Dalbavancin: A Novel Once-Weekly Lipoglycopeptide Antibiotic

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The increasing prevalence of drug-resistant gram-positive cocci, such as methicillin-resistant *Staphylococcus aureus,* has underscored the need for new agents for the treatment of this type of infection. Dalbavancin, a new lipoglycopeptide, has the desirable characteristics of increased in vitro activity, compared with vancomycin, for most gram-positive pathogenic bacteria, as well as an extremely long half-life, permitting once-weekly intravenous dosing. Clinical studies comparing linezolid with 2 doses of dalbavancin have shown comparable efficacy for the treatment of skin and soft-tissue infection. Dalbavancin has also proven to be effective for therapy of catheter-related bloodstream infections. It has an excellent safety profile in studies to date. Dalbavancin will likely have a significant role in outpatient intravenous therapy for patients with potentially serious drug-resistant gram-positive coccal infections.

For >60 years, antibiotics have drastically altered the course of human bacterial diseases. With the expanded use of penicillin in 1946 and after, penicillin resistance in staphylococci was almost immediately recognized. Today, with widespread use of antibiotics, an aging population, and profound immunosuppression in many patients, antimicrobial resistance continues to increase, yet the pace of development of new antimicrobials lags far behind the rate of development of antibiotic resistance. The emergence of drug resistance in gram-positive cocci has resulted in clinical failures, as well as in increased morbidity and mortality. The magnitude of the increased incidence of community- and hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is illustrated by the isolation of MRSA from 59% of patients presenting to emergency departments with skin and soft-tissue infections (SSTIs) across the United States [1]. In this study [1], the prevalence of MRSA ranged from 15% to 74%, and MRSA was noted to be the most common identifiable cause of SSTI in 10 of 11 emergency departments.

Vancomycin, the prototype glycopeptide, has been the gram-positive workhorse antimicrobial for half a century. The emergence of vancomycin-resistant enterococci (VRE) and strains of *S. aureus* with reduced susceptibility or resistance to vancomycin has created an urgent need for antimicrobial agents with activity against drug-resistant gram-positive bacteria. The past few years have seen a surge in the development of antimicrobial agents with gram-positive bacterial activity, but these drugs are not without limitations. Although rare, linezolid resistance has already been documented. Regarding the treatment of bacteremia, daptomycin resistance has emerged during therapy, and strains with decreased susceptibility to vancomycin may also show decreased susceptibility to daptomycin [2–4]. Daptomycin cannot be used for the treatment of pneumonia because of likely drug inactivation by pulmonary surfactant.

It is against this backdrop that we welcome a new addition to our antimicrobial armamentarium. Dalbavancin is a semisynthetic antibiotic derived from a teicoplanin-like glycopeptide agent (A-40926) by modifying the functional groups and sugar moieties of A-40926 while preserving the D-alanyl-D-alanine binding site required for antimicrobial activity (figure 1). The result is a lipoglycopeptide compound (di-[3-demethylaminopropyl] amide, N-alkylated at the aminoglucoronyl moiety). Dalbavancin inhibits bacterial cell wall synthesis by binding with the C-terminal D-alanyl-D alanine of the growing peptidoglycan chains [6], interfering with cross-linking and polymerization. Enhanced pharmacodynamic properties of the molecule, including lipophilic anchoring to the bacterial cell

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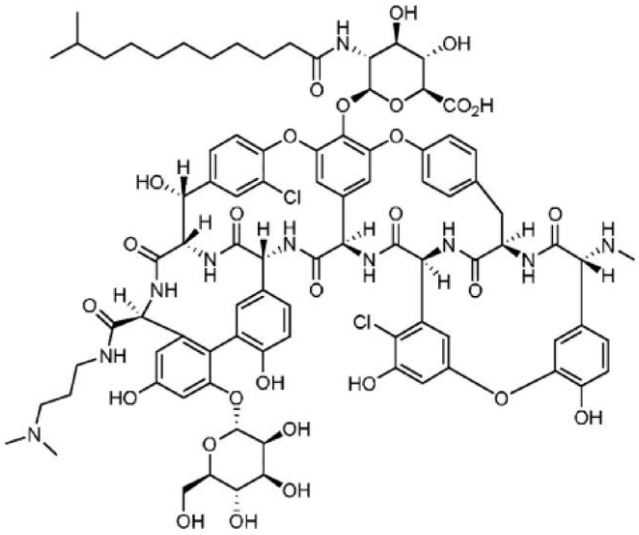

Figure 1. Chemical structure of dalbavancin. Reproduced from Lin et al. [5]. Reprinted with permission.

membrane, has conferred more potent in vitro activity than vancomycin or teicoplanin [7, 8]. An unusually long terminal half-life, ranging from 149 to 250 h in human subjects, allows for once-weekly dosing, a characteristic that makes outpatient intravenous therapy feasible in a manner not possible with agents requiring more-frequent dosing [9].

MICROBIOLOGY

The spectrum of in vitro activity of dalbavancin is similar to that of available glycopeptides, but dalbavancin is more potent than vancomycin against most pathogens (table 1) [7, 10, 14, 16, 21–23]. Streit et al. [7] demonstrated dalbavancin's superior in vitro activity in >6000 gram-positive pathogens collected from worldwide sites with MIC values ranging from 0.015 to 32 μg/mL. The MIC_{90} of dalbavancin was noted to be 0.06 μg/mL for *S. aureus* and coagulase-negative staphylococci resistant to multiple antimicrobial agents. Dalbavancin has potent in vitro activity against glycopeptide-intermediate *S. aureus* strains (dalbavancin MIC_{90}, 0.06–1 μg/mL) [19] and linezolid-nonsusceptible *S. aureus* (MIC_{90}, 0.03–0.06 μg/mL) and has demonstrated activity against 1 of the 2 vancomycin-resistant *S. aureus* Hershey-Pennsylvania USA strains (MIC_{90}, 0.5 μg/mL) [20].

The activity of dalbavancin against vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium* is similar to that of teicoplanin but more potent than that of vancomycin. Dalbavancin maintains activity against strains of VRE expressing *vanB* and *vanC* gene products but is inactive against VRE expressing *vanA* [10, 14, 16]. Dalbavancin is highly active against viridans group streptococci and penicillin-susceptible and penicillin-nonsusceptible *Streptococcus pneumoniae* [21]. Goldstein et al. [22] demonstrated dalbavancin's excellent activity against a variety of gram-positive anaerobic species, fastidious aerobes, and *Corynebacterium* species, with the notable exceptions of *Clostridium clostridioforme* and certain *Lactobacillus* species. Dalbavancin, like other glycopeptides, is not active against gram-negative bacteria.

Dalbavancin is bactericidal against *S. aureus* and coagulase-negative staphylococci at 4 times the MIC after 24 h; the lack of carry-over effect is shown to have little killing at earlier periods (3–12 h) [20].

PHARMACOKINETICS

The pharmacokinetics and tissue distribution of dalbavancin were studied in a rat model in which a 20 mg/kg dose of dalbavancin or [^{3}H] dalbavancin was administered and blood, urine, bile, feces, and tissue concentrations were determined [24]. The distribution of dalbavancin was consistent with a 3-compartment model with elimination from the central compartment. The half-lives of the elimination phases were 0.18 h for the initial phase ($t_{1/2\alpha}$), 11.4 h for the intermediate phase ($t_{1/2\beta}$), and 187.4 h ($t_{1/2\gamma}$) for the terminal phase [24]. The volume of distribution was 0.52 L/kg, with an area under the curve of 3194.2 L/mg/h and total plasma clearance of 6.3 mL/kg/h. Dalbavancin undergoes dual elimination via urine and feces. The distribution of dalbavancin was studied in 40 different tissues [24]. The highest concentrations were found in the kidney and liver 24 h after dosing. Most tissues continued to retain concentrations greater than that in plasma by day 3 after dosing; kidneys, liver, brown fat, skin, and skeletal muscle continued to have measurable concentrations at day 14. Dalbavancin was not selectively retained by any organ or tissue.

The tolerability and pharmacokinetics of dalbavancin were studied in a group of healthy volunteers in a dose ranging study [25]. Volunteers were administered single doses of dalbavancin ranging from 140 mg to 1120 mg intravenously over 30 min or multiple doses with a loading dose to maintenance dose ratio of 10:1. The multiple-dose group received dosing regimens of 300 mg and 30 mg, 400 mg and 40 mg, 600 mg and 60 mg, 800 mg and 80 mg, and 1000 mg and 100 mg daily for 7 days. Dalbavancin was well tolerated at all doses in both the single-dose and multiple-dose groups. The dalbavancin maximum concentration and area under the curve increased proportionally with increasing doses, whereas the half-life and clearance remained unchanged [25]. The mean half-life was 181 h, with a renal clearance of 0.0157 L/h and overall clearance of 0.0472 L/h. Approximately 33% of the total dose was excreted in the urine.

The population pharmacokinetics of dalbavancin were studied in a cohort of 532 patients with SSTI (502 patients) and catheter-related bloodstream infection (30 patients) [26]. Seventy-eight percent of patients received dalbavancin in a 1000-

mg dose on day 1 and 500-mg dose on day 8. There was a linear relationship between body surface area and creatinine clearance and dalbavancin clearance. The half-life was 8.5 days, and the steady state volume of distribution was 15.7 L. This is consistent with the parameters found in healthy volunteers.

Renal excretion of dalbavancin was studied in a group of 6 healthy volunteers who received a single dose of dalbavancin (1000 mg intravenously administered over 30 min) [27]. Plasma and urine samples were collected for 42 days. The amount of the unaltered drug that was excreted into the urine was 42% of the administered drug after 42 days. This suggests that dosage adjustment in renally impaired individuals may not be necessary. Data on degree of removal of dalbavancin by hemodialysis or plasmapheresis are lacking at present.

Dalbavancin has also been studied in patients with mild, moderate, and severe liver impairment [28, 29]. Dalbavancin was administered to 26 individuals with varying degrees of hepatic impairment at a dose of 1000 mg, followed by a 500-mg dose administered 8 days later. There was no difference found in elimination half-life or clearance, indicating that a dosage adjustment in hepatic impairment is unlikely.

In an animal study using the murine thigh and lung infection model, Andes and Craig [30] showed that both the 24-h area under the curve to MIC and maximum concentration to MIC ratios correlated with in vivo efficacy in the treatment of *S. pneumoniae* and *S. aureus* infections.

CLINICAL EFFICACY

Animal infection models. Dalbavancin demonstrated bactericidal activity in a rat granuloma pouch infection model involving *S. aureus* (both methicillin-susceptible *S. aureus* and MRSA); these models also supported once-weekly dosing intervals based on prolonged half-life [31]. In an *S. pneumoniae* rat model involving immunocompetent and neutropenic rats, a single intravenous dose of dalbavancin (10 mg/kg) substantially reduced the bacterial load in lungs, compared with 6 doses of procaine penicillin G [32].

Dalbavancin was found to be more efficacious than vancomycin in treating staphylococcal septicemia in immunocompetent mice. A single daily dose of dalbavancin was equal to or better than multiple doses of vancomycin or teicoplanin in a staphylococcal endocarditis rat model [23]. Rabbit endocarditis models provided evidence of dalbavancin efficacy against *S. aureus,* including strains with reduced susceptibility to glycopeptides. Experiments in rabbits with foreign body infection due to *S. aureus* suggested dalbavancin's usefulness in the treatment and prevention of device-related infection [33].

These animal model data show dalbavancin's promise in the treatment of multidrug-resistant gram-positive bacteria, especially staphylococci and streptococci, with the exception of VRE-expressing *vanA* genes.

Clinical studies of dalbavancin. In a phase 2 clinical trial, 75 adult patients with catheter-related bloodstream infection caused by coagulase-negative staphylococci and *S. aureus,* including MRSA, were treated either with intravenous dalbavancin administered as a single 1-g dose, followed by a 500-mg dose 1 week later, or with intravenous vancomycin administered twice daily for 14 days. Overall success rates of 87% and 50% were noted with dalbavancin and vancomycin, respectively [34].

A phase 2 randomized, controlled, proof-of-concept trial was undertaken to compare 2 dalbavancin regimens with standard of care for treatment of SSTI. In the clinically evaluable population of 51 patients, subjects were randomized to 1 of 3 arms. Thirteen patients received dalbavancin intravenously as a single 1100-mg dose, 17 patients received dalbavancin intravenously at 1000 mg on day 1 and 500 mg on day 8, and 21 patients received prospectively defined standard of care treatment. The majority of the pathogens were *S. aureus,* of which ~38% was MRSA. Clinical success was observed in 94% of patients who received 2 doses of dalbavancin, compared with 76% of those treated with the comparators and 62% of those receiving a single dose of dalbavancin. Rates of microbiological eradication or presumed eradication paralleled rates of clinical success [35].

A recently completed phase 3, randomized, double-blind noninferiority study was performed to determine efficacy and safety of dalbavancin, compared with linezolid, in the treatment of adults with complicated SSTIs. A total of 854 patients with known or suspected complicated MRSA SSTI were randomized in a 2:1 manner to receive either dalbavancin at a dose of 1000 mg intravenously on day 1 followed by a 500-mg dose administered intravenously on day 8 or linezolid at a dosage of 600 mg intravenously or orally every 12 h for 14 days. Primary end point was defined as clinical success at test of cure (TOC) visit. Of patients with SSTI, 51% had infection due to MRSA. The overall success rate was similar between the 2 treatment groups at the end of therapy and at the TOC visit. Among the evaluable patients at TOC visit, 90% and 92% achieved clinical success in the dalbavancin and linezolid arms, respectively. The microbiological response paralleled the clinical results. MRSA eradication rates at TOC visit were 91% and 89% for dalbavancin and linezolid, respectively. Overall success rates were similar between the 2 treatment arms at end of therapy and TOC visit, thus conferring clinical relevance of noninferiority [36]. In other studies [37, 38], dalbavancin was compared with linezolid, vancomycin, and cefazolin for the treatment of *S. aureus* SSTI. In the microbiologically evaluable population, dalbavancin was associated with an eradication rate of 90%, compared with 82% for vancomycin.

SAFETY

Dalbavancin has been studied in >1000 individuals in phase 2 and 3 clinical trials. It has been well tolerated, and the adverse

Table 1. In vitro activity of gram-positive organisms and anaerobes against dalbavancin.

Organism, resistance profile, study(s)	No. of isolates	MIC_{90}, μg/mL	MIC range, μg/mL
Staphylococci			
Quinupristin-dalfopristin resistant [10]	8	NA	0.03–0.06
Vancomycin intermediate [10]	10	0.06	0.06–2.0
Staphylococcus aureus [11–14]	4243	0.06	≤0.008 to 0.5
Methicillin susceptible [7, 12–18, 20]	4838	0.06–0.5	≤0.008 to 0.5
Methicillin resistant [7, 12–18, 20]	2726	0.06–1.0	≤0.015 to 1.0
Glycopeptide intermediate [12, 18]	29	1.0–2.0	0.06–16
Linezolid nonsusceptible [12]	5	NA	0.03–0.06
Coagulase-negative *Staphylococcus* species [10, 12–14]	1775	0.06–0.12	≤0.008 to 1.0
Methicillin susceptible [7, 12–18, 20]	682	0.06–0.5	≤0.008 to 0.6
Methicillin resistant [7, 12–18, 20]	2100	0.06–0.5	≤0.008 to 1.0
Vancomycin nonsusceptible [12]	11	1.0	0.25–2.0
Teicoplanin resistant [10]	15	0.25	0.03–0.25
Staphylococcus epidermidis			
Methicillin susceptible [16, 18]	13	0.25–0.5	≤0.03 to 0.25
Methicillin resistant [16, 18]	12	0.25	≤0.03 to 1.0
Staphylococcus haemolyticus			
Methicillin susceptible [16]	10	0.13	≤0.03 to 0.25
Methicillin resistant [16]	12	0.5	≤0.03 to 4.0
Streptococcus pneumoniae [12–15, 21]	1422	≤0.03 to 0.06	0.004–0.125
Penicillin susceptible [7, 12–14, 16]	1647	0.016–0.06	0.004–0.06
Penicillin nonsusceptible [7, 10, 12–14, 16]	969[a]	≤0.016–0.03	≤0.008 to 0.25
Ceftriaxone resistant [9]	16	≤0.016	≤0.016 to 0.03
Streptococcus pyogenes [12, 16]	211	0.015	≤0.002 to 0.06
Erythromycin susceptible [12]	161	0.015	≤0.002 to 0.06
Erythromycin resistant [12]	45	0.015	≤0.002 to 0.06
Viridans group streptococci [12–15]	313	0.016–0.03	≤0.002 to 0.06
Penicillin susceptible [7, 12]	130	0.03	≤0.002 to 0.06
Penicillin nonsusceptible [7, 12, 16]	6[b]	0.03	≤0.008 to 0.06
Erythromycin susceptible [12]	21	0.03	≤0.002 to 0.03
Erythromycin resistant [12]	31	0.03	≤0.002 to 0.06
ß-Haemolytic streptococci [7, 12–15]	757	0.015–0.06	≤0.002 to 0.25
Streptococcus agalactiae [12]	52	0.015	0.008–0.06
Enterococcus species [13, 14]	2062	0.12–16	≤0.008 to > 16
Vancomycin susceptible [13–16]	1606	0.06–0.5	≤0.008 to 1.0
Vancomycin resistant [11, 13–15]	592	>16 to 32	≤0.015 to >32
Van A resistant [10, 16]	79	32 to >128	0.03 to >128
Van B resistant [10, 16]	21	0.12–1	0.02–2.0
Linezolid resistant [11]	9	NA	≤0.015 to >32
Enterococcus faecalis [7]			
Vancomycin susceptible [7]	586	0.06	≤0.015 to 4
Vancomycin resistant [7, 10]	34	32	≤0.015 to >32
Enterococcus faecium			
Vancomycin susceptible [7]	77	0.12	≤0.015 to 4
Vancomycin resistant [7, 10]	92	32	0.03 to >32
Quinupristin-dalfopristin resistant [10]	29	0.12[c]–8[d]	≤0.016 to >32
Actinomyces species [22]	38	0.5	0.03–0.5
Bacillus species [13, 15]	25	0.12–0.25	0.016–2.0
Clostridium species [22]	16	0.5	≤0.015 to 1.0
Clostridium difficile [22]	26	0.25	0.125–0.5

(continued)

Table 1. ***(Continued.)***

Organism, resistance profile, study(s)	No. of isolates	MIC_{90}, μg/mL	MIC range, μg/mL
Clostridium perfringens [22]	10	0.125	0.03–0.125
Corynebacterium species [13, 15, 22]	51	≤0.03 to 0.5	≤0.015 to 1
Corynebacterium jeikeium [15, 22]	20	0.5	≤0.03 to 0.5
Lactobacillus species [22]	23	>32	0.06 to >32
Listeria species [7]	NA	0.06	NA
Micrococcus species [13]	13	0.03	≤0.008 to 0.03
Peptostreptococcus species [22]	30	0.25	≤0.015 to 0.5
Propionibacterium species [22]	15	0.5	0.03–0.5

NOTE. Adapted from Lin et al. [5] with permission. NA, not available; Van A resistant, vancomycin-resistant enterococci possessing the *vanA* gene; Van B resistant, vancomycin-resistant enterococci possessing the *vanB* gene.

[a] Includes penicillin-nonsusceptible, penicillin-intermediate, and penicillin-resistant isolates.
[b] Includes penicillin-nonsusceptible and penicillin-resistant isolates.
[c] *vanA*–negative isolates.
[d] *vanA*–positive isolates.

effects have been similar to those associated with comparators. There is no known evidence of renal or hepatic toxicity related to dalbavancin therapy [38]. In clinical trials thus far, subjects receiving dalbavancin versus placebo reported similar rates of pyrexia and headaches [25].

The impact of dalbavancin on normal intestinal flora was studied in a group of 6 women and 6 men for 60 days following administration of a 1000-mg dose. There was little impact on the number of enterococci and *Escherichia coli* and no change in the number of lactobacilli, clostridia, and bacteroides. *Clostridium difficle* was not recovered. Dalbavancin does not appear to have a significant impact on normal intestinal flora [39].

Dalbavancin is not a substrate for the cytochrome p450 system. It is neither an inducer nor an inhibitor. No significant drug-drug interactions have been identified between dalbavancin and other medications.

DISCUSSION

As we engage in an evolving battle against pathogenic microbes, antimicrobial resistance continues to pose a significant problem with severe clinical and financial consequences. Although appropriate antimicrobial use and stewardship must be maximized, research and development of new agents with optimal efficacy, safety, and favorable pharmacokinetic and pharmacodynamic properties is crucial. Dalbavancin is a new lipoglycopeptide antimicrobial agent with a broad spectrum of activity against virtually all important gram-positive pathogens, with the exception of *vanA*–expressing VRE. Most importantly, it is a potent bactericidal agent against drug-resistant staphylococci. In animal models and clinical trials, dalbavancin has demonstrated efficacy in the treatment of SSTIs. Its unique pharmacokinetic properties render it particularly useful for outpatient therapy. There are no data to suggest clinical superiority over β-lactam antibiotics or linezolid for infections due to susceptible organisms, nor are there sufficient data on treatment of pneumonia or bone and joint infections to draw conclusions about dalbavancin's clinical usefulness for these indications. The prolonged mean half-life of 181 h in humans allows for convenient once-weekly dosing. Noninvolvement with the cytochrome p450 system makes drug-drug interactions unlikely. Although serious adverse events have not been noted in early clinical trials, this very property of prolonged half-life poses a unique challenge should adverse events occur.

Several other agents with in vitro activity against multidrug-resistant gram-positive bacteria have recently been licensed for use in the United States (e.g., daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline) or are under development (e.g., ceftobiprole, faropenem, iclaprim, oritavancin, and telavancin) [40]. As new therapeutic options for drug-resistant gram-positive cocci organisms evolve, controlled comparative studies will be necessary to define their usefulness, as has occurred with linezolid versus vancomycin for MRSA nosocomial pneumonia [41], febrile neutropenia in patients with cancer [42], and surgical site infections [43]. In addition to comparisons of efficacy and safety, economic analyses of their impact will be helpful and interesting. The potential long-term savings of dalbavancin—associated with avoidance or shortening of hospitalization and avoidance of long-dwell intravenous lines and the attendant line infection risks—will have to be balanced against its cost.

In conclusion, dalbavancin is a welcome and promising addition to our available options in combating drug-resistant gram-positive pathogens. The promise of once-weekly intravenous dosing is exciting in terms of patient convenience and possible cost savings. The development of new agents, such as dalbavancin, along with the education of patients and health

care providers regarding appropriate antibiotic stewardship, will be key investments for the future of antimicrobial therapy.

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