REVIEW

DALBAVANCIN-A NOVEL LIPOGLYCOPEPTIDE ANTIMICROBIAL FOR GRAM POSITIVE PATHOGENS

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ABSTRACT

Glycopeptide antibiotics represent an important class of microbial compounds produced by several genera of actinomycetes. The emergence of resistance to glycopeptides among enterococci and staphylococci has prompted the search for second-generation drugs of this class and semi-synthetic derivatives are currently under clinical trials. Antimicrobial resistance among gram-positive organisms has been increasing steadily during the past several decades. Dalbavancin, a novel lipoglycopeptide, has a mechanism of action similar to that of other glycopeptides. It has *in vitro* activity against a variety of Gram-positive organisms specially multidrug resistant *Staphylococcus aureus*, but no activity against Gram-negative or vancomycin-resistant enterococci that possess vanA gene. Due to its prolonged half-life (6-10 days), dalbavancin can be administered intravenously once weekly. In Phase II and III clinical trials, dalbavancin was effective and well-tolerated for the treatment of skin and soft-tissue infections, catheter-related bloodstream infections, and skin and skin-structure infections. To date, adverse events have been mild and limited; the most common being pyrexia, headache, diarrhea. Dalbavancin appears to be a promising antimicrobial agent for the treatment of Gram-positive infections. Additional clinical data are required to fully assess its use. Despite the remarkable and favorable pharmacokinetic and pharmacodynamic properties, the use of this potent agent should be restricted to severe infections due to multidrug resistant organisms to limit the risk of selection of resistance. It is active against Gram-positive aerobes and anerobes, including resistant pathogens, with the exception of strains producing vanA-mediated resistance.. Its approval by the FDA is expected soon. The extent to which dalbavancin will supplant vancomycin and whether it will be preferred over other newer agents such as linezolid in the next decade remains to be seen.

Keywords: Dalbavancin, lipoglycopeptide, multidrug-resistant, *Staphylococcus aureus,* gram-positive organisms.

INTRODUCTION

As a consequence of antibiotic overuse and misuse, nosocomial infections caused by multidrug-resistant bacteria represent a physician's nightmare throughout the world. The ever-increasing prevalence of bacterial resistance presents a challenging scenario to the clinical practitioner. Antimicrobial resistance among gram-positive organisms has been increasing steadily during the past several decades despite the introduction of new antimicrobials. There is a notable amplification in the incidence of vancomycin resistant enterococci (VRE) reported from the Summary of Notifiable Diseases(Anon., 1994), vancomycin tolerance in *Streptococcus pneumoniae* (Novak *et al*., 1999) and most recently, the identification of *Staphylococcus aureus* isolates with reduced susceptibility (Smith *et al*., 1999) or full resistance to vancomycin (Anon., 2002). Emergence of staphylococci that are intermediate and resistant to methicillin and quinolone and recently to vancomycin, as well as the propensity of these microorganisms to cause serious systemic infections in immunocompromised hosts, necessitates the development of other therapeutic modalities (Blumberg *et al*., 1991; Bozdogan *et al*., 2003; Hershow *et al*., 1998; Hiramatsu, 1998; Linde *et al*., 2001; Nichols, 1999; Schmitz *et al*., 1999; Voss *et al*., 1994).

Infections caused by resistant organisms have a negative impact on clinical and economic outcomes, with an associated increase of 1.3- to 2-fold in morbidity, mortality and cost (Cosgrove and Carmeli, 2003). The annual cost of antimicrobial resistance in the US was estimated to be $US 4 billion in currency value from

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1995. Methicillin-resistant *Staphylococcus aureus* bacteremia(mean mortality rate: 36.4%) had a higher associated mortality than methicillin-susceptible *Staphylococcus aureus* bacteremia(mean mortality rate: 23.4%) with a pooled odds ratio of 1.93 (95% CI: 1.54-2.42; p< 0.001) in a meta-analysis of 3963 patients (Cosgrove *et al*., 2003).

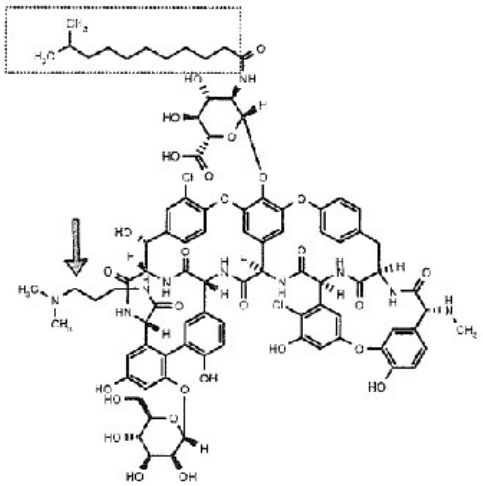
The total usage of vancomycin, which has always been considered the last resort for treatment of resistant Gram-positive infections, in the United States and Western Europe, is estimated to have increased from very small quantities in 1975 to over 14,000 kilograms in 1995 (Kirst *et al*., 1998). Despite the obvious need for new antibacterial agents, the number of approved antibiotics has decreased by 56% from 1983-1987 to 1998-2002 (Spellberg *et al*., 2004).Therefore, much of the focus has been recently given to producing new antimicrobial agents for the treatment and prevention of resistant Gram-positive pathogens, especially semisynthetic derivatives of vancomycin and teicoplanin termed lipoglycopeptides (dalbavancin, oritavancin and telavancin) (Van Bambeke, 2004). In this review article, we will look at available data on one of these new agents', dalbavancin which is under clinical development and currently awaiting an approval from the United States FDA.

History

Dalbavancin (formerly variously codenamed A-A1, BI-397, MDL-63397, and VER-001) is a novel semisynthetic lipoglycopeptide that was designed to improve upon the natural glycopeptides currently available, vancomycin and teicoplanin. It was discovered by Biosearch Italia SpA and outlicensed to Versicor Inc for the North American market(Anon, 1999). Biosearch and Versicor merged in March 2003 to form Vicuron Pharmaceuticals Inc.(Anon, 2003),which was then acquired by Pfizer in September 2005(Anon, 2005). Pfizer is currently pursuing the development of dalbavancin.

Chemistry

Dalbavancin is a semisynthetic teicoplanin analog (fig. 1) and is a dimethylaminepropyl amide derivative of the lipoglycopeptide A-40926, which is a family member of teicoplanin (Van Bambeke, 2004; Malabarba and Goldstein, 2005; Van Bambeke *et al*., 2004). A three-step process is required to produce dalbavancin from A-40926, which is isolated from the *Nonomuria spp.*(Malabarba and Goldstein, 2005; Malabara and Ciabatti, 2001). The process begins with selective methyl esterification of the acylaminoglucuronic acid, followed by amidation of the peptide carboxy group and is completed with saponification of the methyl ester (Malabarba and Goldstein, 2005; Malabara and Ciabatti, 2001). The final product possesses a 3,3-dimethylamino- propylamide in place of the peptide carboxyl group that is present in A-40926, which increases the staphylococci potency of dalbavancin, especially against coagulase-negative staphylococci (CoNS) (Malabarba and Goldstein, 2005; Van Bambeke *et al*., 2004). Consistent with its parent compound A-40926, dalbavancin also lacks the acetylglucosamine that is seen in teicoplanin (Van Bambeke *et al*., 2004; Malabarba and Ciabatti, 2001). The acetylglucosamine was removed with the intention of enhancing activity against vanA enterococci, as demonstrated by the compound MDL-63246, the development of which was later abandoned due to poor tolerability in animal studies (Malabarba and Ciabatti, 2001).



Dalbavancin

Fig. 1: Chemical Structure of Dalbavancin which is a semi-synthetic derivative of teicoplanin. The lipophilic tail(responsible for prolonged half-life and membrane anchoring) is highlighted in a dotted rectangle. The grey arrow indicates the basic amide which increases activity.

Despite the various changes made to the number and position of sugars, chlorine atoms, and methyl and hydroxyl groups, dalbavancin maintains the peptide backbone that is the signature of glycopeptide antimicrobial agents (Malabarba and Goldstein, 2005). Its lipophilic side chain, responsible for the lipoglycopeptide label, enhances protein binding and thus results in prolonged half-life (T(1/2)) that is characteristic of teicoplanin-like derivatives (Van Bambeke, 2004; Malabarba and Goldstein, 2005). The side-chain also provides additional mechanisms that enhance the interaction of dalbavancin to its target binding site (Van Bambeke, 2004; Malabarba and Goldstein, 2005; Van Bambeke *et al*., 2004).

Mode of action

Consistent with the activity of other glycopeptides, dalbavancin inhibits bacterial cell wall synthesis by

Table 1: Dalbavancin and comparator agents: Antimicrobial activity against Gram-positive bacterial strains collected worldwide

Organism (No. of isolates)	MIC_{50}(µg/ml)	MIC_{90}(µg/ml)	MIC range(µg/ml)	Susceptible(%)	Resistant(%)
Staphylococcus aureus					
Methicillin susceptible(1815)					
Dalbavancin	0.06	0.06	≤0.015-0.25	*	*
Vancomycin	1	1	0.25-2	100.0	0.0
Levofloxacin	0.12	0.5	≤0.03 to > 4	93.2	5.0
Quinupristin-dalfopristin	0.25	0.5	≤0.06-2	100.0	0.0
Linezolid	2	1	0.5-4	100.0	*&
Methicillin resistant (1177)					
Dalbavancin	0.06	0.06	≤0.015-0.25	-	-
Vancomycin	1	2	0.25-2	100.0	0.0
Levofloxacin	> 4	> 4	≤0.06 to > 4	11.1	65.7
Quinupristin-dalfopristin	0.5	1	≤0.06 to > 8	99.7	0.2
Linezolid	2	2	≤0.25-16	99.9	-
Coagulase-negative staphylococci					
Methicillin susceptible(157)					
Dalbavancin	0.03	0.06	≤0.015-0.25	-	-
Vancomycin	1	2	0.5-2	100.0	0.0
Levofloxacin	0.25	4	≤0.03 to > 4	87.9	8.3
Quinupristin-dalfopristin	0.12	0.25	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Methicillin resistant (617)					
Dalbavancin	0.03	0.06	≤0.015-0.5	-	-
Vancomycin	1	2	≤0.12-4	100.0	0.0
Levofloxacin	4	> 4	0.06 to > 4	40.2	42.6
Quinupristin-dalfopristin	0.25	0.5	≤0.06 to > 8	99.3	0.2
Linezolid	1	1	≤0.25-2	100.0	-
Streptococcus pneumoniae					
Penicillin susceptible(996)					
Dalbavancin	≤0.015	0.03	≤0.015-0.06	-	-
Vancomycin	0.25	0.5	≤0.06-1	100.0	*&
Levofloxacin	1	1	≤0.03 to > 4	98.8	1.2
Quinupristin-dalfopristin	0.25	0.5	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Penicillin non-susceptible (400)					
Dalbavancin	≤0.015	0.03	≤0.015-0.25	-	-
Vancomycin	0.25	0.5	≤0.06-2	99.8	-
Levofloxacin	1	1	0.12 to > 4	98.5	1.5
Quinupristin-dalfopristin	0.5	0.5	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Viridans group streptococci					
Penicillin susceptible (104)					
Dalbavancin	≤0.015	0.03	≤0.015-0.06	-	-
Vancomycin	0.5	1	≤0.12-1	100.0	-
Levofloxacin	1	2	≤0.03 to > 4	97.1	2.9
Quinupristin-dalfopristin	0.5	1	≤0.06-2	99.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-

Table continued ....

inhibiting the final stages of peptidoglycan synthesis by forming a binding pocket with the D-alanyl-D-alanine terminus of peptidoglycan precursors. The complex created between the heptapeptide backbone and the D-alanyl-D-alanine dipeptide blocks access for transpeptidases and transglycosylases, the enzymes that are necessary to pursue polymerization and cross-linking(Malabarba and Goldstein, 2005; Lacy *et al*., 2005). As a consequence, the nascent peptidoglycan chain is halted from further development, leaving cells vulnerable to rupture from changing internal osmotic pressure(Kahne *et al*., 2005).

Dalbavancin is classified as a lipoglycopeptide because of the long lipophilic side chain present on the basic glycopeptide backbone. The addition of this lipophilic

Table 1 continued...

Organism (No. of isolates)	MIC_{50}(µg/ml)	MIC_{90}(µg/ml)	MIC range(µg/ml)	Susceptible(%)	Resistant(%)
Penicillin non-susceptible (30)					
Dalbavancin	≤0.015	0.03	≤0.015-0.03	-	-
Vancomycin	0.5	0.5	0.25-1	100.0	-
Levofloxacin	1	2	0.5 to > 4	100.0	0.0
Quinupristin-dalfopristin	0.5	1	0.12-1	100.0	0.0
Linezolid	1	1	≤0.25-1	100.0	0.0
β-Hemolytic streptococci(234)					
Dalbavancin	≤0.015	0.06	≤0.015-0.25	-	-
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	0.0
Levofloxacin	0.5	1	0.06 to > 4	97.9	2.1
Quinupristin-dalfopristin	0.25	0.5	≤0.06-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Enterococcus faecalis					
Vancomycin susceptible (586)					
Dalbavancin	0.03	0.06	≤0.015-4	-	-
Penicillin	4	8	1 to > 32	96.9	3.1
Levofloxacin	1	> 4	0.25 to > 4	58.5	40.8
Quinupristin-dalfopristin	8	> 8	0.25 to > 8	0.5	94.4
Linezolid	1	2	≤0.25 to 4	99.8	0.0
Gentamicin (high level)	≤500	> 1000	≤500 to > 1000	66.4	33.6
Vancomycin resistant (20)					
Dalbavancin	4	32	≤0.015 to > 32	-	-
Penicillin	4	16	2 to > 32	80.0	20.0
Levofloxacin	> 4	> 4	1 to > 4	5.0	95.0
Quinupristin-dalfopristin	> 8	> 8	4 to > 8	0.0	100.0
Linezolid	1	2	0.5-2	100.0	0.0
Gentamicin (high level)	> 1000	> 1000	≤500 to > 1000	25.0	75.0
Enterococcus faecium					
Vancomycin susceptible (77)					
Dalbavancin	0.06	0.12	≤0.015-4	-	-
Penicillin	> 32	> 32	0.5 to > 32	23.4	70.1
Levofloxacin	> 4	> 4	0.25 to > 4	32.5	61.0
Quinupristin-dalfopristin	1	2	0.25-8	62.3	7.8
Linezolid	2	2	< 0.25-2	100.0	0.0
Gentamicin (high level)	≥ 500	> 1000	≤500 to > 1000	85.5	14.5
Vancomycin resistant (51)					
Dalbavancin	8	32	0.03 to > 32	-	-
Penicillin	> 32	> 32	2 to > 32	2.0	96.1
Levofloxacin	> 4	> 4	1 to > 4	2.0	98.0
Quinupristin-dalfopristin	1	1	0.25-8	96.0	4.0
Linezolid	2	2	0.5 to > 16	98.0	2.0
Gentamicin (high level)	≥ 500	> 1000	≤500 to > 1000	54.9	45.1

Adapted from Streit *et al.,* 2004.
*No breakpoint has been established by the National Committee for Clinical Laboratory Standards of the USA.
& no interpretative criteria have been established for resistance with vancomycin (against streptococci) or linezolid (against streptococci and staphylococci).
MIC = Minimum inhibitory concentration.

side chain seems to endow dalbavancin with more ways in improving its association with D-alanyl-D-alanine peptides(Malabarba and Goldstein, 2005; Kahne *et al*., 2005; Beauregard *et al*., 1995). It is hypothesized to allow for dimerization (as with vancomycin) and membrane anchoring (as with teicoplanin), which increases the binding affinity of dalbavancin for the target site(Malabarba and Goldstein, 2005; Kahne *et al*., 2005; Beauregard *et al*., 1995). Homodimers formed between glycopeptide molecules lock the binding pocket into a prime position to facilitate cooperative binding (Van Bambeke, 2004; Van Bambeke *et al*., 2004). Membrane anchoring helps to localize dalbavancin nearer to its target (Van Bambeke, 2004; Van Bambeke *et al*., 2004; Kahne *et al*., 2005). These features are considered to attribute to the antimicrobial activity of dalbavancin.

Table 2: Semisynthetic lipoglycopeptides and vancomycin: Antimicrobial activity against Gram-positive bacterial pathogens*.

Organism	Dalbavancin MIC range(µg/ml)	Oritavancin MIC range(µg/ml)	Telavancin MIC range(µg/ml)	Vancomycin MIC range(µg/ml)
Staphylococcus aureus				
Methicillin susceptible	0.06-0.5	0.12-2	0.12-2	0.25-2
Methicillin resistant	0.06-1	0.12-4	≤ 0.06-2	0.5-4
Coagulase-negative staphylococci				
Methicillin susceptible	≤0.03-0.25	0.25-1	0.12-2	0.12-1
Methicillin resistant	0.06-1	0.25-4	≤ 0.12-2	1-4
Streptococcus spp.				
Streptococcus pneumoniae	0.008-0.12	≤0.002-0.06	0.004-0.03	0.25-2
β-Hemolytic streptococci	≤0.03-0.12	0.016-0.12	0.03-0.12	0.5
Enterococcus spp.				
Vancomycin susceptible	≤0.03-1	0.06-0.25	0.06-1	0.25-4
Vancomycin resistant (VanB)	0.02-2	0.12-2	0.12-2	8-128
Vancomycin resistant (VanA)	0.5 to > 128	1-4	0.12-8	> 128

Adapted from Pace and Yang, 2006; *Number of isolates not provided. MIC= Minimum inhibitory concentration.

Although it was initially envisioned to be active against vanA-resistant strains, dalbavancin fails to act against them. Glycopeptides would require specific changes to its core backbone to permit binding to the D-alanyl-D-alanine carried by vanA enterococci (Malabarba and Ciabatti, 2001). Telavancin is capable of overcoming vanA resistance due to a second mechanism of action, cellular membrane depolarization and permeabilization, as with daptomycin (Higgins *et al*., 2005).

Spectrum of activity and resistance

Dalbavancin has excellent *in vitro* activity against Gram-positive organisms but it fails to provide any protection against Gram-negative pathogenic bacteria (Jones *et al*., 2001; Kim *et al*., 2007). In general, dalbavancin is more potent than vancomycin, teicoplanin and to some extent oritavancin against staphylococci (with MICs ranging from < 0.03 to 1 mg/L for susceptible and methicillin-resistant strains, respectively) and *S. pyogenes* (MIC in the < 0.002 – 0.06 mg/L range) (Candiani *et al*., 1999; Jones *et al*., 2001; Hackbarth *et al*., 1999). It has favorable *in vitro* activity against methicillin-susceptible *S. aureus* (MSSA) (Bowker *et al*., 2004; Flamm *et al*., 2004; Streit *et al*., 2004; Gales *et al*., 2005; Lin *et al*., 2005; Lopez *et al*., 2005; Stephen *et al*., 2003; Ednie *et al*., 2003), methicillin resistant *S. aureus* (MRSA) (Bowker *et al*., 2004; Flamm *et al*., 2004; Streit *et al*., 2004; Gales *et al*., 2005; Lin *et al*., 2005; Lopez *et al*., 2005; Stephen *et al*., 2003; Ednie *et al*., 2003; Mushtaq *et al*., 2004), vancomycin intermediate *S. aureus* (VISA)(Bowker *et al*., 2004; Flamm *et al*., 2004; Lopez *et al*., 2005; Mushtaq *et al*., 2004), vancomycin resistant *S. aureus* (VRSA) (Flamm *et al*., 2004; Bozdogan *et al*., 2004) and linezolid-resistant *S. aureus* (Flamm *et al*., 2004). It is also very active against *S. pneumonia* with MICs 2-4 fold higher than those of oritavancin or teicoplanin against vancomycin-susceptible enterococci but does not offer the same advantage as oritavancin against glycopeptide resistant strains. So dalbavancin loses activity toward enterococci or staphylococci harboring the vanA gene cluster but remain extremely active against staphylococci and streptococci (Candiani *et al*., 1999; Malabarba and Ciabatti, 2001). It is also active against Gram-positive anaerobes, antibacterial activity similar to that of metronidazole and more active than vancomycin (Goldstein *et al*., 2003; Goldstein *et al*., 2005). Dalbavancin also demonstrated activity against Bacillus spp. (Streit *et al*., 2004; Jones *et al*., 2004; Heine *et al*., 2005), Corynebacterium spp. (Streit *et al*., 2004; Gales *et al*., 2005; Jones *et al*., 2004), Listeria spp. (Streit *et al*., 2004; Gales *et al*., 2005; Jones *et al*., 2004), and Micrococcus spp. (Jones *et al*., 2004). Table 1 exhibits the *in vitro* activity of dalbavancin against a worldwide collection of Gram-positive bacteria(Streit *et al*., 2004). Table 2 displays the comparative *in vitro* activity of dalbavancin and other novel lipoglycopeptides against Gram-positive bacteria (Pace and Yang, 2006).

Pharmacokinetics

Dalbavancin is not effective orally due to poor systemic absorption. It is only available as an intravenous formulation (McEvoy, 2005). It displays an unusually prolonged half life (6-10days) (Bowker *et al*., 2004; Leighton *et al*., 2004; Dorr *et al*., 2005; Dowell *et al*., 2004). It is highly protein bound (>90%) and was found to be bacteriocidal at free fractions of 1%-5% against *S. aureus*, with MICs of 0.06-0.12 µg/ml (Bowker *et al*., 2004) and also bacteriocidal at free fractions of 5% against VISA at an MIC of 1µg/ml(Bowker *et al*., 2004). It has been shown to be moderately concentrated in macrophages (Bulgheroni *et al*., 2004) and concentration in skin have been found to be equal to or greater than those in plasma which is essential in treating skin and soft tissue infections (Cavaleri *et al*., 2005). Due to prolonged

half life, high protein binding and retention within the cells, it can be administered intravenously once weekly (Dorr *et al*., 2005; Guay, 2004). Dalbavancin has dual routes of elimination, both renal and nonrenal routes (with around two-thirds of the excreted drug-derived radioactivity being found in the urine and around one-third in the feces) (Leighton *et al*., 2004; Dowell *et al*., 2004; Cavaleri *et al*., 2005). It was excreted at 25-45.5 % unchanged in urine and there is no need for dosage adjustments in population with varying degrees of hepatic insufficiency (Dowell *et al*., 2004).

Efficacy Studies/Profile

A. In animal models of infection – animal models of disseminated infection, foreign body infection or endocarditis, staphylococcal granuloma pouch and pneumococcal pneumonia demonstrated that dalbavancin is as efficacious as comparator at less frequent doses (Candiani *et al*., 1999; Jabes *et al*., 2004; Lefort *et al*., 2004; Darouiche and Mansouri, 2005), which is advantageous in clinical practice. In a rat model of experimental sepsis, lobar pneumonia and endocarditis, dalbavancin treated groups were similar to those of teicoplanin for MSSA and *S. pneumoniae* groups and slightly more active than vancomycin (Candiani *et al*., 1999). It also significantly reduced cardiac bacterial load and achieved 100% survival in *S. aureus* endocarditis (Candiani *et al*., 1999). Experimental endocarditis in a rabbit model, caused by *S. aureus*, with or without glycopeptide resistance, dalbavancin treated group achieved a significant reduction in colony count compared to control group (Lefort *et al*., 2004). In a rat granuloma pouch model, dalbavancin reduced bacterial loads and regrowth results also favoured dalbavancin over both vancomycin and linezolid (Jabes *et al*., 2004). In an intravenous catheter colonization in a rabbit model, dalbavancin had no significant difference over control in preventing colonization (Darouiche and Mansouri, 2005). There are other reports demonstrating that dalbavancin had bactericidal activity against *S. pneumoniae* and *S. aureus* (Andes and Craig, 2004) and it increased survival (70-100% vs 0%) in *B. anthracis* infections (Heine *et al*., 2005).

B. Clinical Studies- In clinical trials, dalbavancin was highly effective in treatment of skin and soft tissue infections (in phase II and phase III trials) and catheter-related blood stream infections (in phase II trial) (Lin *et al*., 2006; Seltzer *et al*., 2003; Jauregui *et al*., 2005; Raad *et al*., 2005). In phase II study, administration of two doses (1000mg on day 1 and 500 mg on day 8) was found to be as effective as comparators (7-21 days with clindamycin, ceftriaxone, vancomycin or, cefazolin) for the treatment of deep skin and soft tissue infection caused by methicillin-susceptible *S. aureus* or MRSA (Seltzer *et al*., 2003). In a multicentre, double blind, randomized, noninferiority, phase III trial compared dalbavancin with linezolid for complicated skin and soft tissue infection in 854 adult patients (Jauregui *et al*., 2005). Approximately 90% of all pathogens isolated were *S. aureus*, of which a relatively high percentage(51%) were MRSA. The dalbavancin dosage was 1000 mg intravenously on day 1 followed by 500 mg on day 8 (571 patients). The linezolid dosage was 600 mg twice daily IV or orally for a total of 14 days (283 patients). The primary outcome was clinical success in evaluable patients at the test-of-cure visit. In this clinically evaluable population, 88.9% and 91.2% achieved clinical success in the dalbavancin and linezolid arms, respectively. The results of three recently concluded phase III trials in skin and soft tissue infections were presented in abstract format in Dec 2005 (Goldstein *et al*., 2005). Similar clinical and microbiologic response was reported in all three trials with once-weekly dalbavancin compared with linezolid, cefazolin, and vancomycin.

A phase II, open-label, randomized, controlled, multicenter study of 75 adult patients with catheter-related bloodstream infections (CR-BSIs) compared treatment with intravenous dalbavancin, administered as a single 1000-mg dose followed by a 500-mg dose 1 week later, with intravenous vancomycin, administered twice daily for 14 days (Raad *et al*., 2005). Gram-positive bacteria isolated in this study included coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA). Primary outcome, based on the microbiologic intent to treat population, was combined clinical and microbiological response assessed at the test-of-cure visit 18-24 days after the end of therapy. Infected patients who received weekly dalbavancin (n = 33) had an overall success rate (87%; 95 percent confidence interval [CI], 73.2-100%) that was significantly higher than that of those who received vancomycin (n=34) (50%; 95 percent CI, 31.5-68.5%). Microbiologic success at the end of therapy for dalbavancin was 95.6% and for vancomycin was 92.9%.

Safety Profile

To date, a number of clinical trials have evaluated the efficacy and adverse effects associated with dalbavancin and the observed adverse events have been mild and limited(Leighton *et al*., 2004; Lin *et al*., 2006). No statistically significant differences in overall adverse event rates were reported in any of the comparative clinical trials (Seltzer *et al*., 2003; Jauregui *et al*., 2005; Raad *et al*., 2005). In a double-blind study (52 healthy adult male and female volunteers), there were no serious adverse effects or deaths reported (Leighton *et al*., 2004). No dose effects were seen for adverse effects or laboratory values. The most common adverse effects in both the single- and multiple-dose groups were pyrexia (50% vs 38%), headache (25 % vs 31%) in dalbavancin and placebo group respectively. Early discontinuations due to adverse events occurred in 3.9% and 3.2% of

patients receiving dalbavancin and linezolid, respectively (Jauregui *et al*., 2005). Adverse effects like hypotension, diarrhea and hypokalemia also occurred with higher prevalence in the dalbavancin arm than in the vancomycin arm (Raad *et al*., 2005), but there were no effects on QT intervals(Seltzer *et al*., 2005) and no reports of 'red man syndrome' type of reactions with dalbavancin (Seltzer *et al*., 2003; Jauregui *et al*., 2005; Raad *et al*., 2005). Dalbavancin is not expected to carry the nephrotoxicity risk that has been associated with vancomycin as there is no clinically significant serum creatinine concentration abnormalities with the use of dalbavancin (Leighton *et al*., 2004; Seltzer *et al*., 2003; Jauregui *et al*., 2005; Raad *et al*., 2005; Seltzer *et al*., 2005). No dosage adjustments are necessary in case of mild renal insufficiency(Dowell *et al*., 2003). No auditory or vestibular toxicity was noted with either the single dalbavancin dose of 1120mg or, in patients receiving the cumulative dose of 1600mg over a 1 week period (Campbell *et al*., 2003). There are also reports of transient asymptomatic elevations of liver enzymes (Leighton *et al*., 2004; Jauregui *et al*., 2005) and asymptomatic hyperglycemia (Leighton et al., 2004) that occurred with dalbavancin but did not require intervention.

CONCLUSIONS

Dalbavancin appears as a potent molecule with favorable pharmacokinetic(linear, dose-proportional with concentration-dependent activity) and pharmacodynamic properties. The potency, tissue penetration, and long serum elimination half-life of dalbavancin may permit more flexible and convenient dosing regimens than currently exist for other glycopeptides (Streit *et al*., 2004). Despite its high protein binding, dalbavancin produces sufficient concentrations that are capable of bactericidal activity. Strictly a Gram-positive agent, dalbavancin is more potent in vitro than standard agents and other lipoglycopeptides. Once-a-week dosing with dalbavancin may obviate the need for the continued presence of intravenous lines in some patients, which could translate into fewer local infections and blood stream infections. This could also lead to pharmacoeconomic benefits, such as shorter hospital stays, decreased administration and monitoring costs, and less need for follow-up. The most notable advantages are the highly bactericidal character against multiple drug resistant MRSA. Dalbavancin has been granted priority review status by the FDA for the treatment of MRSA and complicated skin and soft tissue infection (Anon, 2005). Dalbavancin was generally well-tolerated with mild-to-moderate gastrointestinal adverse effects.

However, opposing views note that a long T(1/2) may be disconcerting as it seems that subtherapeutic concentrations of dalbavancin can linger for months beyond the treatment duration, which could potentially generate bacterial resistance. Furthermore, the effects may be sustained for a lengthy period of time if toxicity were to occur.

Despite the remarkable properties, the use of this potent agent should be restricted to severe infections, as should the older glycopeptides, with an extension towards resistant or poorly sensitive bacteria, to limit the risk of potential selection of resistance. Additional clinical data are required to fully assess its use. Large clinical studies (including safety studies) will aid in positioning this compound in the arsenal of new anti-Gram-positive agents.

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