Oritavancin: A Long-Half-Life Lipoglycopeptide

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Oritavancin is a lipoglycopeptide antibiotic that has been shown to be effective for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). This antibiotic has multiple mechanisms of action including inhibiting peptidoglycan cell wall synthesis and disrupting bacterial cell membrane, leading to cell death. Oritavancin is highly active against common gram-positive pathogens including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus*, vancomycin-resistant *S. aureus*, and vancomycin-resistant enterococci. The drug is administered as a single intravenous dose of 1200 mg over 3 hours in adult patients, and because of its terminal half-life of 393 hours, repeat dosing is not required in the treatment of ABSSIs. There is a very slow elimination from tissue sites, and no dosing adjustments are required for renal or hepatic insufficiency. Two clinical trials have demonstrated noninferiority compared with vancomycin in the treatment of ABSSSIs. Other than liver enzyme elevation and the occurrence of osteomyelitis, oritavancin has been associated with adverse events similar to those of vancomycin in follow-up for up to 60 days. Patients should be monitored for osteomyelitis and alternate therapy given in the case of confirmed or suspected osteomyelitis. Although oritavancin is an attractive antibiotic to consider in the outpatient area, its efficacy and safety in the treatment of other sites of infection are yet to be established.

**Keywords.** oritavancin; MRSA; *Staphylococcus aureus*; antibacterial agents.

Vancomycin is the most commonly prescribed antimicrobial agent in many academic medical centers in the United States because of the widespread occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) [1, 2]. Vancomycin does require long-term intravenous access and monitoring of blood levels and has had limitations for some patients in terms of tolerability. Increasing numbers of strains of MRSA have reduced susceptibility to vancomycin (isolates with minimum inhibitory concentration [MIC] = 1–2 µg/mL) as well as those with intermediate levels of resistance, known as vancomycin-intermediate *S. aureus* (VISA), which have been associated with clinical failure when treated with vancomycin [3]. Isolates with reduced susceptibility to daptomycin and resistance to linezolid have also been reported [4, 5]. The concern over the limitations of vancomycin because of evolving resistance as well as the occurrence of reduced activity by newer agents against MRSA has heralded a need for additional antistaphylococcal agents. In addition, community-acquired MRSA has become the predominant phenotype for *S. aureus* infections treated in the outpatient setting and has prompted interest in developing parenteral long-half-life agents that can be conveniently used in the ambulatory treatment of serious MRSA infections.

Oritavancin (Orbactiv) is a newly approved lipoglycopeptide that was initially conceived because of its activity against vancomycin-resistant *Enterococcus faecalis*. The need for a drug with excellent MRSA activity and a prolonged half-life provided further momentum for the development of this antimicrobial agent. At present it has been approved by the US Food and Drug Administration (FDA) as a single intravenous dose of 1200 mg for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). This article reviews the chemistry, mode of action, antimicrobial activity, pharmacokinetics and pharmacodynamics, clinical indications, adverse events, and formulary considerations of oritavancin.
CHEMISTRY AND MODE OF ACTION

Oritavancin, previously referred to as LY333328, is an analogue of vancomycin that contains an additional unsubstituted sugar and an aromatic lipophilic side chain [6]. This compound contains both hydrophobic and lipophilic groups and belongs to the lipoglycopeptide group of antimicrobial agents that also includes dalbavancin and telavancin. These structural modifications impart a significant increase in their potency against gram-positive bacteria compared with vancomycin [7]. These lipoglycopeptides also have the ability to dimerize, which improves their ability to bind to the peptidoglycan cell wall. These dimers can anchor themselves to the bacterial membrane using their hydrophobic substituents, thus increasing binding affinity to their target (e.g., D-Ala-D-Ala) and enhancing potency.

Unlike vancomycin, oritavancin exerts rapid and concentration-dependent killing against rapidly growing organisms [8]. This occurs via multiple mechanisms of action including blocking the transglycosylation step of peptidoglycan synthesis, inhibiting transpeptidation (cross-linking), and perturbations of membrane potential (depolarization and increased permeability) [6]. Oritavancin has also exhibited bactericidal activity against stationary phase inocula of gram-positive cocci [9].

Oritavancin accumulates in macrophages, reaching intracellular concentrations 200-fold above extracellular concentrations after 24 hours of in vitro incubation [10]. The bactericidal activity of macrophages was not affected by this accumulation in these experiments, and the killing of S. aureus was substantially enhanced. These findings provide some reassurance that oritavancin accumulation does not prevent phagocytic killing and suggests that this antibiotic can help eradicate intracellular staphylococci.

The newer lipoglycopeptides are known to interfere with phospholipid reagents used in coagulation tests. This effect can lead to false elevations in the activated partial thromboplastin time and the prothrombin time.

ANTIMICROBIAL ACTIVITY

The activity of oritavancin is summarized in Table 1 and compared to other parenteral agents with gram-positive activity [11–14]. Overall, there is very good activity of oritavancin against common gram-positive pathogens. Oritavancin’s antimicrobial activity is reduced when vancomycin activity is reduced, with minimum inhibitory concentration of 90% (MIC90) of 1 µg/mL and 2 µg/mL for VRSA and VISA, respectively [14]. This difference was not due to adherence, as polysorbate 80 was included in the in vitro testing as described below. Noteworthy is the activity against vancomycin-resistant enterococci (VRE), which has become problematic in many hospital settings in the United States. In addition, oritavancin is active against Micrococcus species, Listeria monocytogenes, and Corynebacterium species, each with MIC90 <0.06 µg/mL [11].

<table>
<thead>
<tr>
<th>Table 1. Comparative In Vitro Minimum Inhibitory Morbidity Concentrations of Oritavancin for Gram-Positive Organisms</th>
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<tr>
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</tr>
<tr>
<td>MSSA</td>
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<td>VRSA</td>
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<td>CoNS</td>
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<td>Vancomycin susceptible</td>
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<td>Enterococcus faecalis</td>
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<td>Enterococcus faecium</td>
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<td>Vancomycin resistant (VanA)</td>
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<td>E. faecalis</td>
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<td>E. faecium</td>
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<tr>
<td>Vancomycin resistant (VanB)</td>
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<tr>
<td>E. faecalis</td>
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<tr>
<td>E. faecium</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
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<tr>
<td>Viridans group streptococci</td>
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<tr>
<td>β-hemolytic streptococci</td>
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Data are presented as MIC90 (µg/mL).
Source: [11–14].

Abbreviations: CoNS, coagulase-negative staphylococci; MIC90, minimum inhibitory concentration of 90%; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; VISA, vancomycin-intermediate Staphylococcus aureus; VRSA, vancomycin-resistant Staphylococcus aureus.
organisms that include Clostridium difficile (MIC$_{90}$ = 1 µg/mL), Clostridium perfringens (MIC$_{90}$ = 1 µg/mL), Peptostreptococcus species (MIC$_{90}$ = 0.5 µg/mL), Peptococcus species (MIC$_{90}$ = 0.5 µg/mL), Propionibacterium acnes (MIC$_{90}$ = 0.25 µg/mL) [11].

The susceptibility breakpoint criteria from the package insert are ≤0.12 µg/mL for S. aureus and E. faecalis and ≤0.25 µg/mL for Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus intermedius. The breakpoints are based on broth microdilution methods. In addition, oritavancin powder should be dissolved and the broth test medium should be supplemented with polysorbate 80 to a final concentration of 0.002% to prevent adsorption of the drug to the plastic wells. When these guidelines are not adhered to, the potency of the oritavancin is reported as less, with MICs that may be 4- to 64-fold higher in the absence of polysorbate [11].

Oritavancin has demonstrated in vitro synergy against staphylococci when combined with gentamicin, linezolid, moxifloxacin, and rifampin [15]. The addition of gentamicin combined with oritavancin demonstrated in vitro synergistic bactericidal activity against VRE, including both VanA and VanB phenotypes [16].

**PHARMACOKINETICS/PHARMACODYNAMICS**

Oritavancin is poorly absorbed from the gastrointestinal tract and needs to be administered intravenously to achieve therapeutic systemic concentrations. Dose-ranging studies have shown that this antibiotic displays linear pharmacokinetics with renal excretion being the major route of elimination [17]. Oritavancin displays multieponential decline and has a terminal half-life of >10 days (Table 2). Following a 1200-mg dose (over 3 hours) of oritavancin, the terminal half-life is predicted to start at concentrations of 5–20 µg/mL [18]. The free (active) drug concentrations will be significantly less, as 85% of oritavancin is protein bound.

**Table 2. Mean Pharmacokinetic Parameters in Patients Based on a Single 1200-mg Dose of Oritavancin**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
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<tr>
<td>C$_{max}$ µg/mL</td>
<td>140 (32)</td>
</tr>
<tr>
<td>AUC$_{0-24}$, mg h/L</td>
<td>730 (320)</td>
</tr>
<tr>
<td>T½β, h</td>
<td>31 (11)</td>
</tr>
<tr>
<td>T½γ, h</td>
<td>393 (74)</td>
</tr>
<tr>
<td>Cl, L/h</td>
<td>0.6 (0.2)</td>
</tr>
</tbody>
</table>

Source: [17].

Abbreviations: AUC$_{0-24}$, area under the plasma concentration-time curve from time zero to 24 hours; Cl, total clearance; C$_{max}$, maximum plasma concentration; SD, standard deviation; T½β, plasma elimination phase half-life; T½γ, plasma terminal elimination half-life.

Oritavancin has extensive tissue distribution with a volume of distribution of approximately 1 L/kg. Its mean blister fluid/plasma ratio was found to be 0.19 (19%) [19]. Oritavancin is slowly eliminated from tissue sites with <5% recovered in the urine 7 days after dosing [20]. No metabolites have been detected in urine or feces. Results from drug interaction studies found that oritavancin can be a weak inhibitor or inducer of cytochrome P450 isoenzymes. The inhibitory effect on warfarin metabolism warrants monitoring of the international normalized ratio following a dose of oritavancin. No dosing adjustments are recommended in obese patients or those with moderate renal or hepatic impairment.

Oritavancin displays primarily concentration-dependent killing, and its bactericidal efficacy correlates best to its maximum serum concentration to MIC ratio (maximum plasma concentration [C$_{max}$/MIC]) [18]. A C$_{max}$/MIC ratio of 4 is sufficient to produce cidal activity (3-log kill) in vitro against a standard (10$^5$) inoculum of MRSA. In an in vitro pharmacodynamic model, a simulated single 1200-mg dose of oritavancin decreased bacterial viability as effectively as once-daily dosing with daptomycin and twice-daily dosing of vancomycin against MRSA isolates over 72 hours [21]. Due to the long plasma half-life of oritavancin, the time during the concentration of drug in plasma exceeds the MIC (T > MIC) and the area under the concentration-time curve to MIC ratio (AUC/MIC) are also highly correlated with efficacy [22]. In a phase 2 study in patients with S. aureus bacteremia receiving daily doses of oritavancin, longer free-drug T > MIC exposures resulted in higher microbiological responses [23].

**ANIMAL MODELS**

Oritavancin has been studied in a variety of animal models to determine its efficacy against drug-resistant bacterial pathogens [18]. In a rabbit model of experimental left-sided MRSA endocarditis, oritavancin was found to be as effective as vancomycin in clearing bacteria and reducing bacterial counts in vegetations and tissues [24]. In rabbits with aortic endocarditis, oritavancin produced significant decreases in bacterial counts in vegetations infected with vancomycin-resistant E. faecalis [25]. The addition of gentamicin was shown to enhance the activity of oritavancin against VanA and VanB strains of E. faecalis in this model and prevented the emergence of resistant strains [16]. In a murine model of a central venous catheter (CVC) infection by a strain of E. faecium with the VanA phenotype, a single dose of oritavancin cleared the bacteremia as well as prevented metastatic disease and only 12.5%, compared with 87.5% of untreated animals, had organisms recovered from the CVC [26].

In a rabbit model of pneumococcal meningitis, a single dose of oritavancin was shown to reduce bacterial titers in cerebrospinal fluid (CSF) in a similar manner as ceftriaxone [27]. The
CLINICAL EXPERIENCE

Although oritavancin was discovered >2 decades ago by Lilly, the drug’s clinical trial development has been hampered by transitions from the original manufacturer to 2 other companies including the current developer, The Medicines Company. Early trial efforts were conducted with multidose injections of oritavancin for 3–7 days. Additional dose-finding trials were required along with the changes in regulatory requirements, both of which contributed to the delay in the development of this drug. The phase 2 clinical dose-ranging study, Simplifi, identified a 1200-mg dose of oritavancin, which was used in subsequent trials. [30]. When originally reviewed by the FDA, these studies did not provide support for approval, and additional phase 3 trials were needed and performed by The Medicines Company.

The 2 phase 3 trials that led to the approval of oritavancin were summarized by Corey et al in 2 separate publications [31, 32]. These 2 studies were referred to as SOLO 1 and 2 and were identically designed and incorporated regulatory guidance from the FDA and the European Medicines Agency. These 2 studies were double-blinded, active controlled multicenter, randomized trials that enrolled 1959 patients. Patients had ABSSIs that involved wound infections, cellulitis, or major skin abscesses (minimum surface area of 75 cm² of erythema, edema, and or induration) that the clinician thought needed at least 7 days of parenteral therapy. Lesions had a median area of erythema, edema, and induration of approximately 235 cm². A number of patients were excluded according to the eligibility criteria [31]. Patients received either a single intravenous dose of 1200 mg of oritavancin or intravenous vancomycin (1 g or 15 mg/kg every 12 hours) for 7–10 days. Patient populations were similar in terms of patient characteristics that included age, sex, race, type of infection, diabetes, hepatic impairment, and renal function. The studies were designed as noninferiority trials. Patients were evaluated early in the course of treatment (2–3 days after drug was started), at the end of treatment, and at a posttherapy evaluation (7–14 days posttherapy). In each of these evaluations for the SOLO 1 and 2 trials, the outcomes met the noninferiority margin of 10 percentage points for oritavancin vs vancomycin. The primary efficacy endpoint for the SOLO studies was a composite outcome at the time of the early clinical evaluation that comprised the cessation of spreading or a reduction in the size of the baseline lesion, the absence of fever, and the absence of a need for rescue antibiotic medication. In SOLO 1, the oritavancin and vancomycin arm endpoints were 82.3% and 78.9%, respectively [31]. For SOLO 2, the primary composite endpoints were 80.1% vs 82.9%, respectively, for oritavancin vs vancomycin [31]. The outcomes were also similar according to pathogen type. Among the patients with baseline pathogens recovered, there were 405 MRSA isolates among the 945 S. aureus isolates. Clinical response for MRSA infections at early clinical evaluation was 81.4% for the oritavancin arm vs 80.6% for the vancomycin arm, and the clinical cure at the posttreatment evaluation was 83.3% for the oritavancin arm vs 84.1% for the vancomycin arm. In addition, a key secondary endpoint of ≥20% reduction in lesion area from baseline was 86.9% for oritavancin vs 82.9% for vancomycin in SOLO 1 and was 85.9% for oritavancin vs 85.3% for vancomycin for SOLO 2. Safety was assessed for up to 60 days’ follow-up because of the prolonged half-life of oritavancin. The occurrences of study drug–related adverse events (22.2% vs 28.4%), severe adverse events (5.2% vs 4.9%), and discontinuations due to adverse events (3.7% vs 4.2%) were similar whether the patient received oritavancin or vancomycin, respectively. Among adverse events reported, nausea was the most common side effect in the oritavancin arm (9.9%) which was less than the vancomycin arm (10.5%). There is a warning in the package insert related to osteomyelitis adverse events, as this occurred in 5 patients on oritavancin and none in the vancomycin arm as reported in SOLO 2 [32]. Other events appear to be similar in the 2 treatment arms. The rates of abnormalities in liver tests (alanine aminotransferase rises) were higher in the oritavancin arm than the vancomycin arm for both SOLO 1 (2.3% vs 1.0%) and SOLO 2 (3.2% vs 2.0%) [31, 32]. Other laboratory abnormalities were similar in both treatment arms. Noteworthy was that no difference in rises in serum alanine or aspartate aminotransferase levels, total bilirubin, or serum creatinine was observed. There were no differences in the safety outcomes assessed at 60 days in the 2 treatment arms.

FORMULATORY CONSIDERATIONS

MRSA has emerged as the most common cause of complicated skin infections [33]. This has led to a shift in choice of empirical therapy from β-lactam antibiotics to those with activity against MRSA for ABSSIs. Most of these infections occur in relatively healthy patients and, if limited in size, may be treated with oral
antibiotics such as trimethoprim-sulfamethoxazole, doxycycline, or linezolid [34]. Oritavancin provides another choice for the treatment of MRSA and also has a potential role for the treatment of VRE infections, as a need still exists in this area. Outpatient parenteral antimicrobial therapy (OPAT) is useful for patients who do not respond to or do not tolerate oral therapy and patients who are more severely ill but not requiring hospitalization [35]. The recently approved lipoglycopeptides have the potential to significantly advance OPAT for serious infections [36].

Oritavancin as a single dose has been shown to be an effective treatment for ABSSSI based on the results of the SOLO clinical trials. Moreover, this infusion does not require a peripherally inserted central catheter, and patients will no longer need to maintain vascular access for daily administrations of antibiotic therapy. These factors will enhance compliance as well as limit noninfectious complications of long-term intravenous catheter use [37]. In contrast to vancomycin, no monitoring of blood concentrations is required with oritavancin. In addition, there is no need to use an oral agent to complete a course of therapy due to the long duration of activity of oritavancin. Finally, adherence to multiple-dose regimens would be eliminated by a single-dose parenteral agent.

The use of oritavancin will also generate concerns and limitations. Although oritavancin exhibited a low rate of side effects in clinical trials, clinicians should be cautious in patients with a history of adverse reactions to antimicrobials due to the 10-day terminal half-life of this drug. If a delayed hypersensitivity reaction or other toxicity were to occur, this injury could persist for weeks before the exposure was eliminated. However, the adverse event rate was observed over 60 days and, except for osteomyelitis, higher adverse event rates did not occur with oritavancin compared with vancomycin. Trials leading to approval had very few cases of bacteremia and were conducted predominantly in an inpatient setting and not an infusion center. The lack of a physician conducting daily patient follow-up evaluations for serious infections, as would occur in a hospital, may lead to a delay in identifying clinical failures and is a concern following single-dose therapy. In addition, the overall use of this drug to date has been limited and the effectiveness of oritavancin in bacteremia, pneumonia, bone and joint infections, and prosthetic infections has not been established. In view of the warning issued by the FDA for osteomyelitis, close monitoring, as well as carefully designed animal and human studies, must be done in this area to understand oritavancin’s role in this condition. We also know that the ongoing selective pressure of drugs continues to be a concern to the infectious disease community, and how a drug with extended duration of levels will play a role in the future selection of resistance will need to be monitored.

The use of oritavancin for treatment of ABSSSIs can reduce outpatient infusion services and home care, as well as improve patient satisfaction, but the acquisition cost ($2900) of this antibiotic may ultimately limit its use [38]. Costs in healthcare are frequently limited by acquisition costs as many of the other associated costs are fixed or not easily reduced. Also, as the occurrence of MSSA ranges between 30% and 60% of isolates of S. aureus, use of a β-lactam after a short inpatient course of vancomycin, telavancin, or daptomycin may be a more acceptable cost-effective strategy. In addition, we need to be mindful that this drug to date has not been assessed in the most serious conditions including bacteremia or bone and joint infections, and in less serious conditions, one may readily use an oral drug with good bioavailability. Resolution of reimbursement and copay issues along with carefully conducted cost-benefit analyses of oritavancin vs other antibiotics used for OPAT of ABSSSIs are needed [39]. Furthermore, additional clinical experience with response to transition therapy from other regimens is needed to further assess oritavancin’s role in treatment of ABSSSIs.

Oritavancin is a long-half-life lipoglycopeptide that demonstrates activity comparable to that of vancomycin against common pathogens causing ABSSSIs. It appears to be able to be safely administered as a single dose, with cure rates noninferior to vancomycin. This drug warrants careful consideration for outpatient management of ABSSSIs.

Note

Potential conflict of interest. L. D. S. has received research support for conducting in vitro work with oritavancin supported by Targanta Therapeutics (Cambridge, Massachusetts), which is now a wholly owned subsidiary of The Medicines Company. G. E. S. reports no potential conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References