Dalbavancin: A Review of Its Use in the Treatment of Gram-positive Infections

Kristin H. Busse¹, Kate M. Oltrogge², Carolyn J. Oxencis³ and William J. Peppard⁴

¹Investigational Drug Pharmacist, Froedtert Hospital, Milwaukee, Wisconsin, USA. ²Critical Care Pharmacy Resident, Froedtert Hospital, Milwaukee, Wisconsin, USA. ³Neurosurgical Critical Care Pharmacist, Froedtert Hospital, Milwaukee, Wisconsin, USA. ⁴Surgical Critical Care Pharmacist, Froedtert Hospital, Milwaukee, Wisconsin, USA.

Abstract: Dalbavancin is an intravenous semisynthetic lipoglycopeptide which has demonstrated potent in vitro activity again most clinically significant Gram-positive pathogens such as methicillin-resistant Staphylococcus aureus, vancomycin-intermediate Staphylococcus aureus, and some vancomycin-resistant Enterococci. The long half-life of dalbavancin allows for once weekly dosing. In published clinical trials, a dose on day 1 and 8 of treatment provided 14 days of antimicrobial activity. In clinical trials, dalbavancin has demonstrated non-inferiority as measured by safety and efficacy for the treatment of uncomplicated skin and skin structure infections (Phase II as compared to cefazolin), catheter-related bloodstream infections (Phase II as compared to vancomycin), and complicated skin and skin structure infections (Phase III as compared to linezolid). Due to feedback from the Food and Drug Administration, all marketing has been withdrawn and an additional phase III trial is currently underway; therefore the future for dalbavancin is unclear. An acquisition cost has not yet been projected; consequently pharmacoeconomic analyses are not yet underway.

Keywords: antibiotic, resistance, lipoglycopeptide, gram-positive, MRSA, VRE


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Introduction

Increasing resistance of Gram-positive bacteria to antimicrobials remains a constant public health burden, and development of new antimicrobials must remain a top priority to continue treatment of infections caused by these resistant strains. In 2004, the LEADER program in the United States identified a rate of 54.2% of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from 50 labs in 33 states. Similarly, 2007 data revealed a resistance rate of 58.1% for MRSA.1

Additionally, concern is growing for the emergence of community-associated MRSA (CA-MRSA), which is associated with infections in patients without recent history of hospitalization.1 Of note is the difference in resistance profiles between the epidemic hospital MRSA strains and the CA-MRSA strains. Typically, CA-MRSA is only resistant to β-lactam antibiotics; while hospital-acquired MRSA frequently includes resistance to fluoroquinolones, macrolides, tetracyclines, and aminoglycosides, in addition to β-lactams.1 Furthermore, the emergence of *S. aureus* with decreased susceptibility to vancomycin (vancomycin-intermediate *S. aureus* [VISA]) and the increased prevalence of vancomycin-resistant Enterococci (VRE) have prompted the need for development of antimicrobials with activity against these resistant Gram-positive strains.

Due to the growing need for antimicrobials to treat emerging infectious diseases, several new drugs have been developed to fight the increasing threat of MRSA (and other Gram-positive bacteria). Linezolid, daptomycin, and tigecycline have all been approved by the Food and Drug Administration (FDA) within the last several years for various indications in the battle against resistant Gram-positive infections.3–5 Development of antibacterial agents with unique properties has continued with the addition of dalbavancin to the armamentarium. The FDA issued an approvable letter for dalbavancin for the treatment of skin and skin-structure infections in December 2007.6 With its unique pharmacokinetic profile, increased *in vitro* potency, and clinical efficacy and tolerability, dalbavancin appears to be a viable alternative for treating resistant Gram-positive infections. This article reviews the pharmacokinetics, clinical efficacy, safety, and place in therapy of dalbavancin.

Pharmacokinetics

Glycopeptide antibiotics inhibit bacterial cell-wall synthesis by binding to terminal D-alanyl-D-alanine residues exclusive to bacterial cell-wall precursors.7 Hydrophobic interactions and hydrogen bonding instigate a stable complex between the glycopeptide and the peptidoglycan precursors, disrupting initiation of the nascent peptidoglycan backbone chains.7 Dalbavancin is a semisynthetic lipoglycopeptide derived from a naturally occurring glycopeptide produced by actinomycete *Nonomurcia* species, A40926. Improved antimicrobial potency occurs from the long, lipophilic side chain on the heptapeptide backbone, resulting in a membrane anchor which allows for enhanced binding and improved antimicrobial efficacy.9 Hence, dalbavancin is considered a second-generation glycopeptide.

Dalbavancin is poorly absorbed after oral administration and is only available as an intravenous preparation.9 The maximum plasma concentration (C_{max}) occurs immediately following the end of infusion and is also linear and dose proportional.10 Distribution occurs as a log-linear decline over 12 hours, eventually distributing into a volume of approximately 8 to 12 liters.9,10 The pharmacokinetic profile is best described as a two-compartment model with first-order elimination.9,11 Dalbavancin binding to plasma proteins is approximately 93% and reversible.10

Dalbavancin is not a substrate for, an inhibitor of, or an inducer of the cytochrome P-450 (CYP) hepatic isoenzyme system.9,10 The terminal elimination half-life (t_{1/2}) ranges from 149–198 hours (mean, 181 hours) which greatly exceeds the t_{1/2} of vancomycin (4–6 hours).9,10,12 Dalbavancin’s elimination occurs both renally and non-renally. The total body clearance (CL), in healthy volunteers, of dalbavancin was approximately 0.047 L/h; however, the renal clearance was 0.015 L/h.13 Renal excretion accounts for approximately 33% (range, 25%–45%) of the total dose, mostly recovered from the urine as intact drug.13

Dosage adjustment for mild-to-moderate hepatic impairment, mild-to-moderate renal impairment, or end-stage renal dysfunction requiring dialysis is not required.14 Dalbavancin concentrations were increased in subjects with severe renal dysfunction (CL_{cr}, <30 mL/min) but not receiving dialysis, thus
indicating the potential need for dose adjustment in this population. Specific dose recommendations are not yet available for this population.

**Spectrum of Activity and Resistance**

Though no interpretive breakpoint has been established by the Clinical and Laboratory Standards Institute, breakpoints have been proposed to be MIC ≤ 1 mcg/ml for Staphylococci and MIC ≤ 2 mcg/ml for Streptococci. Dalbavancin has demonstrated low minimum inhibitory concentrations (MICs) against most clinically significant Gram-positive pathogens such as Staphylococci including MRSA, Enterococci including VRE (except VanA isolates), Streptococci pneumoniae (both penicillin- and ceftriaxone-resistant), and coagulase-negative Staphylococci. Additionally, dalbavancin maintained good in vitro activity against Staphylococci that harbor decreased susceptibility to glycopeptides, quinupristin/dalfopristin, and linezolid. Data specific to the development of dalbavancin-resistance or cross-resistance between dalbavancin and other antimicrobials are limited. The emergence of isolates with elevated dalbavancin MICs was not observed in Phase II or III trials.

**Clinical Trials**

**Animal**

Dalbavancin was evaluated along with teicoplanin and vancomycin in rats infected with methicillin-susceptible *S. aureus* (MSSA) and MRSA, penicillin-susceptible and penicillin-resistant *S. pneumoniae*, *S. epidermidis*, and *E. faecalis*. Dalbavancin had similar effectiveness to teicoplanin and was more efficacious than vancomycin in rat models of MRSA septicemia and *S. pneumoniae* infections. Dalbavancin was more active than teicoplanin and vancomycin against *S. epidermidis*, but inferior to teicoplanin in infections with vancomycin-susceptible *E. faecalis*. In a rat endocarditis model, dalbavancin was as effective as vancomycin against strains of *S. aureus* and *S. epidermidis* with less frequent administration. Dalbavancin reduced bacterial loads in models of lung infection in both immunocompetent and neutropenic rats. Dalbavancin successfully treated infections caused by both MSSA and MRSA in a rodent pouch infection model using a once-weekly dosing regimen. Rabbit endocarditis models have shown dalbavancin’s activity against strains of *S. aureus* with reduced susceptibility to other glycopeptides.

Experiments in rabbits with foreign body colonization and infection caused by strains of *S. aureus* suggest a potential benefit using dalbavancin in the treatment and prevention of device-related infections. Results from these animal models of infection established the groundwork for use of dalbavancin in humans.

**Human**

In a Phase II, randomized, controlled, open-label, proof-of-concept multicenter trial, 51 clinically evaluable adult patients with uncomplicated skin and soft tissue infections (uSSTI) caused by Gram-positive organisms (including both MSSA and MRSA) were randomized to receive either a one-time 1100 mg intravenous dose of dalbavancin (n = 13), a two-dose regimen of 1000 mg of dalbavancin on day 1 and 500 mg of dalbavancin on day 8 (n = 17), or a standard-of-care comparator regimen (n = 21) predetermined by the investigator. The primary efficacy endpoint was improvement, clinical cure, or failure based on clinical and microbiological data at a follow up visit. Clinical success rates measured during follow-up visits were 94% among patients treated with 2 doses of dalbavancin, 76% among patients treated with a standard-of-care regimen, and 62% among patients treated with one dose of dalbavancin; rates of microbiologic success paralleled those of clinical response. This trial showed dalbavancin was efficacious in treating adults with uSSTI caused by Gram-positive organisms (including those with MRSA) utilizing a once weekly two-dose dalbavancin regimen.

Dalbavancin was compared to vancomycin in a Phase II, randomized, controlled, open-label, multicenter trial in 75 adult patients with catheter-related bloodstream infections (CR-BSI) caused by Gram-positive organisms, including coagulase-negative Staphylococci and *S. aureus* (both MSSA and MRSA). A regimen of intravenous dalbavancin 1000 mg dose on day 1 followed by a 500 mg intravenous dose on day 8 was compared with intravenous vancomycin 1000 mg twice daily for 14 days. The primary endpoint was overall efficacy based on clinical and microbiological data at a follow up visit. Among the 51 subjects in the microbiologically confirmed intention-to-treat population, clinical success rates
were 87% among patients treated with dalbavancin and 50% in patients treated with vancomycin. Results of this trial demonstrated superiority of dalbavancin when compared with vancomycin for treatment of CR-BSI caused by various Gram-positive organisms including MRSA.

A Phase III, randomized, double-blind, multicenter, noninferiority study was conducted comparing dalbavancin with linezolid for the treatment of complicated skin and soft tissue infections (cSSTI) in 854 adult patients. Participants were randomized in a 2:1 fashion to receive either a two dose regimen of 1000 mg of dalbavancin on day 1 and 500 mg of dalbavancin on day 8 (n = 578) or linezolid 600 mg every 12 hours for 14 days (n = 283). The primary efficacy endpoint was clinical success at a follow-up test of cure visit. Among the 660 patients deemed clinically evaluable, clinical success was achieved in 92% of patients treated with dalbavancin and 90% of patients treated with linezolid; rates of microbiologic success paralleled those of clinical response. This trial demonstrated dalbavancin was as effective as linezolid for treatment of patients with cSSTI (including those infected with MRSA) and established non-inferiority. Two additional phase III trials, comparing dalbavancin to cefazolin for uSSTI and vancomycin for cSSTI, have been completed but are currently in abstract form and not yet published.

**Safety**

Clinical studies demonstrate dalbavancin to be well-tolerated by study patients. Most adverse drug events (ADEs) have been mild to moderate in severity. No dalbavancin-associated deaths have been reported in clinical trials.12,26,27,30,31

In a Phase I double-blind, placebo-controlled trial, Leighton et al reported on healthy subjects (n = 39) who were randomized to receive a single- or multiple-dose regimen of dalbavancin or placebo.12 In the single-dose group, doses of dalbavancin ranged from 140–1120 mg. Multiple-dose regimens consisted of a loading dose followed by six daily doses equal to one-tenth of the loading dose with doses ranging from 300:30 to 1000:100 mg. No serious ADEs or deaths were reported, and no dose-limiting ADEs or laboratory abnormalities were observed. The most common ADEs reported in the dalbavancin groups were pyrexia (50%), headache (25%), and nausea (6%). The placebo group reported similar rates of pyrexia (38%) and headache (31%). One subject who received a single 350 mg dose of dalbavancin experienced mild (less than 5-times the upper limit of normal) elevations in alanine aminotransferase and aspartate aminotransferase, which were asymptomatic and transient. One subject experienced hyperglycemia (blood glucose level greater than 160 mg/dl) in the dalbavancin group and one in the placebo group had mild hyperglycemia (blood glucose greater than 135 mg/dl). Overall, there were no clinically significant changes from baseline with laboratory findings, vital signs, physical examinations, or electrocardiograms.

Audiologic monitoring was completed on the subjects reported by Leighton et al but were published separately. All subjects underwent two baseline audiologic assessments two days prior to drug (or placebo) administration. Audiologic assessments were then repeated in the single-dose group on days 2, 7, and 14, and on days 2, 7, 14, and 21 for the multiple-dose group. No auditory or vestibular ototoxicity was observed.

In two Phase II trials, both employing a dalbavancin regimen consisting of a single 1000 mg dose followed by 500 mg one week later, therapy was well tolerated with ADE rates similar to comparator.26,27 No serious ADEs were attributed to the study drug in either trial, and no patients discontinued dalbavancin therapy during treatment due to ADEs. The first of the two Phase II trials consisted of 62 patients with uSSTI.26 Most ADEs attributed to dalbavancin were considered to be mild to moderate in severity. Drug-related ADEs were reported in 11 patients (55%) who received a single 1100 mg dose of dalbavancin, 10 patients (48%) who received multiple doses of dalbavancin, and 12 patients (57%) who received comparator regimens. There were no clinically meaningful laboratory changes in the dalbavancin study group, and treatment was not stopped early due to an ADE. The second trial evaluated 33 patients with CR-BSI.27 The most common treatment-related ADEs reported for dalbavancin were diarrhea (21.2%), pyrexia (18.2%), constipation (18.2%), and oral candidiasis (12.1%). No ADEs resulted in withdrawal from the study or discontinuation of dalbavancin. The incidence of laboratory changes was low and similar between the treatment and control groups, with anemia (18.2%) and hypokalemia (18.2%) being the most common. The most
common ADEs reported in the control (vancomycin) group were oral candidiasis, loose stools, fungal infections of the skin and vaginal area, acute renal failure, and renal impairment.

In a Phase III study comparing dalbavancin to linezolid for the treatment of cSSTI, similar results were seen with regards to safety and tolerability. ADEs were reported in 56% of the patients receiving dalbavancin and 61% of the patients receiving linezolid; in both cases ADRs were generally mild or moderate. ADEs that were considered to be possibly or possibly related to treatment were more frequent in the linezolid group (32.2%) than in the dalbavancin group (25.4%). The median duration of ADEs was 1 day shorter for the dalbavancin group than the linezolid group, however, the mean duration of ADEs was similar between the two. The types of ADEs reported were similar, with the most common being nausea (3.2% versus 5.3%) and diarrhea (2.5% versus 5.7%) for dalbavancin and linezolid, respectively. Thrombocytopenia was higher in the linezolid arm (2.5%) than the dalbavancin arm (0.2%). Of the serious ADEs reported (8%), only 3 were considered to be related to the study medication (1 in the dalbavancin arm and 2 in the linezolid arm) and pertained to laboratory abnormalities. The serious ADE that occurred with dalbavancin was a case of mild leukopenia, which resolved spontaneously.

The effects of dalbavancin on normal intestinal flora were investigated in 12 healthy subjects who received a single 1000 mg dose. Plasma and fecal samples were collected over a 60-day period. Dalbavancin was found to have some impact on the aerobic and anaerobic microflora, but the authors concluded that it was not significant. There was an increase in the numbers of Enterococci and Escherichia coli, but no specific changes in colonization were found. There were no significant changes on anaerobic intestinal microflora (Lactobacilli, Clostridia, and Bacteroides).

**Patient Preference**

Patient preference, usually related to acquisition cost and ADR profile, is often considered when selecting a particular agent over another for the treatment of chronic disease states. This is less often a consideration with antimicrobials when used to treat acute and sometimes life-threatening infections. While these factors should still be considered by the practitioner, patient preference is not necessarily made a priority.

**Place in Therapy**

The broad spectrum and potent *in vitro* activity make dalbavancin an attractive antimicrobial agent. If FDA approved, it will likely serve as an alternative to other antimicrobials which possess activity against MDR Gram-positive pathogens, including quinupristin-dalfopristin, linezolid, daptomycin, and vancomycin which are currently included in treatment guidelines for cSSTI. A new drug application was filed in 2004, resulting in an approvable letter from the FDA in 2007, though the future of this drug remains unclear. Following additional feedback from the FDA, Pfizer announced in September 2008 that it will withdraw all dalbavancin marketing applications for the treatment of cSSTI in adults, including the U.S. new drug application and the European marketing authorization application.

Durata Therapeutics, Inc., a recently formed biopharmaceutical company, acquired dalbavancin from Pfizer, Inc. in December 2009 and plans to continue development with an additional phase III trial evaluating dalbavancin for the treatment of cSSTI. Once approved, this is expected to be dalbavancin’s first indication, then likely followed by CR-BSI. Given this delay, it is unlikely dalbavancin will be included in the updated treatment guidelines for cSSTI which are currently in progress.

The once-weekly dosing regimen with dalbavancin’s prolonged $t_{1/2}$ makes this antimicrobial an interesting formulary consideration. Acquisition price will play a major role in the success of this agent. No cost data are currently available, though one might expect the pricing to be competitive with its branded competitors but more expensive than generic alternatives. In the inpatient setting, there is a general reluctance to use long-acting agents which provide pharmacotherapy beyond the inpatient stay, due to economically disadvantageous reimbursement. However, this barrier may be overcome if an appropriate drug development and marketing strategy is implemented. For example, a pharmacoeconomic analysis, which demonstrates a cost saving as compared to the standard of care by decreasing length of hospital stay and/or total treatment cost irrespective of drug acquisition cost, would be beneficial.

The outpatient setting represents a market in which lies great potential for this agent. In contrast
to other intravenous alternatives for the treatment of Gram-positive infections, dalbavancin’s long $t_{1/2}$ allows a patient to receive a full course of intravenous therapy in as little as two doses with minimal therapeutic drug monitoring. This regimen may be advantageous for treatment in home healthcare, outpatient office visits, outpatient infusion clinics, or even the emergency department. Economic considerations in the outpatient setting may include improved compliance, reduction in the use of ambulatory resources, and overall improved efficiency of care.

An oral formulation of dalbavancin is not available, nor is there one in development. Currently, oral alternatives are available for the treatment of infections caused by MRSA, and to a lesser extent, VRE. This may push prescribers to utilize this agent for more difficult infections where an oral agent may not be generally accepted.

In the setting of increasing microbial resistance and a dwindling antibiotic pipeline, only a few anti-microbial agents with potent Gram-positive activity are currently in development. These include the glycopeptides telavancin and oritavancin, the cephalosporins ceftobiprole and ceftarolene, and iclaprim, a dihydrofolate reductase inhibitor. Of these agents, all of which have been evaluated for the treatment of cSSTI, telavancin shows the most promise and is the closest to market.

Summary
Dalbavancin, an intravenous semisynthetic lipoglycopeptide, has demonstrated potent in vitro activity against most clinically significant Gram-positive pathogens, including multi-drug resistant pathogens such as MRSA, VISA, and to a lesser extent VRE. In two published phase II and one published phase III trials, dalbavancin was non-inferior to cefazolin for the treatment of uSSTI, vancomycin for the treatment of CR-BSI, and linezolid for the treatment of cSSTI. Safety and tolerability of dalbavancin were similar to comparator in the aforementioned trials and the drug was generally well tolerated. Two additional phase III trials comparing dalbavancin to cefazolin for uSSTI and vancomycin for cSSTI have been completed but are not yet published. The long $t_{1/2}$ of dalbavancin allows for once-weekly dosing, a characteristic unique to dalbavacian. Currently, all marketing has been withdrawn and an additional phase III trial is underway; therefore the future for dalbavancin is unclear. If dalbavancin is to gain acceptance, practitioners will need to be provided with both robust outcome data and sound pharmacoeconomic analyses.

Disclosures
This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

References
Dalbavancin and gram-positive infections


