 year, a total of 62 patients were enrolled. In total, 41 patients received dalbavancin and 21 received a comparator. The clinical response rates in the evaluable population at the follow-up visit were higher in the arm two (94.1%) as compared to the arm one (61.5%) and arm three (76.2%).[20] Thus, in non-compliant patients, administration of only the 1,100 mg IV dose of dalbavancin could allow bactericidal levels to fall below the minimum bactericidal concentration (1 μg/mL) before the entire 14-day treatment period for *S. aureus* infections. Dalbavancin-free drug levels that fall below 1 μg/mL during treatment may result in consecutive below-MIC levels in tissues and blood, potentially resulting in the emergence of resistance.

With the surfacing of a new study evaluating the administration of a single dose of dalbavancin, there is potential for improved compliance. However, it is necessary to ensure that the single-dose regimen of dalbavancin would allow for effective bactericidal concentrations before this dosing is employed. Until further studies are completed, the effective use of single-dose dalbavancin cannot be recommended in all patients.

The use of dalbavancin also has implications on antimicrobial stewardship, specifically on the ability to target antimicrobial therapy. Even if an organism is isolated, which allows for narrowing of therapy, the long half-life and once-weekly dosing of dalbavancin preclude antibiotic de-escalation. Additionally, there is potential for overuse of dalbavancin in patients without significant risk for MRSA ABSSSIs because of the ease of use. This may result in unnecessary exposure to a broad-spectrum antimicrobial agent in many patients.

Moreover, dalbavancin has been reported to cause severe hypersensitivity and anaphylactic reactions. Therefore,

if a patient has a reaction to dalbavancin after the single dose, reactions would persist despite discontinuation of the drug.

Conclusion and place in therapy

For the empiric treatment of severe ABSSSIs, dalbavancin is not included in the most recent Infectious Diseases Society of America guidelines, as it was not approved for treatment at the time of publication.[4] The linear kinetics, prolonged distribution phase (half-life of 5–7 days), tissue penetration, and bactericidal activity of dalbavancin against Gram-positive bacteria including MRSA make it an attractive medication for the treatment of ABSSSIs.[17] However, dalbavancin may not be appropriate for use in all patients. Disadvantages include a high acquisition cost, overuse of dalbavancin in mild and moderate cases of ABSSSIs, inability to narrow therapy based on culture results or clinical response, and potential for the development of increased resistance in non-compliant patients.[33] Owing to its recent drug approval, there is a paucity of pharmacoeconomic data evaluating the use of dalbavancin for the treatment of ABSSSIs compared to other treatment options. In a patient with severe ABSSSIs who has tried and failed other therapies, dalbavancin may be considered in the outpatient setting, including home health care, outpatient infusion clinics, or in the emergency department to avoid delay in treatment and prevent inpatient hospital admissions.[20]

Disclosure

The authors report no conflicts of interest in this work.

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