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REVIEW

Oritavancin: A New Lipoglycopeptide Antibiotic in the Treatment of Gram-Positive Infections

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ABSTRACT

Resistance among Gram-positive organisms has been steadily increasing over the last several years; however, the development of new antibiotics to treat infections caused from these organisms has fallen short of the emergent need. Specifically, resistance among *Staphylococcus aureus* and *Enterococcus* spp. to essential antibiotics is considered a major problem. Oritavancin is a semisynthetic lipoglycopeptide antibiotic that was recently approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI). While structurally related to vancomycin, oritavancin also possesses unique mechanisms of action that greatly enhance its antimicrobial potency against multi-drug resistant pathogens including both VanA- and VanB-mediated vancomycin-resistant enterococci. Owing to the addition of the highly hydrophobic tail group, oritavancin possesses a prolonged half-life ranging from 200–300 h. Although oritavancin is only currently Food and Drug Administration approved for ABSSSI, this agent may eventually play a role in additional indications where new innovative therapy is needed including bacteremia and deep-seeded, Gram-positive infections such as infective endocarditis or osteomyelitis. This review will focus on oritavancin's spectrum of activity, mechanisms of action and resistance, pharmacokinetic and pharmacodynamic properties, and the completed and ongoing clinical studies evaluating its use.

Keywords: Acute bacterial skin and skin structure infection; Lipoglycopeptide; Oritavancin

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INTRODUCTION

Resistance among Gram-positive organisms has been steadily increasing over the last several years; however, the development of new antibiotics to treat infections caused from these organisms has fallen short of the emergent need. Specifically, resistance among *Staphylococcus aureus* and *Enterococcus* spp. to essential antibiotics in the US is considered a major problem with 56.8% of *S. aureus* being methicillin-resistant (MRSA) and 87.1% of *Enterococcus faecium* being vancomycin resistant (VRE) [1]. Additionally, data from the most recent US National Healthcare Safety Network and Center for Disease Control and Prevention's report identified these two organisms as being the most commonly reported organisms isolated from hospital-acquired infections [2]. With the high frequency of these organisms implicated in serious infections and the concerns with their resistance to the mainstay of treatment, there is clearly a need for alternative therapies. Fortunately, the Food and Drug Administration (FDA) has recently approved several new antibiotics for the treatment of these resistant Gram-positive infections.

Oritavancin is a semisynthetic lipoglycopeptide antibiotic that is one of the new agents that was recently approved for the treatment of acute Gram-positive skin and skin structure infections. This review will focus on oritavancin's spectrum of activity, mechanisms of action and resistance, pharmacokinetic and pharmacodynamic properties, and the completed and ongoing clinical studies evaluating its use. The search for articles in this review was performed using the search terms oritavancin and LY33328 with the PubMed database for articles published between the dates of 2010 to 2015.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CHEMICAL STRUCTURE

Oritavancin is a lipoglycopeptide derived from the naturally occurring chloroeremomycin, a member of the eremomycin class of glycopeptides [3]. While structurally similar to vancomycin (Fig. 1), the eremomycin-glycopeptides possess two 4-epi-vancosamine monosaccharides, one replacing vancosamine and the other linked to ring-6 via an amino acid residue. Oritavancin additionally includes a highly hydrophobic *N*-alkyl-*p*-chlorophenylbenzyl substituent linked to the disaccharide sugar. These pharmacophore features, as well as associated modifications in stereochemistry, are believed to be largely responsible for the greatly enhanced antimicrobial potency of oritavancin against Gram-positive organisms including those possessing both VanA- and VanB-mediated vancomycin-resistance [4].

MECHANISMS OF ACTION AND RESISTANCE

The progenitors of the lipoglycopeptide class, the glycopeptides, are known to inhibit bacterial growth by binding to the D-alanyl-D-alanine terminus of the peptidoglycan precursor linked to the C_{55}-lipid transporter (collectively referred to as Lipid II; Fig. 2). Lipid II is responsible for transporting peptidoglycan precursor monomers across the lipid bilayer and aligning with a template

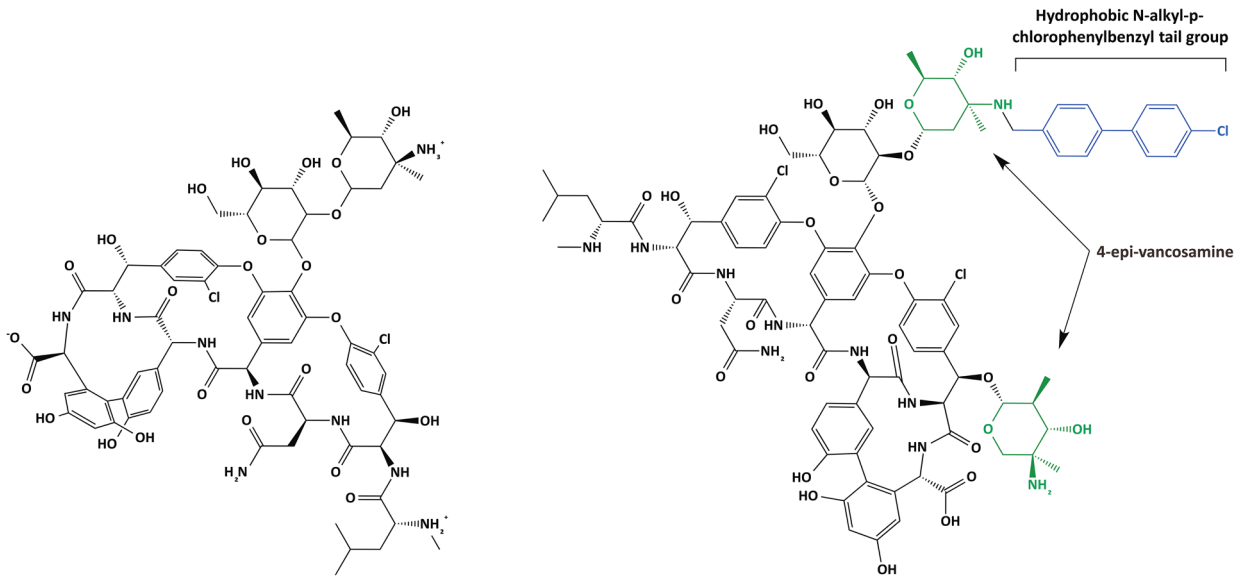

Fig. 1 Structures of vancomycin (*left*) and oritavancin (*right*)

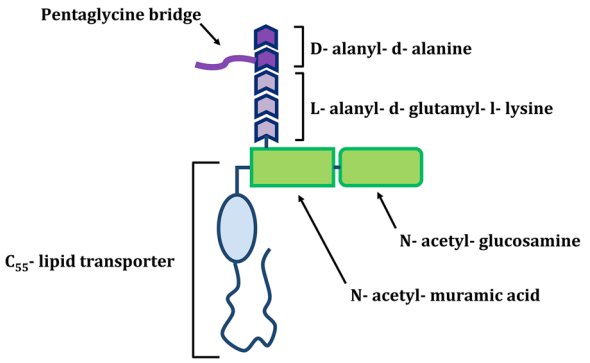

Fig. 2 Components of lipid II

peptidoglycan chain to position the monomer for incorporation to the growing nascent peptidoglycan chain. When glycopeptides, such as vancomycin, bind to the terminal peptide stem of Lipid II, they effectively block the bacterial enzyme transglycosylase from transferring the peptidoglycan precursor to the growing nascent peptidoglycan chain [5]. Thus, peptidoglycan polymerization is impeded and cell wall integrity and cell survival are compromised.

Vancomycin-resistant enterococci (VRE) and vancomycin-resistant *S. aureus* (VRSA) elude the antimicrobial activity of most glycopeptides by substituting the terminal D-alanine of the peptidoglycan precursor with D-lactate or D-serine upon exposure to glycopeptides via a two-component signaling system [6]. This substitution greatly decreases the binding affinity of glycopeptides, such as vancomycin, and allows peptidoglycan polymerization to proceed uninhibited. Alternatively, *S. aureus* with reduced or intermediate susceptibility to vancomycin, such as heterovariant vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-intermediate *S. aureus* (VISA), express the wild-type D-alanyl-D-alanine peptide termini, but produce significantly thicker cell walls [7]. This effectively creates excessive vancomycin-peptidoglycan binding sites within the cell wall and decreases the amount of vancomycin that ultimately binds Lipid II near the division septum, lessening the antimicrobial impact of the agent.

Oritavancin, while structurally related to vancomycin, possesses unique mechanisms of action secondary to the inclusion of the highly hydrophobic *N*-alkyl-*p*-chlorophenylbenzyl

group and two 4-epi-vancosamine residues (Fig. 3). Though it has been shown that oritavancin is capable of binding to the D-alanyl-D-alanine peptidoglycan termini of Lipid II by means similar to vancomycin, a second distinct peptidoglycan-binding pocket has also been identified [5, 8–10]. This binding pocket, between the hydrophobic tail group and the nearby 4-epi-vancosamine, is believed to interact with peptides near, but distinct from the terminal D-alanyl-D-alanine (or D-lactate) in both *S. aureus* and enterococci [8, 11]. Thus, oritavancin is capable of maintaining binding affinity for the modified peptidoglycan peptide termini of vancomycin-resistant organisms.

Additionally, oritavancin has been observed to inhibit transpeptidation, the other essential enzymatic step in peptidoglycan polymerization. When oritavancin binds to newly formed template peptidoglycan chains near the cell membrane in a fashion independent of Lipid II, the activity of the bacterial transpeptidase is obstructed by steric hindrance associated with the hydrophobic tail group of oritavancin [11]. Inhibition of transpeptidase prevents the cross-linking of neighboring peptidoglycan chains and reduces cell wall integrity. Though both binding of oritavancin to Lipid II and mature peptidoglycan has been observed, it appears that oritavancin, contrary to vancomycin, displays greater inhibition of transpeptidation than transglycosylation [5, 11].

In another departure from the earlier glycopeptides, lipoglycopeptides including oritavancin have been proposed to possess bacterial membrane binding capabilities. While some investigators have observed bacterial membrane insertion to occur only in the absence of cell wall associated peptidoglycan-binding sites, more recent research has identified oritavancin associated membrane depolarization and permeabilization among intact staphylococci and enterococci [10, 12]. This membrane-targeted mechanism of action is proposed to be independent of

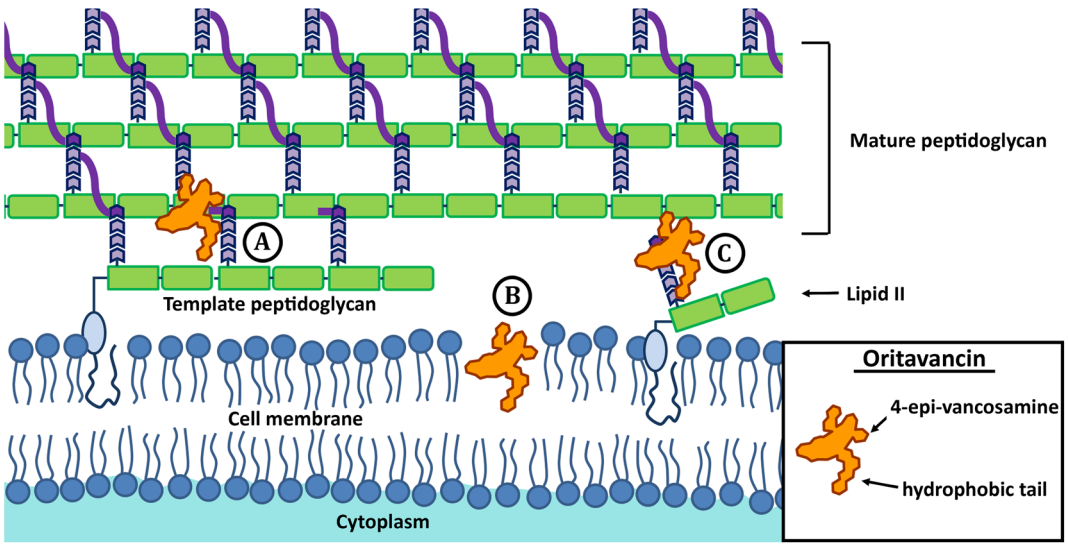

Fig. 3 Oritavancin bacterial binding sites. **a** Oritavancin binding to template peptidoglycan at cleft between hydrophobic tail group and 4-epi-vancosamine. **b** Oritavancin hydrophobic tail group insertion into bacterial cell membrane. **c** Oritavancin binding to D-alanyl-D-alanine stabilized by hydrophobic tail group

cellular growth and division. This is supported by the rapid bactericidal activity of oritavancin against stationary phase and biofilm-associated organisms, both often more resilient to antimicrobial treatment [13].

Although the lipoglycopeptides, including oritavancin, have been observed to dimerize through interactions between hydrophobic tail groups, dimerized oritavancin has not been observed bound to Lipid II, peptidoglycan, or bacterial membranes. Thus, it is currently unclear if this capability plays a role in the increased antimicrobial potency of oritavancin.

MICROBIOLOGY

Oritavancin exhibits potent activity against many resistant Gram-positive organisms including methicillin-susceptible *S. aureus* (MSSA), MRSA, VRSA, VISA, and both vancomycin-susceptible enterococci (VSE) and VRE [14–18]. Against MRSA, oritavancin has been shown to be eightfold more potent than daptomycin and 16- to 32-fold more potent than vancomycin and linezolid when tested against isolates in both the US and Europe [16]. Regardless of geographic region, it demonstrated equal activity, inhibiting 75.9% and 73.7% of MRSA isolates at a concentration of 0.03 mg/L from the US and Europe, respectively. Additionally, against multi-drug resistant (MDR) strains, oritavancin had minimum inhibitory concentrations (MICs) that were 8- to 32-fold lower than those of active comparators with a MIC for 50% of isolates (MIC_{50}) of 0.03 mg/L and a MIC for 90% of isolates (MIC_{90}) of 0.06 mg/L, compared to vancomycin with a MIC_{50} and MIC_{90} of 1 mg/L, daptomycin with a MIC_{50} of 0.25 mg/L and MIC_{90} of 0.5 mg/L, and linezolid with a MIC_{50} of 1 mg/L and MIC_{90} of 2 mg/L. It is important to note that these MIC data were collected using 0.002% polysorbate-80 as recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines, which results in lower MIC data than historically seen with this agent. Oritavancin also demonstrates potent activity against methicillin-resistant coagulase-negative Staphylococci (MRCoNS) as well as several strains of Streptococci, with a MIC_{50} and MIC_{90} of 0.06 and 0.12 mg/L for MRCoNS, 0.06 and 0.25 mg/L for *S. pyogenes*, and 0.03 and 0.06 mg/L for *S. agalactiae* [18]. MIC_{50}, MIC_{90}, and MIC ranges of oritavancin against staphylococci, streptococci, and enterococci causing SSTIs from the US in 2010–2013 are shown in Table 1. Of note, the CLSI susceptibility breakpoint for oritavancin against staphylococci, streptococci, and VSE are $\leq$0.12, $\leq$0.25, and $\leq$0.12 mg/L, respectively, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) break points are $\leq$0.125, $\leq$0.25 mg/L for *S. aureus* and streptococci, respectively [19]. In addition to MRSA, oritavancin has in vitro activity against hVISA, VISA, and VRSA with reported MIC ranges of 0.03–2, 0.12–4, and 0.12–2 mg/L, respectively [20–22]. The reported MIC_{90} for oritavancin against these organisms is 1, 2, and 0.5 compared to a MIC_{90} for vancomycin of 2, 8, and >512 mg/L for hVISA, VISA, and VRSA, respectively [20]. Additionally, oritavancin has been shown to have activity against daptomycin non-susceptible strains of *S. aureus* with a MIC range of 0.03–0.12 mg/L [21]. Although oritavancin clearly has some activity against these organisms in vitro, the MIC ranges do cross above the susceptibility breakpoint so caution should be used if considering use of this agent for these organisms clinically.

Table 1 MIC_{50}, MIC_{90}, and MIC ranges of oritavancin against staphylococci, streptococci, and enterococci causing skin and skin structure infections from the US in 2010–2013 [15]

Organisms	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
MSSA	≤0.008–0.25	0.03	0.06
MRSA	≤0.008–0.25	0.03	0.06
S. pyogenes	≤0.008–0.5	0.03	0.12
S. agalactiae	≤0.008–0.25	0.03	0.12
VSE (*E. faecium*)	≤0.008	≤0.008	≤0.008
VRE (*E. faecium*)	≤0.008–0.12	0.015	0.06

MIC minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *VRE* vancomycin-resistant enterococci, *VSE* vancomycin-susceptible enterococci

A unique characteristic about oritavancin, compared to other lipoglycopeptides, is that it has potent in vitro activity against both VSE and VRE [17, 18]. When tested against enterococci from bacteremic patients, the MIC_{50} and MIC_{90} for oritavancin against vancomycin-susceptible *E. faecalis* were 0.015 and 0.03 mg/L and *E. faecium* of ≤0.008 and ≤0.008 mg/L, both of which were lower than the MICs for ampicillin, vancomycin, daptomycin, and linezolid. Oritavancin also exhibited two- to eightfold greater activity than ampicillin, daptomycin, and linezolid against VanA-mediated vancomycin-resistant *E. faecalis* with an oritavancin MIC_{50} of 0.25 mg/L and MIC_{90} of 0.5 mg/L, and was 8- to 64-fold more potent against VanA-mediated vancomycin-resistant *E. faecium* than quinupristin-dalfopristin, linezolid, and daptomycin with an oritavancin MIC_{50} of 0.03 mg/L and MIC_{90} of 0.12 mg/L. However, it is important to note that the MIC range for these organisms did range from 0.03 to 1 mg/L and ≤0.008 to 0.5 mg/L for *E. faecalis* and *E. faecium*, respectively [17, 18]. Additionally, against enterococci from skin and soft tissue infections from the US and Europe, VanA-mediated vancomycin-resistant *E. faecalis* had an oritavancin MIC_{50} of 0.25 mg/L and MIC_{90} of 0.5 mg/L [15]. These values were 16-times higher than for vancomycin-susceptible isolates, for which the observed MIC_{50} and MIC_{90} were 0.015 and 0.03 mg/L, respectively. All vancomycin-susceptible and VanB-mediated vancomycin-resistant strains had equivalent oritavancin MIC_{50} of 0.004 mg/L and MIC_{90} of 0.008 mg/L, while higher MIC_{50} and MIC_{90} of 0.03 and 0.12 mg/L were obtained for VanA strains. Additionally, oritavancin has been shown to have synergistic activity against VRE when given with beta-lactams, reducing the vancomycin-resistant *E. faecium* MIC range from 0.03–0.12 mg/L when given alone to <0.01–0.12 mg/L when given with ceftaroline, ceftriaxone, or ampicillin [21].

In addition to the above mentioned Gram-positive organisms, oritavancin has demonstrated activity against *Clostridium difficile* [23]. When studied against 33 genotypically distinct *C. difficile* isolates, oritavancin MICs by broth microdilution ranged from 0.06 to 1 mg/L with a MIC_{90} of 1 mg/L. Additionally, it had an MIC_{90} two- to fivefold lower than metronidazole and vancomycin and was considered to be at least fourfold more potent than vancomycin against

76% of the *C. difficile* isolates. There have been few studies looking at oritavancin activity against *C. difficile* which have shown that oritavancin may adhere to spores, affecting spore recovery, and retaining antimicrobial activity even after washing [24]. These results are very promising for oritavancin's potential role in *C. difficile* infection in the future. However, additional studies will need to be done before it can be recommended for this indication.

PHARMACOKINETICS

Oritavancin possesses both similarities and distinctions compared to the pharmacokinetic profile of vancomycin. When intravenously administered across a range of doses both as individual and multiple infusions, oritavancin displays consistent linear kinetics [25]. A peak serum concentration of 140 mg/L is obtained following a single 1200 mg dose infused over 3 h [26]. The observed volume of distribution approximates 1 L/kg and 85–90% of the oritavancin is bound to serum proteins [27]. Owing again to the addition of the highly hydrophobic *N*-alkyl-*p*-chlorophenylbenzyl tail group, oritavancin possesses a prolonged half-life. Following an initial distribution phase, the terminal half-life ranges from 200–300 h. Less than 10% of the observed peak concentration remains in serum 24 h post-infusion. Distribution of oritavancin to blister fluid is limited to approximately 20% of simultaneous serum concentrations, but remains several folds above the MIC_{90} of organisms such as *S. aureus* and enterococci [28]. Oritavancin is predominantly cleared via the reticuloendothelial system, accumulating most notably in macrophages of the liver (Kupffer cells), kidney, spleen and lungs, as well as in the intestinal mucosa, thymus, and lymph nodes. Release and subsequent elimination of oritavancin from these tissues has been observed to be slow, and following a single dose of oritavancin only trace amounts of the administered dose are recovered from urine (<5%) and feces (<1%) respectively by day seven [25, 29]. Consequently, dose adjustment for renal or hepatic insufficiency is not required. No evidence of hepatically modified metabolites has been found.

PHARMACODYNAMICS

Oritavancin has been observed to possess rapid bactericidal activity against a broad array of Gram-positive organisms including those with reduced susceptibility to vancomycin. This activity is concentration-dependent and best predicted by the peak serum concentration to MIC ratio (C_{max}:MIC) and the area under the curve to MIC ratio (AUC:MIC) [30–32]. While pharmacodynamic target magnitudes certainly vary by model and isolate tested, in a neutropenic murine thigh infection model utilizing five different isolates of *S. aureus*, the average AUC:MIC at 24 h required for bacterial stasis, 1-$\log_{10}$, and 2-$\log_{10}$ colony-forming unit (CFU) reductions was approximately 90, 100, and 110, respectively [32]. It has also been noted in a number of pharmacodynamic experiments with dose fractionation, that front-loaded regimens with a single dose on day one produce greater reductions in bacterial burden than the same cumulative dose administered over several days [30–32]. This observation in turn supported the early investigation into single 1200 mg doses of oritavancin being used in the treatment of skin and soft tissue infections [33].

In time-kill experiments utilizing static concentrations approximating the unbound oritavancin in serum following either a 200 or 800 mg dose, bactericidal activity against all organisms tested (including MSSA, MRSA, hVISA, VISA, VRSA, vancomycin-susceptible *Enterococcus faecalis*, and VRE) was reported by 24 h [14]. Notably, against the three MRSA isolates tested, bactericidal activity was achieved in 1 h or less. None of the comparator agents [vancomycin, teicoplanin, linezolid and daptomycin (dosed at 4 mg/kg)] were found to possess bactericidal activity across all tested isolates, and no agent other than oritavancin achieved bactericidal activity against any of the VRE isolates tested. Similar rapid bactericidal activity of oritavancin was observed in subsequent experiments utilizing drug concentrations simulating the free oritavancin exposure with a single 1200 mg and three clinical MRSA isolates [34].

Intriguingly, the potent bactericidal activity of oritavancin is maintained against stationary phase and biofilm-associated *S. aureus*, both of which are often less susceptible to antimicrobials [35]. When tested against a substantial inoculum (about 10^7 CFU/mL) of MSSA or MRSA in nutrient depleted media, a static concentration of oritavancin approximating unbound drug at the peak serum concentration (fC_{max}) following a 200 or 800 mg dose (4 and 16 mg/L, respectively) consistently produced bactericidal killing. Additionally, the 16 mg/L dose of oritavancin tested also produced bactericidal activity against a VRSA isolate, while the 4 mg/L dose produced a 2.2 $\log_{10}$ CFU/mL reduction. Of the comparator agents [vancomycin, rifampin, linezolid, and daptomycin (dosed at 4 mg/kg)], daptomycin and rifampin both achieved bactericidal activity against the MRSA isolate tested at their respective $fC_{max.}$ However, no comparator agent achieved bactericidal activity against the MSSA or VRSA isolates at 24 h.

ANIMAL STUDIES

Oritavancin has been studied in a variety of animal models to determine its tissue and bone penetration and therefore potential role against Gram-positive organisms causing invasive diseases including meningitis, endocarditis, and osteomyelitis [30, 36–39]. When studied against VSE and both VanA- and VanB-mediated VRE endocarditis in rabbits, oritavancin displayed heterogeneous distribution throughout the cardiac vegetations [39]. In those rabbits with aortic endocarditis, twice-daily oritavancin was the only glycopeptide antibiotic tested that displayed significant activity regardless of the phenotype of enterococcal strains. When compared against vancomycin in rabbits with MRSA left-sided endocarditis, once-daily oritavancin was determined to be equally effective in both clearing the bacteremia and in reducing bacterial counts in the vegetations and tissues [36]. In a rabbit model of meningitis caused by *Streptococcus pneumoniae*, a single dose of oritavancin was shown to reduce bacterial titers in cerebrospinal fluid (CSF) almost as rapidly as continuous infusion ceftriaxone [37]. Maximum concentrations of oritavancin in the CSF were reached several hours after administration, and although the estimated CSF penetration was relatively low at 1–5%, the highly active in vivo activity resulted in reduced bacterial titers, decreased inflammatory markers, and sterilization of the CSF. However, the tolerability of such high doses needed to penetrate into the CSF is still to be determined in humans. Oritavancin has also been studied in rabbits to determine the differential distribution from serum to bone tissue [40]. Following a

5 min infusion, oritavancin serum concentrations were greater than or equal to 10 mg/L for at least 24 h, which is several times higher than the MIC_{90} for *S. aureus* (0.06 mg/L) and *S. pneumoniae* (≤0.008 mg/L). Additionally, bone concentrations remained above the MIC_{90} for *S. aureus* for over 168 h following a single 20 mg/kg dose.

In addition to these above mentioned organisms, oritavancin has been compared to clindamycin and vancomycin on its ability to induce *C. difficile* in hamsters [41]. Following oritavancin exposure, there was no evidence of *C. difficile* germination or toxin production in both the hamsters and the in vitro gut models. Additionally, oritavancin reduced *C. difficile* total counts and demonstrated potential activity against the spores, indicating a possible treatment option for *C. difficile* infections in the future.

Clinical Trials

Clinical trials presented here are related to the registration of oritavancin with a novel therapeutic dosing scheme and earlier trials utilizing different dosing regimens were not included. To evaluate the non-inferiority of front-loaded oritavancin dosing regimens compared to infrequent dosing in complicated skin and skin structure infections (cSSSI), a phase II, multicenter, randomized, double-blind, parallel, active-comparator study was completed.(33) The single or infrequent doses for the treatment of complicated skin and skin structure infections (SIMPLIFI; ClinicalTrials.gov identifier, NCT00514527) study included adult patients with a cSSSI either suspected or proven to be caused by a Gram-positive pathogen. To meet the definition of cSSSI for the purposes of this study, patients were required to have one or more of the following: infection required surgical intervention within 48 h of enrollment; infection suspected or confirmed to involve deep subcutaneous tissue (excluding fascia or muscle layers); significant underlying disease present to complicate treatment, including diabetes, bacteremia, cellulitis with ≥3% of total body surface area, corticosteroid therapy, cirrhosis, burn, radiation therapy, or known immune suppression. There were three oritavancin treatment groups for comparison including daily (200 mg daily for 3–7 days), infrequent (800 mg on day 1 with an optional 400 mg on day 5), and single-dose (1200 mg as one-time dose) groups. The primary objective of the study was the clinical response in the clinically evaluable (CE) and intention-to-treat (ITT) populations at test of cure (TOC) on days 21–29, decided by the investigator, as cure, improvement, failure, or indeterminate based on clinical signs and symptoms.

A total of 302 patients were included in the ITT population (100 in the daily group, 103 in the infrequent group, and 99 in the single-dose group), of which 228 were included in the CE population [33]. Demographics and baseline characteristics were similar among all treatment groups, with 37.7% of patients having major abscesses, 31.8% wound infections, and 30.5% cellulitis. The most commonly isolated pathogen was *S. aureus* (87.6%), 49% being MRSA, with other Gram-positive organisms isolated including *Streptococcus pyogenes* (5.7%), *Streptococcus agalactiae* (3.8%), and *E. faecalis* (3.8%). The oritavancin MIC_{90} for all *S. aureus* isolated was 0.12 mg/L, and the overall range of MICs for *S. aureus* was 0.008–0.5 mg/L. There was no difference in the primary outcome of clinical cure/improvement in the ITT population, occurring in 72.4%, 78.2%, and 81.8% in the daily, infrequent, and single-dose groups,

respectively [90% confidence interval (CI), −1.7 to 17.8 for comparison of 1200 and 200 mg groups; 90% CI, −5.8 to 14.6 for comparison of 800 and 200 mg groups]. Similarly, when evaluating the results for only those with *S. aureus* isolated (both MRSA and MSSA), cure rates were similar among groups with 67.4% for the daily group, 79.5% for the infrequent group, and 78.9% for the single-dose group. Over half of the patients in the study experienced an adverse event (56%, 61.2%, and 55.6% in the daily, infrequent, and single-dose groups, respectively), of which the majority were considered to be mild or moderate in severity (85.7%) and unrelated to study medication (58.0%). Based on these phase II study results, oritavancin is considered safe, effective, and well tolerated as a 1200 mg single dose for the treatment of cSSSI caused by Gram-positive organisms, including MRSA.

Two pivotal double-blind, randomized phase III studies, SOLO I and II (ClinicalTrials.gov identifiers, NCT01252719 and NCT01252732, respectively), were completed to assess the clinical efficacy and safety of the previously studied 1200 mg single dose of oritavancin in acute bacterial skin and skin structure infections (ABSSSIs) [42, 43]. These studies included patients 18 years or older with ABSSSIs thought or proven to be caused by a Gram-positive organism with a lesion surrounded by erythema, edema, or an induration of at least 75 cm^2. Patients were either given oritavancin 1200 mg as a single dose, or vancomycin 1000 mg or 15 mg/kg dosed twice daily for 7–10 days. The primary outcome was a composite endpoint of the following three criteria: cessation of spreading or reduction in lesion size, absence of fever, and no need for a rescue antibiotic at 48–72 h. Non-inferiority of oritavancin against vancomycin was defined by a 10% non-inferiority margin at the 1-sided α level of 0.025, with a primary efficacy outcome rate assumed to be 75%. Key secondary outcomes were investigator-assessed clinical cure at the post-therapy evaluation (PTE) and a reduction in lesion size of 20% or more at the early clinical evaluation (ECE). There were no significant differences in demographics or baseline characteristics between groups or between studies. The majority of patients in SOLO I had cellulitis (51.2% and 48.6% for oritavancin and vancomycin, respectively) and abscesses (29.5% and 29.4%, respectively) while the patients in SOLO II were more evenly split among wound (38.0% and 35.1%, respectively), cellulitis (28.6% and 33.3%, respectively), and abscesses (33.4% and 31.7%). The median lesion area at baseline was 248.0 versus 225.6 cm^2, and 287.8 versus 308.8 cm^2 in the oritavancin versus vancomycin in SOLO I and SOLO II, respectively. A positive culture occurred in 61.1% and 60.5% in the oritavancin and vancomycin groups in SOLO I, and 69.8% and 70.1% in the oritavancin and vancomycin groups in SOLO II. The most common pathogen isolated from the infection site in both studies was *S. aureus* and MRSA, isolated in 201 and 204 patients in SOLO I and SOLO II, respectively. Of note, there were few patients included in these studies with positive blood cultures as baseline. For SOLO I, there were 18 and 9 patients compared to SOLO II with 6 and 10 patients with positive blood cultures in the oritavancin and vancomycin groups, respectively.

Oritavancin met the predetermined non-inferiority criteria against vancomycin in the modified ITT (mITT) population with 82.3% of patients in the oritavancin group versus 78.9% in the vancomycin group (absolute difference 3.4, 95% CI, −1.6 to 8.4) and 80.1% in the oritavancin group versus 82.9% in the

vancomycin group (absolute difference −2.7, 95% CI, −7.5 to 2.0) meeting the primary composite endpoint in SOLO I and SOLO II, respectively. Additionally, when evaluating the clinical cure at PTE [79.6% vs. 80.0%; absolute difference −0.4 (95% CI, −5.5 to 4.7) and 82.7% vs. 80.5%; absolute difference 2.2 (95% CI, −2.6 to 7.0) for oritavancin vs. vancomycin in SOLO I and SOLO II, respectively] and reduction in lesion size of 20% or more at ECE [86.9% vs. 82.9%; absolute difference 4.1 (95% CI, −0.5 to 8.6) and 85.9% vs. 85.3%; absolute difference 0.6 (95% CI, −3.7 to 5.0) for oritavancin vs. vancomycin in SOLO I and SOLO II, respectively], oritavancin also met the predetermined non-inferiority margin of less than a 10% difference. In those patients with isolated MRSA in the microbiological ITT (MicroITT) population, the primary efficacy endpoint occurred in 80.8% of those on oritavancin versus 80.0% of those on vancomycin [absolute difference 0.8 (95% CI, −10.1 to 11.7)] in SOLO I, and 82.0% of those on oritavancin versus 81.2% of those on vancomycin [absolute difference 0.8 (95% CI, −9.9 to 11.5)] in SOLO II, again showing similar efficacy between groups in both studies.

Treatment-emergent adverse events (TEAEs) occurred similarly between groups with 63.8% versus 60.0% and 50.9% versus 50.2% of patients reporting at least one adverse event in the oritavancin versus vancomycin groups in SOLO I and SOLO II, respectively. However, these TEAEs were generally considered to be mild in severity and only 5.8% in the oritavancin group versus 3.8% in the vancomycin group in SOLO I and 3.6% in the oritavancin group versus 2.6% in the vancomycin group in SOLO II reported discontinuation of study drug due to adverse events. Additionally, in SOLO II, 5 cases of osteomyelitis were reported as an adverse event in the oritavancin group compared to 0 cases in the vancomycin group, and in SOLO I, one case of osteomyelitis was reported in each group. It was noted that the 5 events in SOLO II occurred within the first 9 days of initiating the study medication and the authors suggest that the osteomyelitis was likely present at the time of enrollment, but missed by the investigators. Based on this data, osteomyelitis is listed as a warning for oritavancin, and it is recommended to monitor patients for signs and symptoms of osteomyelitis and to initiate appropriate alternative therapy if it is suspected [19]. Of note, due to the extended half-life of oritavancin, safety effects were evaluated at the 60 day follow-up assessment and the investigators failed to identify any prolonged or delayed adverse events in the oritavancin group [42, 43]. Therefore, based on the SOLO I and SOLO II studies, oritavancin is considered a safe and effective single-dose alternative to traditional therapies for ABSSSIs caused by Gram-positive organisms.

In addition to the completed ABSSSI studies, a new trial on the ClinicalTrials.gov registry and results database is currently recruiting for a pediatric study looking to evaluate oritavancin for suspected or confirmed bacterial infections in children (ClinicalTrials.gov identifier, NCT0213430). Furthermore, a safety, tolerability and pharmacokinetics study of a new oritavancin formulation with an adjusted infusion time, concentration, and reconstitution/administration solution is also recruiting at this time (ClinicalTrials.gov identifier, NCT02471690).

SAFETY AND DRUG INTERACTIONS

Overall, the most commonly reported adverse events in SOLO I and SOLO II, reported in ≥3% of patients, were headache, nausea, vomiting, limb

and subcutaneous abscess, and diarrhea [19, 43, 44]. Adverse events leading to discontinuation of therapy only occurred in 3.7% of those patients on oritavancin, with the most common reasons being cellulitis (0.4%) and osteomyelitis (0.3%). Serious adverse events were only reported in 5.8% and 5.9% of patients on oritavancin and vancomycin, respectively. Additionally, laboratory abnormalities were also relatively low with only two laboratory parameters, alanine aminotransferase and aspartate aminotransferase level elevations, occurring in $\geq$1.5% of patients taking oritavancin.

One distinct different between oritavancin and other glycopeptides is its potential for drug–drug and drug-lab interactions. Oritavancin was studied in healthy volunteers and found to be a nonspecific, weak inhibitor of cytochrome P450 (CYP) 2C9 and CYP2C19 and an inducer of CYP3A4 and CYP2D6 [19, 45]. When oritavancin was given with warfarin and omeprazole (CYP2C9 and CYP2C19 substrates, respectively), there was a 31% increase in the mean AUC of warfarin and a 15% increase in the ratio of omeprazole to 5-hydroxy-omeprazole. Additionally, oritavancin interactions with the CYP3A4 and CYP2D6 enzymes resulted in an 18% decrease in the mean AUC of midazolam and a 31% decrease in the ratio of dextromethorphan to dextrorphan concentrations. Oritavancin also interacts with several laboratory values due to its ability to bind to the phospholipid reagent, preventing the activation of coagulation in commonly used laboratory coagulation tests [19]. The laboratory tests affected include prolonged activated partial thromboplastin time, prolonged prothrombin time/international normalized ratio, and, theoretically, prolonged activated clotting time. These drug-laboratory interactions make the use of these labs unreliable and caution must be used when attempting to monitor the anticoagulation effects of heparin and warfarin during this time period. Due to this interaction and the potential concern of these unreliable monitoring tools, heparin is contraindicated during the first 48 h after oritavancin administration [19]. Additional studies are listed on the ClinicalTrials.gov registry and results database that will further evaluate the interaction with warfarin and help clinicians better understand how to handle patients who need anticoagulation while on oritavancin therapy.

CONCLUSIONS

Oritavancin is a semisynthetic lipoglycopeptide antibiotic that was recently approved for the treatment of ABSSSI in a time when there is a rise in the emergence of resistance and a deficit in the development of new antibiotics to treat these MDR organisms. It is unique in that its additional mechanisms of action allow it to have enhanced antimicrobial potency against both VanA- and VanB-mediated VRE, unlike the earlier glycopeptides. Oritavancin possesses a prolonged half-life ranging from 200–300 h, allowing for the convenience of single doses to complete a 7-day treatment duration. Although oritavancin is only currently FDA approved for ABSSSI, this agent may eventually have a role in additional indications where new innovative therapy is needed including bacteremia, infective endocarditis, and osteomyelitis; however, additional studies would need to be completed before they can be recommended in these indications.

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