Dalbavancin, Oritavancin, and Tedizolid for the Treatment of Skin and Soft Tissue Infections

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Learning Objectives

Upon completion of this article, the learner should be able to:

1. Compare and contrast pharmacological characteristics of dalbavancin, oritavancin, and tedizolid.

2. State the FDA-approved indications for dalbavancin, oritavancin, and tedizolid.

3. Describe the efficacy results dalbavancin, oritavancin, and tedizolid demonstrated in Phase III clinical trials.

4. Evaluate Phase III clinical trials of dalbavancin, oritavancin, and tedizolid for strengths, limitations, and potential impact on practice.

5. Describe potential advantages and disadvantages of dalbavancin, oritavancin, and tedizolid compared to each other.

INTRODUCTION

Antibiotic resistance is a global, growing problem, and the Centers for Disease Control and Prevention (CDC) reports that an estimated 2,049,442 illnesses were caused by antibiotic resistant bacteria in the US in 2013.¹ Ultimately, these infections resulted in at least 23,000 deaths.
**Staphylococcus aureus** is a gram-positive organism that may be found as part of the normal flora found on human skin. Methicillin-resistant *S. aureus* (MRSA) is a type of multi-drug resistant *S. aureus* that has developed resistance to the most commonly used anti-staphylococcal antibiotics (e.g., nafcillin, oxacillin). In 2013, 11,285 patients died from MRSA infections. Other gram-positive bacteria with emerging resistance include vancomycin-resistant enterococcus (VRE) which caused 1,300 deaths in 2013, and vancomycin-resistant *S. aureus* (VRSA) (13 cases 2002-2013). Acute bacterial skin and skin-structure infections (ABSSSI) are commonly caused by *Streptococcus pyogenes*, methicillin-sensitive *Staphylococcus aureus* (MSSA), MRSA, and less commonly by other *Streptococcus* species, *Enterococcus faecalis*, and gram-negative pathogens.

Antimicrobial therapy for skin and soft tissue infections due to staphylococcal species should be selected based on infection type, whether the infectious organism is most likely to be MSSA or MRSA, severity of illness, and other patient-specific factors. For ABSSSI caused by MSSA, first generation cephalosporins, nafcillin, oxacillin, and dicloxacillin are considered preferred agents. The agent of choice for ABSSSI caused by MRSA is vancomycin; however, other options such as trimethoprim/sulfamethoxazole (TMP/SMX), tetracyclines, linezolid, and daptomycin may be used. Factors such as disease severity and patient factors help determine specific agents, as well as whether intravenous (IV) or oral formulation is preferred.

Due to the growing rates of antimicrobial resistance, the Infectious Disease Society of America (IDSA) has called for the development of 10 systemic antibiotics by the year 2020, the “10 X ’20” initiative. In September 2014, the US government introduced the National Strategy for Combating Antibiotic Resistant Bacteria which calls for the development of at least two new antibiotics by government research agencies by 2018. The past two years have seen several new antibiotics approved by the US Food and Drug Administration (FDA) for ABSSSI due to MRSA. These include dalbavancin, oritavancin, and tedizolid. These antibiotics offer new treatment options against resistance and have unique advantages and disadvantages relative to each other and currently approved agents. It will be important for medical professionals to compare and contrast newly approved agents, and assess their place in therapy, as they come on the market and enter clinical practice.

PHARMACOLOGY, PHARMACOKINETICS, AND MICROBIOLOGICAL ACTIVITY

**Dalbavancin (May 2014)**

Dalvance® (dalbavancin) was approved by the FDA in May 2014 to treat skin and soft tissue infections (SSTIs) caused by gram-positive microorganisms. Dalbavancin, a semisynthetic lipoglycopeptide similar to vancomycin, binds to the terminal of the D-alanyl-D-alanine pentapeptide chain in nascent peptidoglycan preventing cross-linking and inhibiting cell wall synthesis. Dalbavancin has a long lipophilic side chain, which helps to stabilize and anchor with peptidoglycan to ensure prolonged interaction. This
interaction is the cause for dalbavancin’s extended half-life.

It is recommended to initiate at a dose of 1000 mg IV followed one week later (day 8) by a second dose of 500 mg IV. Dalbavancin is highly protein bound (93%) and volume of distribution ranges from 7 to 13 liters, with a half-life of 346 hours. These pharmacokinetics allow for the unique approach to dosing. Dalbavancin is excreted unchanged through the urine (33%) and does require renal dose adjustments. In patients with CrCl less than 30 mL/min, it is recommended to adjust the dose to 750 mg IV followed one week later (day 8) by 375 mg. However, patients on regularly scheduled hemodialysis do not require a dosage adjustment. There are no recommended dosage adjustments for hepatic impairment, gender, or age. Dalbavancin is bactericidal in vitro against gram-positive microorganisms such as MSSA, MRSA, Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus anginosus.

Oritavancin (August 2014)

Oritavancin (Oritavancin) was approved by the FDA in August 2014 to treat SSTIs as a single IV dose of 1200 mg. Similar to dalbavancin, oritavancin is a semisynthetic lipoglycopeptide and therefore has common pharmacology to vancomycin. Owing to oritavancin’s hydrophobic tail (4’-chlorobiphenylmethyl), it differs from vancomycin in two other mechanisms which may allow activity against vancomycin-resistant organisms. Oritavancin inhibits cross-linking via transpeptidation and promotes cell membrane permeability via self-assembly of dimers to increase depolarization. This bactericidal agent is approved to treat adults with SSTIs caused by gram-positive organisms: MSSA, MRSA, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group, and vancomycin-susceptible Enterococcus faecalis. Like dalbavancin, oritavancin is highly distributed into tissues (Vd = 87.6 L) and primarily excreted unchanged very slowly by renal route with feces as minor route. Likely due to the hydrophobic tail, it has 85% protein-binding and a long elimination half-life of 245 hours. No dose adjustments are required for age, weight, diabetes status, gender, renal, and hepatic impairment.

Tedizolid (June 2014)

Sivextro® (tedizolid phosphate) is a novel oxazolidinone prodrug that was approved by the FDA in June 2014. Tedizolid is FDA approved for the treatment of ABSSSI at oral or IV doses of 200 mg once daily for 6 days. Linezolid (Zyvox®), approved in 2000, is the only other member of this antibiotic class. Tedizolid phosphate is rapidly converted to tedizolid by endogenous phosphatase enzymes and binds to the bacterial 50S ribosomal subunit to inhibit bacterial protein synthesis. Both oxazolidinones are bacteriostatic against MSSA, MSRA, Enterococcus species. Linezolid, but not tedizolid, is bactericidal for Streptococcal species (tedizolid is bacteriostatic). Tedizolid is well distributed into tissues (Vd = 67.1-80.1 L) with IV administration. It has 85% protein binding and a half-life of 245 hours.

Activity 1: Develop a table that describes the mechanism of action for dalbavancin,
oritavancin, and tedizolid. Which agent(s) is (are) bactericidal? (Learning Objective 1)

Activity 2: List the FDA-approved indication(s) for each of the three medications. (Learning Objective 2)

CLINICAL TRIALS

Dalbavancin

Dalbavancin for Infections of the Skin Compared to Vancomycin at an Early Response (DISCOVER) 1 and 2 were identically designed randomized, double-blind, double-dummy, international, multicenter trials. The two trials enrolled and randomized 1312 patients in a 1:1 ratio to receive either dalbavancin 1 gram IV over a period of 30 minutes on day 1, followed by 500 mg IV infused over 30 minutes on day 8 or vancomycin 1 gram, or 15 mg/kg, IV over 120 minutes every 12 hours for a minimum of 3 days, with the option to switch to linezolid 600 mg orally every 12 hours for a total duration of 10 to 14 days. Randomization was stratified for type of SSTI, major abscess, and fever. Patients with a proven or suspected gram-positive pathogen SSTI with two local and at least one systemic sign of infection were included. Qualifying systemic signs of infection included fever, white blood cell (WBC) count greater than 12,000/mm³, or greater than 10% immature neutrophils. Patients with gram-negative infections or who received antibiotics within the previous two weeks were excluded. The primary efficacy endpoint was early clinical response at 48-72 hours, which was defined as cessation of primary ABSSSI lesion margin spread and afebrile at three consecutive readings completed 6 hours apart. Secondary endpoints included safety and clinical status at end of therapy.

Baseline characteristics between the dalbavancin and vancomycin/linezolid groups were well distributed, with more than 85% of patients having a fever greater than 100.4°F at baseline, a median size of 351 cm² for the infected area in DISCOVER 1, and a median size of 336 cm² for the infected area in DISCOVER 2. When evaluating pooled results, there were 659 patients in the dalbavancin group and 653 in the vancomycin/linezolid group. Infection types in each group (dalbavancin and vancomycin/linezolid) were cellulitis (53.7% and 53.4%), major cutaneous abscess (24.6% and 26.5%), and traumatic wound (21.5% and 20.1%).

In the intention-to-treat (ITT) pooled analysis of the primary outcome, the dalbavancin group and vancomycin/linezolid group had similar percentages of responders (79.7% vs 79.8%, see Table 1). Dalbavancin was considered non-inferior to vancomycin/linezolid because the lower limit of this confidence interval was above the pre-set -10% non-inferiority margin. Secondary efficacy results in sensitivity populations were similar. Adverse events reported with dalbavancin were less frequent in respect to vancomycin/linezolid. In the dalbavancin group, 32.8% of patients reported an adverse event, compared with 37.9% of patients in the vancomycin/linezolid group. The most common types of treatment-related adverse events were nausea (2.5% vs 2.9%; p=0.62), diarrhea (0.8% vs 2.5%; p=0.02), and pruritus (0.6% vs. 2.3%; p=0.01).

Patient baseline characteristics were well-balanced, with the exception of more patients with diabetes mellitus enrolled in the vancomycin/linezolid group (14.1%) compared to the dalbavancin group.
This confounding variable could increase likelihood of a positive outcome with dalbavancin. The nature of the study design (e.g. RCT, double-blinded, double-dummy), and stratification of treatment groups were also strengths. The design of the studies were also adherent to FDA guidelines in regards to definitions of infections, non-inferiority, sample size, and enrolling less than 30% of patients with major abscesses. The primary outcomes were based upon early clinical response rather than the end of treatment or follow-up visits. This is beneficial due to the concern of natural resolution of the infection rather than successfulness of medications.

This study also had some limitations, in particular related to control, duration, and blinding. IDSA guidelines recommend empiric antibacterial with vancomycin in addition to antipseudomonal antibiotics during the initial episode of fever with neutropenia. However, linezolid is an alternative agent in the guidelines based on the lack of clinical data. The duration of therapy may not have been applicable to real world scenarios. Guidelines recommend treatment duration for most bacterial SSTIs should be 7 to 14 days; however, therapy is often extended if symptoms have not resolved, which could reveal additional efficacy or adverse effects. Although the study participants and investigators were blinded to treatment arms, the study did not describe which vancomycin patients were switched to oral linezolid. Adherence to the twice daily vancomycin/linezolid regimen may be greater than the adherence observed in typical clinical practice. This could have provided higher success rates in the vancomycin/linezolid arm than seen in actual practice. Vancomycin trough levels were not reported, and patients could have been assigned to a fixed dose of 1 g twice daily, regardless of weight. Therefore, appropriate dosing of vancomycin could not be determined. Overall, dalbavancin met criteria for non-inferiority to vancomycin/linezolid in the primary outcome, which correlated with the secondary outcome, and similar rates of adverse events were seen between the two groups. Based on non-inferiority, dalbavancin may be considered an alternative to vancomycin for the treatment of ABSSI.

Oritavancin

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections (SOLO 1) was an international, randomized 1:1 ratio, double-blind phase III, non-inferiority trial of 954 adults with SSTI (wound infection, cellulitis/erysipelas, or major cutaneous abscess) diagnosis suspected by a gram-positive pathogen requiring at least 7 days of IV therapy. Patients either received single IV dose of oritavancin 1200 mg or IV vancomycin regimen (1 g or 15 mg/kg) twice daily for 7 to 10 days. Consistent with the FDA Guidance for Industry, each lesion required erythema, edema, or an induration of at least 75 cm². In addition to meeting SSTI diagnosis, at least one sign of systemic inflammation, 70 years or older, diabetes mellitus, or immunosuppressive therapy in the last 3 months must be present. Patients who required anticoagulant monitoring were excluded. The endpoint descriptions are presented in Table 1.

In the modified ITT population, baseline characteristics were well-balanced between oritavancin and vancomycin arms, with wound infections (19.4% vs. 21.9%; 21% MRSA), cellulitis (51.2% vs 48.6%; 21% MRSA), and abscesses (29.5% vs
29.4%; 58% MRSA). Baseline temperature of at least 100.4°F (14.3% vs 16.5%), median lesion area (248 vs 225.6 cm²), and positive blood cultures for *S. aureus* (1.9% vs 0%) were also similar between groups. In the safety population, the mean total daily dose of vancomycin was 2.3±0.94 g with a duration of 8.1±2.43 days. Before the fourth dose, the mean trough level was 15.4 mcg/mL (11.1 mcg/mL median).

The primary endpoint met the non-inferiority margin of 10% which occurred in 82.3% in the oritavancin arm and 78.9% in the vancomycin arm (see Table 1). Clinical cure occurred in 79.6% and 80.0% of patients (-0.4% absolute difference, 95% CI -5.5% to 4.6%). Other results for secondary efficacy endpoints were similar between groups. There were no significant differences in meeting the primary endpoint for patients with a BMI >30 kg/m² or MRSA infection. Sixty percent of oritavancin patients and 63.8% of vancomycin patients experienced at least one adverse event. Adverse events reported with oritavancin at different frequencies compared to vancomycin included nausea (11% vs 8.9%), pruritus (3.4% vs 9.1%), and infusion-site reaction (4.0% vs 7.1%).

SOLO 2 was a second non-inferiority trial of the same design as SOLO 1 consisting of 1,005 adults with SSTIs. In the modified ITT population, baseline characteristics were well-balanced between oritavancin and vancomycin arms, in terms of wound infections (38% vs 35.1%; 23% MRSA), cellulitis (28.6% vs 33.3%; MRSA 10%), and abscesses (33.4% vs 31.7%; MRSA 27%). Baseline temperature of 100.4°F or greater (23.5% vs 21.2%), median lesion area (287.8 vs 308.8 cm²), and positive blood culture for *S. aureus* (2% vs 2%) were similar between groups.

Compared to SOLO 1, SOLO 2 had more wound infections, less cellulitis, and more patients with fever. In the safety population, the mean total daily dose of vancomycin was 2.1±0.63 g with a duration of 8.4±2.12 days. Before the fourth dose, the mean trough level was 14.2 mcg/mL (10.5 mcg/mL median). The vancomycin dosing and levels are similar to SOLO 1.

Early response was achieved in 80.1% of patients in the oritavancin arm and 82.9% of patients in the vancomycin arm (see Table 1). Clinical cure occurred in 82.7% and 80.5% (absolute difference 2.2%, 95% CI -2.6% to 7.0%). There were no significant differences in meeting the primary endpoint for patients with a BMI >30 kg/m², age, MRSA infection, sex or race. Adverse events reported with oritavancin at different frequencies compared to vancomycin included nausea (8.9% vs 12%), headache (7% vs 5.6%), pruritus (2.6% vs 5.8%), and infusion-site phlebitis (3.2% vs 1%).

Strengths of the oritavancin studies included baseline characteristics that were well-balanced taking into consideration of clinical variables. The study design was adherent to the FDA guidelines in terms of definitions of infections, non-inferiority, sample size, and enrolling no more than 30% of patient with major abscesses. Endpoints were partially adherent to the FDA guidelines where the primary is recommended to measure clinical response at 48 to 72 hours as a reduction in lesion size of at least 20%. Secondary endpoints at 7 to 14 days are recommended further assessing lesion size, symptoms, and pain.

There were several limitations in the SOLO studies. The vancomycin regimen correlates with the IDSA guidelines of 30
mg/kg/day in 2 divided doses with a target trough level of 15 to 20 mcg/mL in severe infection; however, it is likely the 1 g every 12-hour dosing could be too low if applied to overweight and obese patients. Prevalence of the two dosing options was not clear. Although SOLO 2 was double-blinded, the study did not explain how it addressed monitoring trough levels in placebo infusions. Utilizing vancomycin may not fully represent practice since SSTI treatment is based on stratifying patients by severity and other patient factors; not all patients in the study had severe infections or S. aureus. In addition, about 15 to 20% of patients had baseline fever, yet the absence of fever was used for the primary endpoint as part of determining clinical status. This could increase probability for meeting the primary endpoint. Finally, a protocol for adjunctive therapies such as wound dressing changes for the treatment of SSTIs were not described. Overall, results from SOLO 1 and SOLO 2 suggest that oritavancin is non-inferior to vancomycin for treatment of SSTI, and may be considered as an alternative agent in relevant patients.

**Tedizolid**

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections (ESTABLISH-1), randomized 667 patients in a 1:1 ratio to receive either tedizolid 200 mg orally once daily for 6 days or linezolid 600 mg orally twice daily for 10 days. Patients with a documented or suspected gram-positive-pathogen ABSSSI with one local and one regional, or at least one systemic, sign of infection were included. Qualifying systemic signs of infection included fever, white blood cell (WBC) count of ≥10,000/mcL or <4,000/mcL, or >10% immature neutrophils. Patients with gram-negative infections or who received antibiotics with gram-positive activity within the previous 96 hours were excluded. The primary efficacy endpoint was the early clinical response at 48-72 hours, which was defined as patient being alive and afebrile with cessation of primary ABSSSI lesion margin spread and without use of additional antibiotics with gram-positive activity. Secondary endpoints included safety, clinical response at end of treatment (EOT), and at 7 to 14 days following EOT.

Baseline characteristics between groups were similar. There were 332 patients in the tedizolid group and 335 patients in the linezolid group. Infection types in each group (tedizolid and linezolid) were cellulitis/erysipelas (40.7% and 41.5%), major cutaneous abscess (30.1% and 29.3%), and wound (29.2% and 29.3%). About 63% of patients had at least one pathogen isolated and identified at baseline. The identified pathogens, over 80% were Staphylococcus aureus in each group with the tedizolid group having 42.1% and the linezolid group having 43.1% of identified isolates being MRSA.

In the ITT analysis of the primary outcome, 79.5% of the tedizolid phosphate group and 79.4% of linezolid group were responders at 48 to 72 hours. The results represented a treatment difference of 0.1% (95% CI, -0.6% to 0.2%, see Table 1). Similarly, treatment response at EOT was 69.3% and 71.9% (absolute difference - 2.6%, 95% CI -9.6% to 4.2%) for tedizolid and linezolid groups, respectively. These numbers may have been somewhat lower due to treatment failures at 48-72 hours being carried over at the EOT assessment regardless of symptoms. In the tedizolid group, 40.8% of patients reported an adverse effect, compared with 43.3% of patients in
the linezolid group. The most common types of adverse events were nausea (8.5% tedizolid, 13% linezolid), headache (6% tedizolid, 5% linezolid), diarrhea (4.5% tedizolid, 5% linezolid), and abscess (4% tedizolid, 2% linezolid).

The second trial, ESTABLISH-2, was a randomized, double-blind, phase 3, non-inferiority trial designed to evaluate the safety and efficacy of IV to oral tedizolid for treatment of patients with ABSSSI. Investigators randomized 666 patients with cellulitis/erysipelas (50%), major cutaneous abscess (20%), or wound infections >75 cm² (30%). Gram-positive pathogens were suspected or documented in all cases, and patients were required to have at least one systemic or regional sign of infection (lymphadenopathy, fever, WBC ≥10,000/µL or <4,000/µL, or >10% immature neutrophils) in addition to the size of the lesion (minimum lesion area 75 cm²). Patients were randomized in a 1:1 ratio to receive 200 mg tedizolid phosphate IV once daily for 6 days or 600 mg linezolid twice daily for 10 days with the option for oral step-down after at least two doses of IV treatment with no signs of worsening infection and one or more signs of infection improvement. The primary endpoint was early clinical response (ECR) at 48-72 hours after starting treatment, which was defined as afebrile with ≥20% reduction in lesion size without having received other any systemic antibiotics with gram-positive activity. These criteria differed from ESTABLISH-1 based on new FDA recommendations released in 2011 after ESTABLISH-1 began. Patients with missing data were considered non-responders. Secondary endpoints included patient reported pain and treatment response at days 7, EOT, and post therapy assessment (PTA) on day 7 to 14 following EOT.

The groups were well matched at baseline in regards to region of enrollment and type of ABSSSI due to stratification. The 334 patients in the linezolid group had more comorbidities such as obesity, diabetes, and hepatitis C, but the 332 patients in the tedizolid group had higher rates of WBC count above 10,000/µL or below 4,000/µL. Gram-positive pathogens were isolated in approximately 59% and 60% of patients tedizolid and linezolid groups, respectively; 27% and 28% of these were MRSA.

Early clinical response (ECR) was achieved in 85% of the patients in the tedizolid group and 83% of the patients in the linezolid group (see Table 1). Results at the EOT were consistent with ECR findings. Eighty-five percent of the patients in the tedizolid group and 83% of patients in the linezolid group had achieved clinical response (absolute difference -2.6%, 95% CI -3% to 8.2%). The rate of adverse events was similar between groups (45% and 43%) with 1 patient in the tedizolid group and 4 patients in the linezolid group discontinuing therapy due to adverse events. The most common adverse events were nausea (8% tedizolid, 11% linezolid), headache (6% tedizolid, 7% linezolid), and abscess (4% tedizolid, 3% linezolid).

Like the DISCOVER and SOLO studies, both ESTABLISH-1 and ESTABLISH-2 were set up using appropriate design (e.g., randomization, blinding), and use a 10% non-inferiority margin in accordance with FDA guidelines. Each study included a variety of ABSSSI types (e.g., cellulitis, erysipelas, cutaneous abscess, wound infection), increasing external validity for a variety of infection types. Pathogen types were
similarly variable. Both studies had high concordance between groups as to average length of IV treatment prior to oral switch, increasing internal validity. Finally, the use of ≥20% reduction in lesion area as a criterion for early treatment response was an improvement in ESTABLISH-2 compared to ESTABLISH-1,19 that was consistent with changes in practice and updates to FDA guidelines.16 The updated endpoint could have increased sensitivity for predicting treatment failure.20

While investigators were able to determine that IV tedizolid was non-inferior to linezolid, the study had several limitations.20 The study did not enroll severely ill patients (e.g., only 2% and 4% of the tedizolid and linezolid groups had bacteremia in ESTABLISH-2; rates of elevated white blood cell count were 39.7 to 42.2% in ESTABLISH-1 and 45 to 53% in ESTABLISH-2), and results can only be projected on patients with similar infection severity. Formal severity assessments were not reported. The study population also had low rates of comorbidities, especially in patients enrolled from the community setting. Only about 42.5% of patients enrolled in the study were admitted to or already in the hospital at the time of the study. This could also be limiting when applying the results to sicker patient populations. Antibiotic therapy is often extended by prescribers, and longer durations of treatment could reveal additional adverse effects and other safety risks not observed in this study. Linezolid was observed to have higher rates of decreased platelet count and GI upset in ESTABLISH-1, but linezolid treatment was also longer. While tedizolid and linezolid may be of interest for use targeting resistant pathogens, only about 27% of patients in ESTABLISH-2 had MRSA infections, compared to about 43% of patients in ESTABLISH-1. Higher rates of MRSA would have been ideal for evaluating the efficacy of tedizolid against this resistant pathogen in ESTABLISH-2. A final limitation was that the manual measurement of lesion size had the potential to introduce error. This is especially important due to the response criteria of ≥20% reduction in lesion area for the primary endpoint. The results from ESTABLISH-1 and ESTABLISH-2 supported the conclusion that tedizolid is non-inferior to linezolid for the treatment of ABSSSI, more studies, especially studies including longer duration of IV treatment in sicker, hospitalized patients are merited. Comparisons to vancomycin, an important first-line agent, are also warranted.

Learning Activity 3: Create a table comparing results from DISCOVER 1 and 2, SOLO 1, SOLO 2, ESTABLISH-1, and ESTABLISH-2. Brainstorm two ways you could apply the results in your practice. (Learning Objective 3)

Learning Activity 4: Identify one way you would improve the design or methods of DISCOVER 1 and 2, SOLO 1, SOLO 2, ESTABLISH-1, and ESTABLISH-2, given the information provided. (Learning Objective 4)

POTENTIAL IMPACT ON PRACTICE

See Table 2 for a list of general considerations for using dalbavancin, oritavancin, and tedizolid in practice.

Advantages

The extended half-lives of dalbavancin and oritavancin offer an innovative approach to treatment, theoretically maximizing exposure to the
medication while minimizing the number of doses needed.\textsuperscript{6,8} Use of dalbavancin, and especially single dose oritavancin, could potentially result in higher adherence rates in high risk patients, as well as a reduced need for long-term use of IV lines in patients at risk for drug abuse. These medications likely have a niche place in these areas; however, benefits will need to be weighed against high costs. A trial evaluating single-dose versus two-dose dalbavancin has been completed; results (not yet published) could increase the appeal of dalbavancin relative to oritavancin.\textsuperscript{21} Tedizolid has an advantage of being available in an oral dosage form, and was studied using short duration of therapy (6 days) compared to clinical practice guidelines.\textsuperscript{3,13} These convenient characteristics might be preferable for some patients.

Considering the similar mechanism of action of these medications to standard agents (i.e., dalbavancin and oritavancin to vancomycin; tedizolid to linezolid), these medications have the potential to be used for other common gram-positive-associated indications such as endocarditis, osteomyelitis, bacteremia, and prosthetic-joint infections\textsuperscript{10}; however, clinical trials have not been completed in these areas. Ongoing studies are in progress.\textsuperscript{22} Until results from these studies become available, caution and clinical pharmacist oversight in managing any proposed off-label use, highly common for antimicrobial agents, is essential.

Dalbavancin requires a dose adjustment if CrCl is less than 30 mL/min, unless patients are on regularly scheduled hemodialysis; no other adjustments are needed for dalbavancin, oritavancin, or tedizolid.\textsuperscript{6,8,13} In addition, these agents do not require therapeutic drug monitoring to adjust dosing. Finally, development of bacterial resistance has not yet been observed in any of these agents. This is significant due to the current limited available treatments for resistant bacteria like MRSA, VRE, and VRSA. All agents have demonstrated an early and sustained clinical response and provide more options for practitioners to treat gram-positive bacteria causing SSTI or ABSSSI, depending on the study.\textsuperscript{15,17-20}

Disadvantages

One limitation of dalbavancin and oritavancin is that they cannot be removed by dialysis; this has considerable implications for patients with serious infections who develop renal failure, due to the medications’ extended half-lives (dalbavancin 346 hours and oritavancin 245 hours).\textsuperscript{6,9} Similar concerns exist regarding patients who might develop anaphylactic reactions or toxicity while receiving treatment. Another aspect of once or once weekly dosing to consider is that these patients may be more likely to be seen in an outpatient setting, and could be at an increased risk for delayed diagnosis of more serious infections such as necrotizing fasciitis or delayed identification of treatment failure. In addition, if the patient misses the second dalbavancin dose, there could be an increased risk for resistance and poor outcomes, depending on results of ongoing studies.\textsuperscript{21}

It should be noted that oritavancin is contraindicated with concomitant use of unfractionated heparin, since it falsely elevates aPTT for 48 hours after administration. This could limit oritavancin’s role in inpatient settings, or potentially result in increased risk for erroneous heparin management. PT/INR
may also be falsely elevated for 24 hours. Additionally, a major concern regarding tedizolid is potential monoamine oxidase inhibitor (MAOI) effects, similar to those seen with linezolid. This limits the use of linezolid in patients on psychoactive drugs and drugs that interact with MAOIs due to the risk of serotonin syndrome. While tedizolid has not shown high potential for MAOI effects in vitro, this has not been well studied in human subjects.

Although primary endpoint results were similar across the three medications (see Table 1), it should be noted that there was slight variability across trials in terms of primary endpoint definitions and included patients. Additionally, it should be noted that none of these drugs have been compared directly to each other in trials, so the efficacy benefits of using one or the other are currently unknown. Tedizolid has not been compared in a large, phase 3 trial to vancomycin, which may be considered a more relevant control than linezolid. On a related note, each of these drugs was approved on the basis of non-inferiority results; no published studies were designed to evaluate superiority to controls.

Learning Activity 5: List three advantages and disadvantages of dalbavancin, tedizolid, and oritavancin. (Learning Objective 5)

CONCLUSION

Dalbavancin, oritavancin, and tedizolid were found to be non-inferior to current standards of care in clinical trials. Each agent has theoretical benefits based on dosage and administration; however, none has been assessed for superiority to standard agents or each other in terms of efficacy, and such studies are not likely to be conducted. At the time of writing, published clinical studies are only available in skin and soft tissue infections; future studies are needed to clarify the role of these agents in other indications.

Considering availability of other agents, resistance patterns, principles of antimicrobial stewardship, and costs, all three agents will may have a similar place in therapy SSTI or ABSSSI where there is presumed or identified MRSA. The benefits for compliance and tolerability compared to other agents (i.e., vancomycin, linezolid) will need to be weighed against the high cost of therapy on a patient-specific basis. Additionally, the factors in Table 2, particularly drug-drug interaction risk, should be taken into account.

In conclusion, results from DISCOVER 1 and 2, SOLO 1, SOLO 2, ESTABLISH-1, and ESTABLISH-2 support use of dalbavancin, oritavancin, and tedizolid for treatment of SSTI or ABSSSI where there is presumed or identified MRSA; however, treatment guidelines, alternative agents with longer history of use, and patient-specific considerations should be considered when selecting the ideal agent.
REFERENCES


<p>| Table 1. Results from Phase III RCTs of Dalbavancin, Oritavancin, and Tedizolid |</p>
<table>
<thead>
<tr>
<th>Design</th>
<th>Sample size</th>
<th>Control</th>
<th>Primary endpoint</th>
<th>Primary endpoint results*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dalbavancin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISCOVER 1</td>
<td>International, randomized, active controlled, double-blind, double-dummy, Phase III non-inferiority trial</td>
<td>573</td>
<td>Vancomycin followed by linezolid</td>
<td>At 48 to 72 hours, cessation of spread of infection and afebrile</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td></td>
<td>739</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISCOVER, pooled</td>
<td></td>
<td>1312</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oritavancin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLO 1</td>
<td>International, randomized, active controlled, double-blind, double-dummy, Phase III clinical non-inferiority trial</td>
<td>954</td>
<td>Vancomycin</td>
<td>At 48 to 72 hours, cessation of spread or reduction in lesion size, afebrile, and no rescue antibiotic</td>
</tr>
<tr>
<td>SOLO 2</td>
<td></td>
<td>1005</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tedizolid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESTABLISH-1</td>
<td>International, randomized, active-controlled, double-blind, Phase III clinical non-inferiority trial</td>
<td>667</td>
<td>Linezolid</td>
<td>At 48-72 hours, cessation of primary lesion margin spread, afebrile, and no rescue antibiotic</td>
</tr>
<tr>
<td>ESTABLISH-2</td>
<td></td>
<td>666</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AD = absolute difference; CI = confidence interval. *All studies used a -10% non-inferiority margin consistent with FDA standards. Since the lower limit of all confidence intervals were above -10%, all studies demonstrated non-inferiority.
## Table 2. Practice Considerations for Dalbavancin, Oritavancin, and Tedizolid

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Oritavancin&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Tedizolid&lt;sup&gt;13&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulations</strong></td>
<td>500 mg powder for IV solution</td>
<td>400 mg powder for IV solution</td>
<td>200 mg oral tablets and powder for IV solution</td>
</tr>
<tr>
<td><strong>IV Preparation and Administration</strong></td>
<td>Reconstitute each vial with 25 mL of sterile water or D5W. Further dilute with D5W to a final concentration of 1 to 5 mg/mL. The product is recommended to be given over a 30-minute infusion.</td>
<td>Reconstitute 3 vials with 40 mL sterile water each. Remove 120 mL from a 1,000 mL D5W bag. Add the 3 vials of reconstituted solution to bring the total bag volume to 1,000 mL. The product is recommended to be given over a 3-hour infusion.</td>
<td>The IV product is first reconstituted with 4 mL sterile water before being added to a 250 mL bag of normal saline. The IV product is recommended to be given over a 1-hour infusion.</td>
</tr>
<tr>
<td><strong>Common Adverse Effects</strong></td>
<td>Nausea (6%), headache (5%), diarrhea (4%), skin rash (3%), vomiting (3%)</td>
<td>Nausea (10%), headache (7%), vomiting (5%), diarrhea (4%), dizziness (3%), increased ALT (3%), injection site phlebitis (3%), tachycardia (3%)</td>
<td>Nausea (8%), headache (6%), diarrhea (4%), vomiting (3%)</td>
</tr>
<tr>
<td><strong>Major Drug-Drug Interactions</strong></td>
<td>No major drug-drug interactions have been described.</td>
<td>Contraindicated with heparin use within 120 hours (5 days) due to potential alterations of laboratory tests used to monitor effectiveness and safety.</td>
<td>It is recommended to avoid use with MAO inhibitors and serotonin agonists due to increased risk for serotonin syndrome; monitor concomitant use with other serotonergic medications (e.g., antipsychotics, SSRI, SNRI).</td>
</tr>
</tbody>
</table>

ALT = serum alanine aminotransferase; D5W = dextrose 5% in water; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors