New Gram-Positive Agents: the Next Generation of Oxazolidinones and Lipoglycopeptides

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The growing problem of antimicrobial resistance among bacterial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), has reached a critical state. Tedizolid phosphate, dalbavancin, and oritavancin have recently been approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and represent the next generation of oxazolidinones and lipoglycopeptides. All three agents exhibit *in vitro* activity and clinical efficacy against MRSA. Tedizolid phosphate and oritavancin demonstrate *in vitro* activity against VRE. These new Gram-positive agents are reviewed here.

Antimicrobial resistance among bacterial pathogens is a growing problem that has reached a critical state. Infection control, antimicrobial stewardship, and rapid diagnostics are important components in helping to curb this disturbing trend. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) remain problematic, as highlighted by their rank as “serious threats” in the United States by the Centers for Disease Control and Prevention (<http://www.cdc.gov/drugresistance/threat-report-2013>). Infections caused by these pathogens are associated with significant morbidity and mortality, even with appropriate treatment.

Skin and skin structure infections are among the most common indications for antibiotic treatment, with MRSA being a frequent cause (1). The Infectious Diseases Society of America guidelines for the treatment of MRSA infections and management of skin and soft tissue infections recommend vancomycin or linezolid (A-I), daptomycin or telavancin (A-I), or clindamycin (A-III) for treating patients hospitalized with MRSA skin and skin structure infections and as both definitive MRSA or empirical therapy in severe purulent skin infections (2, 3). The challenges of vancomycin dosing, therapeutic drug monitoring, and toxicity make the use of this agent problematic in many settings. In addition, while *vanA*-mediated vancomycin resistance is rare, strains of *S. aureus* with reduced susceptibility to vancomycin are encountered not infrequently in clinical practice (4).

Tedizolid, dalbavancin, and oritavancin were recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). These agents offer promise as alternatives to vancomycin in combating resistant Gram-positive bacterial pathogens and are reviewed here.

TEDIZOLID PHOSPHATE

Tedizolid phosphate is a novel expanded-spectrum oxazolidinone prodrug that is U.S. FDA approved for the treatment of ABSSSIs (5).

Microbiology. The prodrug tedizolid phosphate is rapidly converted *in vivo* to tedizolid by hydrolysis of the phosphate group. Tedizolid inhibits the synthesis of bacterial proteins by interacting with the 23S rRNA component of the 50S ribosomal

subunit (5). The drug has activity against staphylococci, streptococci, and enterococci, including some strains that have lost susceptibility to vancomycin, daptomycin, and linezolid (Table 1) (6–8). Additionally, tedizolid has activity against linezolid-resistant *Staphylococcus aureus* with the *cfr* multidrug resistance gene mutation (6). Compared to linezolid, tedizolid has been shown to have 4- to 16-fold greater *in vitro* activity against methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA, streptococci, and enterococci (9). Increased *in vitro* activity versus linezolid allows for a lower dose to be given with similar *in vivo* efficacy and the potential for reduced toxicity (5). The current FDA-approved susceptible, intermediate, and resistant MIC breakpoints for tedizolid against *Staphylococcus aureus* are ≤ 0.5 , 1, and 2 $\mu\text{g/ml}$, respectively. Mutations of the 23S rRNA gene, including G2576T (the most common 23S rRNA mutation type), have increased the MIC to >4 $\mu\text{g/ml}$ (7, 10). Currently, no commercially available antimicrobial susceptibility testing method is available for clinical microbiology laboratories; however, a commercial lyophilized broth microdilution system (Sensititre) was recently evaluated and is anticipated to be available in the near future (11).

Dosing. Tedizolid phosphate is available in both oral and intravenous formulations, with the same dosing (200 mg once daily) recommended for both routes of administration. No dosing adjustments are warranted in patients with renal or hepatic impairment. Based on population pharmacokinetic analyses, no clinically relevant pharmacokinetic changes based on patient demographics or other clinical factors were identified (5).

Pharmacokinetics/pharmacodynamics. Tedizolid phosphate has nearly equivalent oral (91%) and intravenous bioavailability. Tedizolid is highly protein bound (70 to 90%) and is primarily

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TABLE 1 *In vitro* activity of new Gram-positive agents (4, 6–9, 29, 30, 36–39)

Organism	MIC ₉₀ (μg/ml) ^a					
	Tedizolid	Linezolid	Dalbavancin	Oritavancin	Telavancin	Vancomycin
MSSA	0.5	2–4	0.06	0.06	0.06	1
MRSA	0.5	2–4	0.06	0.06	0.06	1
VISA	0.5	4	0.5–2 ^b	1	0.12	8
hVISA	0.5	1	0.5	2	0.12	2
Linezolid-resistant <i>S. aureus</i> (<i>cfr</i> -gene-mediated resistance)	0.5–1 ^b	8–32 ^b			0.06 ^c	1
Linezolid-resistant <i>S. aureus</i> (23S rRNA mutations)	8	>32			0.06 ^c	2
Coagulase-negative staphylococci	0.5	1–2	0.06–0.12	0.06	0.06	2
Vancomycin-susceptible <i>E. faecalis</i>	1	2	0.06	0.03	0.12	2
Vancomycin-resistant <i>E. faecalis</i>	0.5	2	>4	0.03, 0.5 ^d	>2 ^e	>32
Vancomycin-susceptible <i>E. faecium</i>	1	2–4	0.12	≤0.008	0.03	1
Vancomycin-resistant <i>E. faecium</i>	0.5	2	>4	≤0.008, 0.12 ^d	2 ^e	>32
<i>Streptococcus pneumoniae</i>	0.25	1	0.03	≤0.008	≤0.015	0.5
β-Hemolytic <i>Streptococcus</i>	0.5	1	≤0.03	0.12	0.03	0.5
Viridans group <i>Streptococcus</i>	0.25	1	≤0.03	0.03, 0.06 ^f	0.03	1

^a Susceptibility breakpoints for tedizolid phosphate with *S. aureus* are ≤0.5 (susceptible), 1 (intermediate), and ≥2 μg/ml (resistant); against *E. faecalis*, ≤0.5 μg/ml is susceptible (no intermediate or resistant breakpoints are established with *E. faecalis*). The susceptibility breakpoints for linezolid with *S. aureus* are ≤4 μg/ml for susceptible and ≥8 μg/ml for resistant; against enterococci, ≤2 μg/ml is susceptible, 4 μg/ml is intermediate, and ≥8 μg/ml is resistant. The susceptibility breakpoint for dalbavancin with *S. aureus* and most streptococci is ≤0.12 μg/ml; with *Streptococcus pneumoniae*, it is ≤0.03 μg/ml, with no intermediate or resistant breakpoints established. The susceptibility breakpoint for oritavancin with *S. aureus* and *E. faecalis* (vancomycin-susceptible isolates only) is ≤0.12 μg/ml (susceptible); with streptococci, it is ≤0.25 μg/ml, with no intermediate or resistant breakpoints established. The susceptibility breakpoint for telavancin with *S. aureus* is ≤0.12 μg/ml, and against *E. faecalis*, ≤0.25 μg/ml is susceptible. The susceptibility breakpoints for vancomycin with *S. aureus* are ≤2 μg/ml for susceptible, 4 to 8 μg/ml is intermediate, and ≥16 μg/ml is resistant; against enterococci, ≤4 μg/ml is susceptible, 8 to 16 μg/ml is intermediate, and ≥32 μg/ml is resistant.

^b Shown as MIC range (MIC₉₀ not available due to limited number of isolates).

^c MIC₉₀ values shown for linezolid-resistant *S. aureus* (resistance mechanism not specified).

^d Shown as MIC₉₀ (*vanB*, *vanA*) for vancomycin-resistant organisms.

^e MIC₉₀ values shown for *vanA*-containing enterococci.

^f Shown as MIC₉₀ (penicillin-susceptible, penicillin-non-susceptible) for viridans group *Streptococcus*.

metabolized in the liver, with 82% eliminated in the feces and 12% in the urine, as summarized in Table 2. Time-kill studies have illustrated the bacteriostatic activity of tedizolid phosphate against enterococci, staphylococci, and streptococci. The area under the concentration-time curve (AUC)-to-MIC ratio (AUC/MIC) was found to be the pharmacodynamic parameter that correlated best with tedizolid activity in early animal infection models (5). However, a marked increase in the activity of tedizolid in the presence of granulocytes was realized during clinical development and ultimately led to the current 200-mg daily dose being studied in late-stage clinical trials (12).

Clinical efficacy. U.S. FDA approval was based on the results of a phase II dose-ranging study and two identical phase III clinical trials, ESTABLISH-1 and ESTABLISH-2 (13, 14). The phase III trials compared a 6-day course of tedizolid phosphate (200 mg daily) and a 10-day course of linezolid (600 mg twice daily) in patients with ABSSSI. Both were double-blind, multicenter, multinational, and noninferiority studies in design. ESTABLISH-1 compared oral tedizolid phosphate and oral linezolid, whereas in ESTABLISH-2, patients received at least two doses of intravenous therapy prior to allowing a switch to oral tedizolid phosphate or linezolid. In both trials, MRSA was identified at similar rates in the tedizolid phosphate and linezolid groups (42.1% versus 43.1% and 27% versus 28%, respectively). Tedizolid phosphate met the criteria for noninferiority to linezolid in both trials based on the primary endpoint of early clinical response at 48 to 72 h. In a pooled analysis, a similar early clinical response was observed for tedizolid (81.6%) and linezolid (79.4%) (15). Secondary efficacy

outcomes, including sustained clinical response at end of therapy (EOT) and the posttherapy evaluation, were also similar between tedizolid phosphate and linezolid (13, 14).

Ongoing studies. Tedizolid phosphate (200 mg intravenously [i.v.] daily for 7 days) is currently being investigated for treating nosocomial pneumonia due to Gram-positive organisms in a randomized, double-blind, multicenter, and multinational phase III study in comparison with linezolid (600 mg i.v. every 12 h for 10 days). At the time of this writing, no results from this study had been reported (<https://clinicaltrials.gov/ct2/show/NCT02019420>).

Safety. The safety profile of tedizolid phosphate is primarily based on findings from the phase III trials and is summarized in comparison with other Gram-positive agents in Table 3. The most common treatment-emergent adverse events (TEAEs) reported in clinical trials were nausea, headache, and abscess. Gastrointestinal disorders were reported less frequently with tedizolid (16%) than with linezolid (23%). Most TEAEs were mild and infrequently led to discontinuation of therapy (0.5% with tedizolid and 0.9% with linezolid). Fewer patients treated with tedizolid phosphate (6.4%) than with linezolid (12.6%) had platelet counts of <150,000 cells/mm³ at any time through the last dose of active drug, although most were not considered clinically relevant. In addition, the duration of linezolid therapy was 10 days compared to six for tedizolid (15), which may partially explain the disparity in thrombocytopenia rates noted between linezolid and tedizolid.

There are no currently available data regarding the use of tedizolid phosphate beyond 21 days, making it difficult to evaluate the

TABLE 2 Dosing and pharmacokinetics of new Gram-positive agents (5, 17, 18, 27, 40–42)

Parameter ^a	Oxazolidinones		Lipoglycopeptides			Glycopeptides (vancomycin)
	Tedizolid phosphate	Linezolid	Dalbavancin	Oritavancin	Telavancin	
Dosing	200 mg oral or intravenous daily	600 mg oral or intravenous every 12 h	1,000 mg intravenous, followed 1 week later by 500 mg intravenous or 1,500-mg single intravenous infusion	1,200-mg single intravenous infusion (over 3 h)	10 mg/kg intravenous every 24 h	1,000 mg (or 15–20 mg/kg) intravenous every 12 h
C_{max} (μg/ml)	Oral, 2.0; intravenous, 2.3	Oral, 12.7, 21.2; intravenous, 12.9, 15.1 ^b	287, 423 ^c	138	93.6, 108 ^b	63
T_{max} (h)	Oral, 2.5; intravenous, 1.1	Oral, 1.03, 1.28; intravenous, 0.5 ^b	NR ^d	Immediately following 3-h infusion	NR	Immediately following 60-min infusion
Half-life (h)	12	4.6	346	245	8.0, 8.1 ^b	4–6
AUC _{0–infinity} (μg · h/ml)	Oral, 23.8; intravenous, 26.6	Oral, 91.4, 138; intravenous, 80.2, 89.7 ^b	23,443 for 1,000-mg dose	2,800	747	NR
Clearance (liters/h)	Oral, 6.9; intravenous, 6.4	Oral, 4.8, 7.62; intravenous, 7.38, 8.28 ^b	0.0513	0.445	0.917, 0.973 ^b	4.06
Volume of distribution (liters)	67–80	40–50	7–13	87.6	9.3, 10.2 ^b	60.5
Protein binding (%)	70–90	31	93	85	90	55
Metabolism	Sulfation (liver)	Oxidation	No apparent metabolism	No apparent metabolism	No apparent metabolism	No apparent metabolism
Elimination (%)	Urine, 18; feces, 82	Urine, 30 (additional 50 as metabolites); feces, minimal	Urine, 33 unchanged; 12 hydroxy metabolite; feces, 20	Urine, <5; feces, <1 ^e	Urine, 76; feces, <1	Urine, 75 over 24 h

^a AUC, area under the concentration-time curve; C_{max} , maximum serum concentration; T_{max} , time to C_{max} .

^b Parameters shown following both single and multiple doses (parameter following single dose, parameter following multiple doses).

^c Pharmacokinetic parameters determined from a 1,000-mg single intravenous infusion and a 1,500-mg single intravenous infusion, respectively.

^d NR, not reported.

^e After 2 weeks of collection.

possibility of adverse effects characteristic of linezolid when administered long term, such as optic and peripheral neuropathy.

Tedizolid and tedizolid phosphate do not appear to substantially inhibit the monoamine oxidase (MAO) system *in vivo*. Linezolid, an oxazolidinone antibiotic related to tedizolid, is a weak reversible MAO inhibitor. Coadministration of linezolid with serotonergic agents, such as selective serotonin reuptake inhibitors (SSRIs), is not recommended due to sporadic postmarketing reports of such combinations leading to serotonin syndrome. During studies designed to evaluate MAO inhibition, tedizolid phosphate did not produce hypertensive or serotonergic-related adverse reactions in humans or animal models. Therefore, tedizolid phosphate may not have clinically significant interactions with serotonergic compounds (16). However, patients receiving serotonergic agents, such as SSRIs, were excluded from phase III clinical trials, making it difficult to completely rule out the possibility of tedizolid interactions with these agents (13, 14).

Role in therapy and future directions. Tedizolid phosphate can be considered for use in patients in whom once-daily oral therapy is desired, and its availability in both intravenous and oral dosage forms simplifies the conversion from parenteral to oral therapy. Tedizolid should also be considered as a treatment alternative to linezolid in patients concomitantly taking serotonergic agents, due to its apparent low risk of interaction with these agents.

Investigation of tedizolid for treatment of pneumonia is under way and will ultimately give insight into use of this agent beyond ABSSSIs. The activity of tedizolid against some linezolid-resistant VRE strains (those mediated by *cfr*) is a promising feature of this agent and warrants further study to determine its clinical applicability. The availability of safety data reaching beyond a 6-day course will also likely impact the future use of this agent.

DALBAVANCIN

Dalbavancin, a semisynthetic lipoglycopeptide, is U.S. FDA approved for the treatment of ABSSSI caused by susceptible Gram-positive organisms (17).

Microbiology. Dalbavancin is isolated and modified from a fermentation product of *Nonomuraea* species. Amidation of the peptide carboxyl group during synthesis improves potency against staphylococci, and the addition of a long lipophilic side chain leads to an extended half-life. Dalbavancin interferes with bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of growing peptidoglycan chains, thus preventing cross-linking and inhibiting the bacterial cell wall. This action results in bactericidal activity (17, 18).

The spectrum of activity of dalbavancin is limited to Gram-positive organisms. Dalbavancin is active both *in vitro* and in clinical trials against *S. aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus intermedius* group, and *Streptococcus constellatus*. The current U.S. FDA-approved susceptibility breakpoint for dalbavancin against staphylococci and most streptococci is ≤ 0.12 μg/ml. An FDA breakpoint of ≤ 0.03 μg/ml for susceptibility is approved for *Streptococcus pneumoniae*. Dalbavancin is active against vancomycin-susceptible strains of *Enterococcus faecium* and *Enterococcus faecalis* (17). Additionally, dalbavancin is active *in vitro* against *vanB*-containing strains of VRE but not *vanA*-containing strains; however, the clinical significance of this activity is unknown (19). Furthermore, dalbavancin shows activity against some vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous VISA (hVISA) strains, but MICs up to 2 μg/ml have been identified (4). Dalbavancin also has activity against many anaerobic Gram-positive organisms, including

TABLE 3 Select treatment-emergent adverse effects of new Gram-positive agents reported in phase 3 clinical trials (13–15, 25, 33, 34)

TEAE ^a	Tedizolid phosphate (n = 662)	Dalbavancin (n = 652)	Oritavancin (n = 976)
Gastrointestinal disorders			
Nausea	54 (8.2)	27 (4.1)	97 (9.9)
Diarrhea	26 (3.9)	8 (1.2)	36 (3.7)
Vomiting	19 (2.9)	11 (1.7)	45 (4.6)
Constipation	9 (1.4)	12 (1.8)	33 (3.4)
Infections	91 (13.7)		
Abscesses	35 (5.3)	4 (0.6)	37 (3.8)
Osteomyelitis	ND ^b	ND	6 (0.6)
Nervous system disorders			
Headache	41 (6.2)	25 (3.8)	69 (7.1)
Dizziness	12 (1.8)	8 (1.2)	26 (2.7)
Skin and subcutaneous tissue			
Pruritus generalized	11 (1.7)	ND	11 (2.3) ^d
Pruritus	3 (0.5)	6 (0.9)	16 (3.4) ^d
Psychiatric disorders	17 (2.6)	ND	22 (4.7) ^d
Insomnia	10 (1.5)	ND	14 (3.0) ^d
Hematologic and laboratory			
Decreased PLT count ^c	40 (6.4)	78 (12.3)	1 (0.2) ^d
ALT level increased	15 (2.2) ^e	148 (23.2)	27 (2.8)
AST level increased	11 (1.7) ^e	125 (19.9)	18 (1.8)
Serum creatinine level increased	1 (0.2)	94 (14.6)	1 (0.2) ^d

^a PLT, platelet count (cells/mm³); ALT, alanine transaminase; AST, aspartate transaminase.

^b ND, not documented.

^c Defined as <150,000 cells/mm³ at any time during therapy.

^d Only reported for SOLO I (N = 473).

^e Value ≥2× the ULN and ≥2-fold increase from baseline.

Clostridium difficile, *Clostridium perfringens*, *Peptoniphilus* spp., and *Peptostreptococcus* species (20). No commercially available antimicrobial susceptibility testing methods currently exist for dalbavancin. Dilution techniques for determining dalbavancin susceptibility require the addition of polysorbate-80 at a final concentration of 0.002% to freshly prepared or frozen microtiter trays (17). Inference of dalbavancin susceptibility from vancomycin has recently been suggested as a strategy for predicting dalbavancin activity. However, while dalbavancin susceptibility can be inferred from vancomycin susceptibility, at this time, data on the relationship between the vancomycin intermediate phenotype and dalbavancin activity are lacking (21–23).

Dosing. In adult patients, the recommended two-dose regimen of dalbavancin is 1,000 mg intravenously, followed 1 week later by 500 mg intravenously. The two-dose regimen used in the phase III clinical trials was based on a phase II proof-of-concept study in which the two-dose regimen showed a higher clinical response rate than that for a single dose of dalbavancin (24). Following approval of the initial two-dose regimen, a single 1,500-mg dose was found to be noninferior to the two-dose regimen, and both regimens are currently approved for the treatment of ABSSSI (17).

No dosage adjustment of dalbavancin is necessary in patients

with a creatinine clearance (CL_{CR}) of >30 ml/min or for patients who are receiving regularly scheduled hemodialysis. Less than 6% of an administered dose is removed after 3 h of hemodialysis. The recommended two-dose regimen for patients with a CL_{CR} of <30 ml/min who are not receiving regularly scheduled hemodialysis is 750 mg intravenously, followed 1 week later by 375 mg intravenously, and the recommended single-dose regimen is 1,125 mg. No dosage adjustment is recommended in patients with mild hepatic impairment. There is little clinical experience in patients with moderate or severe hepatic impairment, warranting caution for use in this setting (17).

Pharmacokinetics/pharmacodynamics. Dalbavancin demonstrates linear dose-proportional pharmacokinetics best described using a three-compartment model. Dalbavancin is highly protein bound (approximately 93%) and has a long terminal half-life of approximately 2 weeks (Table 2). Elimination occurs via both renal and nonrenal routes, with an average of 33% and 12% of the administered dose excreted by the kidneys as unchanged dalbavancin and the hydroxyl metabolite, respectively. Dalbavancin exhibits concentration-dependent bactericidal activity. Antibacterial activity has been shown to correlate best with the AUC/MIC ratio, based on animal models of infection (17).

Clinical efficacy. U.S. FDA approval was based on the results of two identically designed phase III noninferiority trials, DISCOVER-1 and DISCOVER-2, of dalbavancin for the treatment of ABSSSI (25). Patients received either a two-dose regimen of dalbavancin (1,000 mg intravenously followed 1 week later by 500 mg intravenously) or vancomycin (1,000 mg or 15 mg/kg of body weight every 12 h) given intravenously, with the option to switch to oral linezolid (600 mg twice daily) after 3 days of treatment. The primary endpoint in both trials was early clinical response at the FDA-recommended time point (48 to 72 h after treatment initiation). To meet the endpoint of early clinical response, cessation of spread of infection-related erythema and absence of fever had to be present.

Early clinical response rates in the dalbavancin group were noninferior to the vancomycin-linezolid group in both DISCOVER-1 and DISCOVER-2. In the pooled analysis of the two trials, 79.7% of patients in the dalbavancin group and 79.8% of patients in the vancomycin-linezolid group had early clinical success. For patients with known *S. aureus* infections, clinical success occurred in 90.6% of patients treated with dalbavancin and 93.8% of patients treated with vancomycin-linezolid. Dalbavancin was determined to be noninferior to vancomycin-linezolid for the treatment of ABSSSI in each trial.

Recently, the efficacy of single-dose dalbavancin 1,500 mg was compared to treatment with the standard two-dose regimen of dalbavancin for the treatment of ABSSSI in a phase III double-blind multicenter randomized study (26). Single-dose dalbavancin was found to be noninferior to the two-dose regimen based on the early clinical response endpoint. Clinical response at 48 to 72 h was achieved in 81.4% and 84.2% of the single-dose and two-dose dalbavancin regimens, respectively.

Ongoing studies. A single-dose pharmacokinetic study of dalbavancin in patients age 3 months to 11 years has been completed, with no results reported to date (<https://clinicaltrials.gov/ct2/show/NCT01946568>). Future studies, which have not yet opened for participant recruitment, include the use of dalbavancin for community-acquired bacterial pneumonia (<https://clinicaltrials.gov/ct2/show/NCT02269644>) and pediatric acute hematogenous osteomyelitis (<https://clinicaltrials.gov/ct2/show/NCT02344511>).

Safety. Dalbavancin appears to be well tolerated. The most common TEAEs noted in clinical trials were nausea, headache, and diarrhea. Among patients with normal baseline alanine aminotransferase (ALT) levels, more patients were found to have postbaseline ALT elevations greater than three times the upper limit of normal with dalbavancin treatment (0.8%) versus vancomycin-linezolid treatment (0.2%). These elevations were reversible in all patients (16, 25). Severe hypersensitivity reactions to dalbavancin have been reported, necessitating caution in patients with an allergy to other glycopeptides, such as vancomycin.

Dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. As such, it has a low potential for drug-drug interactions (16). Of note, although nephrotoxicity was only rarely reported in either arm of the phase III DISCOVER trials, careful evaluation of the potential for this adverse effect with dalbavancin is warranted as this agent continues to transition into clinical practice.

Role in therapy and future directions. Situations warranting consideration for use of dalbavancin to treat ABSSSIs include patients necessitating intravenous therapy who are not candidates for indwelling intravenous catheters or have a history of intravenous catheter-related complications; those in whom deferment of hospital admission is planned; those requiring continuation of therapy at or after hospital discharge; those who are candidates for outpatient parenteral therapy where home health or frequent infusion center visits are not feasible; or those with a history or risk for noncompliance with oral therapy.

A challenge facing clinicians is how best to monitor efficacy of the lipoglycopeptides when used in these aforementioned settings, especially with the current lack of commercially available antimicrobial susceptibility testing methods and readily available assays for therapeutic drug monitoring. Furthermore, identifying patients in whom treatment with these agents is warranted, and the criteria for use will be of critical importance for antimicrobial stewardship programs to deter overuse in clinical practice. Finally, future investigations into the treatment of osteomyelitis with dalbavancin will be eagerly awaited.

ORITAVANCIN

Oritavancin is a lipoglycopeptide antibiotic recently approved by the U.S. FDA for the treatment of ABSSSI (27).

Microbiology. Oritavancin is an analogue of vancomycin with structural modifications (additional sugar and lipophilic side chain) that provide increased potency against Gram-positive bacteria compared to vancomycin, along with unique pharmacokinetic properties. Oritavancin has the ability to dimerize, which enhances its ability to bind the peptidoglycan cell wall of Gram-positive bacteria. The dimers are then able to more effectively anchor to the bacterial cell membrane target, increasing the drug's potency. Oritavancin exhibits rapid bactericidal activity by blocking the transglycosylation and transpeptidation steps of peptidoglycan synthesis, in addition to disrupting bacterial membrane integrity through dimer interactions (28).

Oritavancin demonstrates activity against Gram-positive pathogens, including staphylococci (including MRSA, hVISA, and VISA), streptococci, enterococci (including VRE), *Micrococcus* spp., *Listeria monocytogenes*, and *Corynebacterium* species (Table 1). The current FDA-approved susceptibility breakpoint for oritavancin against *S. aureus* and (vancomycin susceptible) *E. faecalis* is ≤ 0.12 $\mu\text{g/ml}$, whereas the breakpoint for streptococci is ≤ 0.25 $\mu\text{g/ml}$ (27). Additionally, oritavancin is active against

many anaerobic Gram-positive organisms, including *Clostridium difficile*, *Clostridium perfringens*, *Propionibacterium acnes*, *Peptococcus* spp., and *Peptostreptococcus* species (29, 30). While oritavancin is active against hVISA and VISA isolates, elevated MICs of up to 4 $\mu\text{g/ml}$ have been reported for some strains (30). Similar to dalbavancin, there is a lack of a commercially available antimicrobial susceptibility testing method for oritavancin; however, vancomycin has been suggested as a surrogate for predicting oritavancin susceptibility in vancomycin-susceptible isolates (31).

Dosing. Oritavancin requires a single intravenous infusion of 1,200 mg over 3 h (to minimize infusion-related reactions) for the treatment of ABSSSIs. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment ($\text{CL}_{\text{CR}} < 30$ ml/min) were not evaluated in clinical trials, but oritavancin is thought to be largely unaffected by renal dysfunction, as it is minimally eliminated in the urine. Oritavancin is not removed by hemodialysis. No dosage adjustment is recommended for patients with mild or moderate hepatic impairment, although there are no data available to determine appropriate oritavancin dosing in patients with severe hepatic impairment (27).

Pharmacokinetics/pharmacodynamics. Oritavancin displays linear pharmacokinetics best described by a three-compartment model and is extensively distributed into tissues, as shown by a volume of distribution of 87.6 liters (Table 2). Oritavancin is slowly excreted unchanged in feces and urine, with $< 1\%$ and 5% eliminated, respectively, after 2 weeks of collection. The terminal half-life of oritavancin is more than 10 days, allowing for use of a single dose in treating ABSSSIs (27, 32). Oritavancin displays concentration-dependent bactericidal activity, with the AUC/MIC ratio correlating best with activity in animal models of infection (27).

Clinical efficacy. U.S. FDA approval of oritavancin for the treatment of ABSSSIs was based on results of two identically designed phase III trials, SOLO-1 and SOLO-2 (33, 34). The studies were double-blind multicenter multinational noninferiority trials that enrolled a total of 1,959 patients. Patients with ABSSSIs requiring at least 7 days of parenteral therapy were eligible. Patients received either 1,200 mg of oritavancin or intravenous vancomycin (1,000 mg or 15 mg/kg every 12 h) for 7 to 10 days. Rates of MRSA identification were consistent between groups and in both trials (21.9 versus 20.9% in SOLO I and 19.9% versus 20.1% in SOLO II for the oritavancin and vancomycin groups, respectively). The primary efficacy outcome was defined according to FDA guidance as a composite of cessation of infection spread or a reduction in the size of the lesion, absence of fever, and absence of need for rescue antibiotics at the early clinical evaluation (48 to 72 h after drug initiation). Oritavancin met the predetermined definition for noninferiority compared to vancomycin in both studies. Early clinical response rates were similar between oritavancin and vancomycin in both trials (SOLO I, 82.3 versus 78.9%, and SOLO II, 80.1 versus 82.9%, respectively). Noninferiority was also met for the additional predefined efficacy endpoints of investigator-assessed clinical cure and the proportion of patients attaining $\geq 20\%$ reduction in lesion area in both trials.

Ongoing studies. Oritavancin is currently being studied with the coadministration of warfarin in healthy subjects (<https://clinicaltrials.gov/ct2/show/NCT02340988>) and in patients on chronic warfarin (<https://clinicaltrials.gov/ct2/show/NCT02452918>). A pediatric dose-ranging study is also ongoing (<https://clinicaltrials.gov/ct2/show/NCT02134301>).

Safety. Safety data for oritavancin are primarily based on findings from the two phase III trials, which led to its U.S. FDA approval as a one-time infusion for treating ABSSSIs (Table 3). Nausea, headache, and vomiting were the most commonly reported adverse effects of oritavancin, occurring at rates similar to those with vancomycin. Compared to vancomycin, oritavancin had more occurrences of infusion site phlebitis, elevation of ALT levels, and limb abscess (33, 34). Due to more cases of osteomyelitis reported with oritavancin than vancomycin in clinical trials, the manufacturer has recommended that alternate antibacterial therapy be administered in patients with suspected or confirmed osteomyelitis (27). Serious hypersensitivity reactions have been reported with oritavancin, with a median onset of 1.2 days and duration of 2.4 days. Caution is warranted in administering oritavancin to patients with an allergy to other glycopeptides, including vancomycin (27).

Oritavancin interferes with phospholipid reagents used in coagulation tests, potentially leading to falsely elevated activated partial thromboplastin time and prothrombin time within the first 24 to 48 h following administration. Additionally, coadministration with warfarin may result in higher warfarin exposure (31% increased AUC of warfarin) and increased bleeding risk, which may not be completely mitigated in the first 48 h following administration of oritavancin. Interestingly, minimal nephrotoxicity was reported with either oritavancin or vancomycin in phase III trials (27).

Role in therapy and future directions. Consideration for using oritavancin is warranted in the same situations as with dalbavancin. Additionally, activity of oritavancin against *vanA*-mediated VRE is unique among the glycopeptides and may ultimately lead to use of this agent in managing these difficult-to-treat infections, although additional clinical data are needed. While minimal nephrotoxicity with oritavancin or vancomycin was observed in the SOLO trials, this may be indicative of a relatively healthy study population and warrants consideration as the agent is further evaluated in clinical practice. The finding of increased osteomyelitis incidence with oritavancin in clinical trials requires additional clarification to elucidate the role of this agent in more severe infections (especially those with bony involvement). Furthermore, the safety and efficacy of oritavancin in multidose schema and in critically ill patient populations will help determine future use of this agent.

CONCLUSIONS

Several unanswered questions remain regarding tedizolid phosphate, dalbavancin, and oritavancin. Determining the long-term safety of these agents, including the impact of multidose schema for the lipoglycopeptides and extended durations of therapy with tedizolid phosphate, will be of utmost importance in establishing their roles for the treatment of infections other than ABSSSI. The long half-lives of the newer lipoglycopeptides and how prolonged exposure to these agents may affect the resistance profiles of skin and gut microbiota are other areas of uncertainty. Finally, economic comparisons between the new agents and the potential impact of transitioning therapy to outside acute-care settings will likely help shape future usage. Economic modeling illustrates substantial inpatient cost, with an average inpatient stay for ABSSSI lasting nearly 4 days and costing \$5,000 (35). Whether these new agents prevent or shorten hospitalizations associated with ABSSSIs,

which subsequently may help offset their substantial acquisition costs, awaits further study.

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