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## Dalbavancin: A Novel Treatment for Acute Bacterial Skin and Skin-Structure Infections

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An increasing prevalence of antibiotic resistance has created a demand for new antimicrobial agents in recent years. In particular, *Staphylococcus aureus* resistance to methicillin – so called, MRSA – has increased substantially in the United States as evidenced by increasing levels of MRSA among both hospital and community isolates.<sup>1-3</sup> In 2005, direct costs alone for MRSA may have been as much as \$9.7 billion.<sup>4</sup> This surge in MRSA resistance in particular has led to clinical failures from standard treatments along with increased morbidity and mortality.<sup>5-8</sup> Skin and soft tissue community-acquired MRSA infection can progress and cause severe diseases and morbidity, including necrotizing pneumonia, osteomyelitis, urinary tract infections, infective endocarditis, and sepsis.<sup>2,9-15</sup> The currently available intravenous treatment options for MRSA infections include vancomycin, linezolid, tedizolid, quinupristin-dalfopristin, daptomycin, ceftaroline, clindamycin, telavancin, minocycline, and tigecycline. However, these agents are associated with significant adverse effects, inconvenient administration typically requiring an inpatient stay, and importantly, treatment resistance, which has been documented with all of these agents.<sup>16-20</sup> Thus, new antimicrobials are needed to address these concerns.

Dalbavancin (DALVANCE™) received an FDA-approved indication for the treatment of acute bacterial skin and skin-structure infections

(ABSSSIs) on May 23, 2014. Dalbavancin's antimicrobial coverage includes *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus*–group organisms. This novel lipoglycopeptide belongs in the same class of drugs as vancomycin but does not require the labor-intensive serum concentration monitoring. Dalbavancin is administered once weekly as a two-dose regimen, and is being marketed as a potential outpatient alternative to the existing therapies.

The IDSA published updated guidelines for the treatment of SSTIs in June 2014. This update was a response to the recent spike in SSTIs caused by MRSA, and inappropriate management of the infection.<sup>29</sup> The guideline notes the role of dalbavancin in the treatment of mild and severe purulent SSTI caused by *Staphylococcus aureus*, including infections caused by MRSA.<sup>29,30</sup>

The purpose of this article is to provide an overview of the pharmacology, pharmacokinetics, clinical trials, adverse events and dosing considerations of dalbavancin.

### CLINICAL PHARMACOLOGY

Dalbavancin is a semisynthetic lipoglycopeptide, derived from a teicoplanin-like antibiotic, and belongs to the same class of drugs as vancomycin and telavancin. All glycopeptides have a heptapeptide core responsible for inhibiting cell

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wall synthesis in gram-positive bacteria by hindering peptidoglycan synthesis.<sup>22</sup> However, key structural differences in dalbavancin enhance antimicrobial activity compared to teicoplanin. Specifically, amidation of the peptide carboxyl group increases potency and activity against staphylococci, including coagulase-negative staphylococci (CoNS). Furthermore, dalbavancin's extended side chain increases the half-life of this drug, which allows once-weekly dosing. The side chain also improves the affinity of the drug to the microbial membrane.<sup>22</sup> **Table 1** highlights the pharmacokinetic properties of dalbavancin and compares other glycopeptides.

### Pharmacokinetics

Dalbavancin is not well absorbed orally and thus requires intravenous administration. This glycopeptide has a very long half-life, ranging from 147 to 258 hours.<sup>22</sup> Dalbavancin's extensive protein-binding with albumin ( $\geq 93\%$ ) contributes to this sustained half-life and therefore allows for an extended dosing interval.

Dalbavancin achieves good tissue penetration. Studies have demonstrated its ability to reach 60% tissue penetration in blisters, a noteworthy increase from vancomycin (31% to 55%) and linezolid (31%).<sup>3,4</sup> A standard initial dose of 1,000 mg achieves a maximum plasma concentration (C<sub>max</sub>) of 278.3-301 mg/L. Dalbavancin's mean area under the concentration-time curve (AUC) is 23,843 mg•h/L. The steady state apparent volume of distribution ranges from 11.2 L to 13.8 L.<sup>21</sup>

Adolescent population (12-16 years of age) typically achieves a lower C<sub>max</sub> compared to adults. In adolescent patients who received 1000 mg of dalbavancin intravenously or 15 mg/kg in

patients less than 60 kg, the C<sub>max</sub> was 26.1% and 33.4% lower, respectively, than the C<sub>max</sub> reached in adult patients.<sup>21</sup>

Following administration of a single 1000 mg dose in healthy subjects, 20% of the dose was excreted in feces through 70 days post-dose. An average of 33% of the administered dalbavancin dose was excreted in urine as unchanged dalbavancin and approximately 12% of the administered dose was excreted in urine as the metabolite hydroxy-dalbavancin through 42 days post-dose.<sup>21</sup>

### Resistance Patterns

Dalbavancin maintains stable activity against pathogens commonly causing ABSSSI. The most current potency profile published in 2012 highlights dalbavancin's consistently low MIC, indicating a low propensity towards antimicrobial resistance.<sup>28</sup>

Dalbavancin's MIC<sub>50/90</sub> against staphylococci remained low ( $\leq 0.03-0.06/0.06-0.12$  µg/mL) in this update. Only methicillin-resistant CoNS strains presented with a higher MIC<sub>90</sub> value of 0.12 µg/mL. MIC values for MRSA and Methicillin-sensitive *Staphylococcus aureus* (MSSA) remains at 0.06/0.06 µg/mL after more than 10 years.<sup>28</sup>

Although dalbavancin has good activity with gram-positive pathogens, activity against enterococci varies depending on the individual strain. Vancomycin-susceptible strains of *E. faecalis* or *E. faecium* maintained dalbavancin MIC values of 0.25 µg/mL or lower. Vancomycin-resistant Enterococcus (VRE) VanB phenotypes had very low MICs of under 0.12 µg/mL. However, VanA enterococci surpassed MIC values greater than 4 µg/ml.<sup>7,24,28</sup>

**Table 1 | Pharmacokinetic parameters of glycopeptide antibiotics used in MRSA treatment<sup>22</sup>**

Parameter	Dalbavancin	Telavancin	Oritavancin	Vancomycin
Dose	1 g day 1; 500 mg day 8	10 mg/kg od	3mg/kg od	15 mg/kg bid
C <sub>max</sub> (mg/L)	278.3-301	88	29	20-50
AUC (mg•h/L)	23,843	858	146	260
Vd (L/kg)	0.11	0.1	0.65-1.92	0.3
Protein binding (%)	93-98	90-93	86-90	10-55
Terminal half-life	147-258	7-9	398	4-8

Vd, volume of distribution; AUC, mean area under the concentration-time curve; C<sub>max</sub>, maximum plasma concentration; od, once daily; bid, twice daily

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## CLINICAL TRIALS

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The DISCOVER 1 and DISCOVER 2 studies were noninferiority trials comparing dalbavancin to vancomycin or linezolid for the treatment of ABSSSIs.<sup>23</sup> These double-blind, double-dummy, international, multicenter, randomized control trials were similarly designed to allow pooling of the data. The primary endpoint was early clinical response (ECR), defined as absence of fever at 48 to 72 hours and a lack of infection-related erythema spread.

Patients enrolled in these studies required diagnosis of ABSSSI, defined as the presence of cellulitis, a major abscess, or a wound infection, each associated with at least 75 cm<sup>2</sup> of erythema. Eligible patients were those requiring ≥3 days of therapy and having ≥1 systemic sign(s) of infection within 24 hours before randomization. Signs of infections included elevated body temperature (>38°C), a white blood cell (WBC) count >12,000 cells/cm<sup>3</sup>, or >10% bands on differential count of WBCs. At least two local signs were required in addition to erythema: purulent drainage or discharge, fluctuance, heat or localized warmth, tenderness on palpation, and swelling or induration. Patients were excluded if they had a history of antibiotic use within 14 days prior to treatment assignment.<sup>23</sup>

Patients in the dalbavancin arm were administered 1000 mg of dalbavancin on day 1, and a second dose of 500 mg on day 8, intravenously. Patients in the vancomycin treatment arm either received a fixed dose of 1000 mg or 15 mg per kilogram of body weight, depending on the institution's standard of care. Vancomycin was administered by intravenous infusion every 12 hours for 3 to 14 days. Vancomycin-treated patients could be switched to oral linezolid, 600 mg every 12 hours, if they had 4 consecutive temperature readings of 37.6°C or less, separated by 6 hours, along with improved clinical signs of the infection. Patients in the dalbavancin arm received a placebo infusion every 12 hours, or an oral placebo if they were switched to the linezolid therapy.<sup>23</sup>

In the analysis of the primary endpoint of Early Clinical Response (ECR) at 48-72 hours, both trials concluded dalbavancin was noninferior to the regimen of vancomycin/linezolid.<sup>23</sup> In addition,

both trials met their primary endpoint. Specifically, in DISCOVER 1, the dalbavancin arm had 240 out of 288 (83.3%) patients achieving ECR, while the vancomycin/linezolid arm had ECR in 233 out of 285 (81.8%) patients, for a difference of 1.5% (95% CI, -4.6% to 7.9%). In DISCOVER 2, the dalbavancin arm had 285 of 371 (76.8%) patients achieving ECR, while the vancomycin/linezolid arm had ECR in 288 of 368 (78.3%) patients, also achieving a difference of 1.5% (95% CI, -7.4% to 4.6%). The lower limit of each confidence interval for determining noninferiority was -10%; thus, dalbavancin was considered noninferior to the vancomycin/linezolid group in each trial.

Data from the pooled analysis showed successful outcomes in 525 of 659 (79.7%) patients in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin/linezolid, at 48 to 72 hours (difference, 0.1%; 95% CI, -4.5% to 4.2%). The success rate at 48 to 72 hours of achieving at least a 20% reduction in infected area was similar for both arms: 584 of 659 (88.6%) of dalbavancin-treated patients versus 575 of 653 (88.1%) of vancomycin/linezolid-treated patients.<sup>23</sup>

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## ADVERSE EVENTS

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Adverse events from DISCOVER 1 and DISCOVER 2 are summarized in **Table 2**. The most common adverse events seen in the dalbavancin and vancomycin/linezolid groups were nausea (2.5% and 2.9%, respectively), diarrhea (0.8% and 2.5%, respectively;  $p=0.02$ ), and pruritus (0.6% and 2.3%, respectively;  $p=0.01$ ). An infusion-related reaction occurred in 9 (1.4%) patients treated with dalbavancin and 11 (1.7%) patients treated with vancomycin/linezolid. Infusion-related reactions primarily resulted from indwelling catheters required for placebo infusions. Flushing occurred in 1 (0.2%) patient in the dalbavancin arm and 4 (0.6%) patients in the vancomycin-linezolid arm.

Serious adverse events were reported in 17 of 652 (2.6%) patients in the dalbavancin arm and 26 of 651 (4.0%) in the vancomycin/linezolid arm ( $p=0.16$ ). Treatment-related serious adverse events in the dalbavancin group included cellulitis in one patient and anaphylactoid reaction in one patient. In the vancomycin/linezolid group, treat-

ment-related serious adverse events included cellulitis, gastrointestinal disorder, toxic nephropathy, and acute renal failure in one patient each. Death occurred in one (0.2%) patient treated with dalbavancin and in 7 (1.1%) patients treated with vancomycin/linezolid (p=0.03).

### DOSING AND ADMINISTRATION

Dalbavancin is administered via IV infusion over 30 minutes at a dose of 1000 mg on day 1 and 500 mg on day 8.<sup>21</sup> Dose adjustments are not necessary for mild-to-moderate renal impairment. In patients with a creatinine clearance <30 mL/min and not receiving hemodialysis treatment regularly, the recommended dose adjustment is 750 mg as the initial dose followed by 375 mg one week later. Dose adjustments are not required in patients receiving regular hemodialysis.<sup>21</sup>

Mild hepatic impairment, defined as a Child-Pugh Class A, does not require dose adjustments. Currently, data are not available to determine dose adjustments for moderate or severe hepatic impairment, defined as a Child-Pugh Class B or C, respectively, thus caution is advised for using dalbavancin in this patient population.<sup>21</sup>

Dalbavancin's once-weekly dose allows a potential role in outpatient treatment. Outpatient parenteral antimicrobial therapy (OPAT) is an alternative mode of medication delivery for conditions requiring intravenous treatment yet not

warranting hospitalization. Outpatient parenteral antimicrobial therapy facilitates patient convenience, reduces nosocomial infection risks, and cuts healthcare cost. Hospitals with limited bed capacity can efficiently use resources available by allocating less intensive care offsite. Outpatient parenteral antimicrobial therapy is successfully used in different types of infections, including cellulitis, bone and joint infections, and infective endocarditis.<sup>25</sup>

However, OPAT poses limitations to quality care and optimal treatment. Limitations include reduced supervision, infrequent monitoring, and patient-clinician communication gap. Complications of OPAT range from adverse reactions to line-related bacteremia and even treatment failure. Approximately 10% of patients receiving OPAT are readmitted to the hospital.<sup>26,27</sup> Additional studies are needed to define the precise role of dalbavancin as OPAT.

### SUMMARY

Dalbavancin is a novel glycopeptide antimicrobial approved for the treatment of acute bacterial skin and skin-structure infections. Dalbavancin has similar efficacy to current first-line therapy (vancomycin/linezolid) for acute bacterial skin and skin-structure infections, as demonstrated in the DISCOVER 1 and DISCOVER 2 trials. This drug has the advantage of an extended half-life, allowing for once-weekly dosing. Dalbavancin may

**Table 2 | Adverse events in the DISCOVER 1 & 2 trials.**<sup>23</sup>

Variable	Dalbavancin (N = 652)	Vancomycin/Linezolid (N = 651)	P Value
Any adverse event	214 (32.8)	247 (37.9)	0.05
Total number	540	645	0.05
Treatment-related adverse event	80 (12.3)	89 (13.7)	0.45
Total number	139	183	0.02
Serious adverse event	17 (2.6)	26 (4.0)	0.16
Treatment-related	2 (0.3)	4 (0.6)	0.41
Death	1 (0.2)	7 (1.1)	0.03
Treatment-limiting adverse event	14 (2.1)	13 (2.0)	0.85
Most common treatment-related adverse event			
Nausea	16 (2.5)	19 (2.9)	0.62
Diarrhea	5 (0.8)	16 (2.5)	0.02
Pruritus	4 (0.6)	15 (2.3)	0.01

Data represent n (%) unless otherwise specified.

have a significant role in outpatient intravenous therapy for treating MRSA and other Gram-positive organisms. Dalbavancin provides an alternative to the existing therapies that have significant toxicities, dose-limiting side effects, and drug-serum monitoring.

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