Do Labels ABSSSI-lutely Matter?
Evaluating Evidence Supporting Off-label Utilization of Long-acting Lipoglycopeptides for the Treatment of Bone and Joint Infections

Amber N. Welborn, Pharm.D.
PGY2 Infectious Diseases Pharmacy Resident
Department of Pharmacy, South Texas Veterans Health Care System
Division of Pharmacotherapy, University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center, UT Health San Antonio
August 23, 2019

Learning Objectives:
1. Discuss challenges surrounding current management of invasive gram-positive (GP) infections, focusing on bone and joint infections (BJIs)
2. Review the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the long-acting lipoglycopeptides (LA-LGPs): dalbavancin (DAL) and oritavancin (ORI)
3. Evaluate literature surrounding use of LA-LGPs for treating bone and joint infections
4. Determine which clinical scenarios, if any, are best suited for management with a LA-LGP
GRAM-POSITIVE BACTERIAL INFECTIONS

I. INTRODUCTION
A. Gram-positive (GP) bacteria are common human pathogens\(^1\) (Table 1)
   i. Bacteria from \textit{Staphylococcus}, \textit{Streptococcus}, and \textit{Enterococcus} genera frequently cause disease
   ii. A broad range of infection severity exists, from mild skin infections to life-threatening infections
   iii. Treatment strategies are variable and highly dependent on infection type

<table>
<thead>
<tr>
<th>Infection</th>
<th>Typical Gram-positive Organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream infection</td>
<td>\textit{S. aureus}, CoNS</td>
</tr>
<tr>
<td>Line-related infection</td>
<td>\textit{S. aureus}, CoNS</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>\textit{S. aureus}, CoNS, VGS</td>
</tr>
<tr>
<td>Meningitis</td>
<td>\textit{S. pneumoniae}</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>\textit{S. pneumoniae}</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>\textit{S. aureus}</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>\textit{S. aureus}, VGS, Enterococci</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>GAS</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>\textit{S. aureus}</td>
</tr>
<tr>
<td>Surgical implants</td>
<td>\textit{S. aureus}, CoNS</td>
</tr>
<tr>
<td>Complicated urinary tract infections</td>
<td>Enterococci</td>
</tr>
</tbody>
</table>

CoNS = coagulase-negative staphylococci, GAS = Group A streptococci, \textit{S. aureus} = \textit{Staphylococcus aureus}, \textit{S. pneumoniae} = \textit{Streptococcus pneumoniae}, VGS = Viridans group streptococci

B. Management of serious, invasive GP infections is associated with\(^1\)
   i. Relatively long durations of antibiotic therapy
      1. Acute infections often require 2 to 6 weeks of intravenous (IV) antibiotics
      2. Chronic infections may necessitate additional suppressive therapy after initial course
   ii. Longer hospital stays
   iii. Increased costs to healthcare systems and patients

II. ANTIBIOTIC RESISTANCE\(^1,3,4\)
A. GP organisms account for 6 of 15 serious or concerning threats previously outlined by the CDC

<table>
<thead>
<tr>
<th>Serious Threats</th>
<th>Concerning Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant S. aureus (MRSA)</td>
<td>Vancomycin-resistant S. aureus (VRSA)</td>
</tr>
<tr>
<td>Vancomycin-resistant \textit{Enterococcus} (VRE)</td>
<td>Erythromycin-resistant Group A Strep. (GAS)</td>
</tr>
<tr>
<td>Drug-resistant S. pneumoniae</td>
<td>Clindamycin-resistant Group B Strep. (GBS)</td>
</tr>
</tbody>
</table>

B. MRSA and VRE infections are among the most common multidrug-resistant infections in the US
   i. Treatment options can be limited due to high prevalence of resistance to many antibiotics
      1. MRSA is estimated to be responsible for 80,461 infections and 11,285 deaths per year
      2. VRE is estimated to be responsible for 20,000 infections and 1,300 deaths per year
   ii. Clinical need exists for antibiotics with activity against resistant GP organisms and PK properties that allow for more convenient dosing over extended treatment durations
      1. In recent decades major drug companies shifted production efforts to medications with a higher potential for profit, which ultimately led to a dwindling antibiotic pipeline
      2. \textit{Generating Antibiotic Incentives Now (GAIN) Act, 2012}\(^5\)
         a. Extends exclusivity period of certain antibiotics by 5 years
         b. Qualified infectious disease product (QIDP)
            i. Defined as “an antibacterial or antifungal for human use intended to treat serious or life-threatening infections”
            ii. These products receive fast track and priority review status with the FDA
c. Increased number of new antibiotic approvals in recent years:
   i. New approvals more than tripled from 2013-2017 compared to 2008-2012
   ii. Majority of new agents are modifications of existing antibiotic classes

III. CLINICAL ASPECTS OF SELECT RESISTANT GRAM-POSITIVE PATHOGENS
   A. MRSA
      i. *S. aureus* is a common bacterial pathogen in both hospital- and community-acquired infections
         1. Incidence of invasive *S. aureus* infections is as high as 43.3/1000 population per year
         2. Invasive infections are associated with substantial morbidity and mortality as high as 25%
         3. Patient factors associated with highest risk for invasive *S. aureus* infections include:
            a. Hemodialysis or peritoneal dialysis
            b. Human immunodeficiency virus, solid-organ transplant, or cancer
            c. Illicit IV drug use (IVDU) or alcohol abuse
            d. Heart disease, stroke, or COPD
      4. MRSA represents > 60% of *S. aureus* isolates obtained in an intensive care unit.
      ii. An estimated 1/3 of the population are *S. aureus* carriers, with 2-5% of strains being MRSA.
      iii. Hospital-acquired MRSA infections are associated with long stays, high mortality, and increased costs
   B. VRE
      i. Enterococcal species are also a leading cause of US nosocomial infections
         1. VRE now accounts for approximately 30% of enterococcal infections (>90% are *E. faecium*)
         2. Hospital environments and surfaces can be heavily colonized with VRE
      ii. Risk factors associated with VRE colonization and infection include:
         1. Severe underlying disease (e.g., end-stage renal disease) or presence of immunosuppression
         2. Prolonged hospital stays or residence in long term care facility
         3. Previous antibiotic therapy with vancomycin (VAN) or broad-spectrum cephalosporins

BONE AND JOINT INFECTIONS

I. BACKGROUND
   A. Despite ongoing medical and surgical advances, bone and joint infections are considered among the most difficult types of infectious diseases to treat
   B. Few well-designed prospective trials exist, and current clinical management is largely guided by:
      i. Expert opinion
      ii. Retrospective cohort studies
      iii. Experimental animal models
   C. Osteomyelitis (OM)
      i. Inflammatory process caused by an infecting microorganism accompanied by bone destruction
      ii. Data from the Agency for Healthcare Research and Quality regarding OM in Texas in 2007 indicates:
         1. Average hospital length of stay of 14.2 days
         2. Average hospital charges of $45,782
         3. Discharge status: routine (39%), another short-term hospital or institution (34%), home health care (23%), or against medical advice (2%)%
   D. Prosthetic joint infection (PJI)
      i. Infection involving the joint prosthesis and adjacent tissue
      ii. Economic impact of PJI is significant:
         1. Cost to the American health care system in 2009 alone was $566 million
         2. Due to increasing rates of joint replacement, cost is predicted to reach $1.62 billion by 2020

II. EPIDEMIOLOGY
   A. OM incidence is unknown, but estimated to be as high as 1 in 675 US hospital admissions/year
      i. Higher in men than women
      ii. Increases with age
   B. PJI annual US incidence, expressed as a percentage of total arthroplasties, is estimated to be ~2%
i. May be higher with elbow replacement compared to shoulder, hip, or knee
ii. 60-70% of PJIs occur within the first two years after operation
C. Factors that predispose patients to bone and joint infections include

<table>
<thead>
<tr>
<th>Age</th>
<th>Diabetes</th>
<th>Peripheral Vascular Disease</th>
<th>Surgical Implants</th>
<th>Immune Deficiency</th>
<th>IVDU</th>
<th>Bacteremia</th>
</tr>
</thead>
</table>

III. PATHOPHYSIOLOGY\textsuperscript{11,12}

A. Healthy, intact bone is highly resistant to infection
B. Bone can become susceptible to infection in the setting of
   i. Trauma
   ii. Ischemia
   iii. Presence of foreign bodies
C. Bone and joint infections can develop as a result of\textsuperscript{13}
   i. Hematogenous seeding (mostly occurs in long bones of children or vertebral bodies in the elderly)
   ii. Contiguous spread from adjacent soft tissue and joints (can occur at any age and involve any bone)
   iii. Direct inoculation of bone secondary to trauma or surgery
D. Mechanisms of disease\textsuperscript{13} (Figure 1)
   i. Microscopy reveals areas of suppurative inflammation with bacteria embedded in the tissue or bone
   ii. Inflammatory factors and leukocytes contribute to tissue necrosis and bone destruction
   iii. Vascular channels become compressed and obliterated by inflammation, resulting in ischemia
   iv. Segments of bone without blood supply can become separated to form sequestra
   v. Sequestra can continue to harbor bacteria despite antibiotic treatment
   vi. Antibiotics and inflammatory cells cannot reach these avascular areas

![Figure 1. Progression of osteomyelitis.\textsuperscript{17}](image)

E. Causative microorganisms\textsuperscript{13}
   i. Vary by type of bone and joint infection (Figure 2)
   ii. Gram-negative (GN) pathogens are less likely, with GP cocci accounting for \~75% of cases\textsuperscript{17}
   iii. Staphylococcus aureus is the most common organism and possesses numerous virulence factors
      1. Multiple surface adhesins
2. Factors for host defense evasion
3. Exotoxins promote cellular invasion
4. Capable of surviving in osteoblasts

iv. *S. aureus* and *S. epidermidis* form biofilms
   1. Communicate via quorum sensing
   2. Slow diffusion of antibiotics
   3. Lower metabolic rates
   4. Adaptive stress response
   5. Decreased rates of cell division

F. Recurrence rates are high\(^{18,19}\)
   i. Up to 30% within 12 months of appropriate surgical and medical management
   ii. Among recurrences observed in a study with a mean follow-up duration of 28 months
      1. ~60% occurred within 3 months
      2. ~80% occurred within 6 months
      3. ~95% occurred within 12 months
   iii. Risk factors for recurrence include
      1. Diabetes
      2. Peripheral vascular disease
   iv. Survival within cells and formation of biofilms likely contribute to recurrence

IV. DIAGNOSIS\(^{11}\)

A. OM Diagnosis\(^{13}\)
   i. Starts with strong clinical suspicion
      1. Adults often have subacute-to-chronic presentation
         a. Nonspecific pain around infected bone and absence of systemic symptoms
            i. White blood cell (WBC) count elevated in <50% of cases
            ii. Erythrocyte sedimentation rate (ESR) elevated in >90% of cases
            iii. C-reactive protein (CRP) increases within hours of infection and can return to normal within a week of adequate treatment
         b. Fever, chills, local swelling and erythema are seen less commonly
      2. A draining sinus tract over the involved bone may develop over months to years
   ii. Confirmed with a combination of radiologic, microbiologic, and histopathologic tests
      1. Radiologic
         a. Bone destruction not visible on plain films until 10-21 days after infection onset
         b. Early bony edema is visible on MRI, making it useful for early detection
      1. Microbiologic
         a. Identification of causative microorganism is critical to optimizing treatment
         b. Surgical sample or radiology-guided needle aspiration should be obtained
         c. Whenever possible, antibiotics should be withheld until cultures are obtained
      1. Histopathologic\(^{18}\)
         a. Presence of significant amounts of neutrophils indicates infection
         b. Acute OM – inflammatory bone changes present within 2 weeks of infection onset
         c. Chronic OM – necrotic bone, present ~6 weeks after infection onset

B. PJI Diagnosis\(^{12,15,20}\)
   i. Early-onset (<3 months from surgery) and delayed-onset PJI (>3 but <12-24 months from surgery)
      1. Typically acquired at time of surgery
      2. Local signs of inflammation, wound dehiscence, drainage, and erythema are common
   ii. Late-onset PJI (>12-24 months from surgery)
      1. Typically hematogenous in origin
2. Characterized by new onset pain without prominent local signs of infection

iii. Diagnostics
1. ESR >30 mg/L and/or CRP >10 mg/L
2. Synovial fluid with >4200 leukocytes/µL and/or >80% neutrophil fraction
3. Synovial fluid and periprosthetic tissue cultures
4. Presence of sinus tract communicating with prosthesis allows definitive diagnosis

V. CLINICAL MANAGEMENT

A. Clinical goals are eradication of infection and restoration of bone and joint function
B. Most cases require a combination of surgical and medical management
C. Surgical management
   i. Indications for surgery include
      1. Antibiotic failure
      2. Infected orthopedic hardware
      3. Chronic osteomyelitis (necrotic bone)
   ii. Debridement of necrotic or injured bone facilitates penetration of antibiotics and allows for culture
      1. Radical debridement down to living bone often required
      2. Inadequate debridement thought to be one cause of high recurrence rates
   iii. Removal of infected hardware eliminates avascular surface for colonization and increases cure rates
   iv. May be unnecessary in hematogenous OM except for spinal decompression and abscess drainage
   v. Restoration of vascularization may prevent amputation in OM due to diabetic foot infection (DFI)
D. Medical management
   i. No well-designed randomized trials establish superiority for a particular antibiotic regimen
      1. Guideline-preferred regimens based on specific gram-positive organism isolated
         a. MSSA: cefazolin, oxacillin, or nafcillin
         b. MRSA: vancomycin
         c. Streptococci: penicillin or ceftriaxone
         d. Enterococci, penicillin susceptible: penicillin or ampicillin
         e. Enterococci, penicillin resistant: vancomycin
      2. More complete list of commonly used regimens by pathogen can be found in Appendix A
   ii. Optimal duration of antibiotic therapy for OM is unknown
      1. Most clinicians in the US treat with 4 to 6 weeks of IV antibiotic therapy, based on
         a. Expert opinion and clinical experience
         b. Limited bone penetration of most antibiotics used
         c. Belief that it takes 3 to 4 weeks for revascularization of infected bone
         d. Experimental animal model showing higher rates of microbiologic eradication with 28 days of antibiotics compared to 14
         e. Single randomized trial showing noninferiority of 6 weeks vs 12 weeks of antibiotic therapy for native vertebral osteomyelitis (NVO)
      2. Some experts recommend a reduced 2-week course of antibiotics only if
         a. Infected bone is debrided completely
         b. Microbiology and pathology suggest clean margins
   iii. Duration of antibiotic therapy for PJI depends on causative pathogen
      1. Staphylococcal PJI
         a. Initial 2 to 6-week course of IV pathogen-directed antibiotic therapy + oral rifampin
            i. Rifampin 300-450 mg twice daily is recommended
            ii. If rifampin cannot be used, initial IV course should last 4-6 weeks
         b. Followed by 3 to 6-months of rifampin + second highly bioavailable oral antibiotic
            i. Three months for hip, shoulder, elbow, and ankle
            ii. Six months for knee
         b. Indefinite chronic oral antibiotic suppression may follow
2. Non-staphylococcal PJI
   a. Four to 6-week course of IV antibiotic therapy or highly bioavailable oral therapy
   b. Indefinite chronic oral antibiotic suppression may follow
iv. Average reported treatment success rates are highly variable\textsuperscript{15,17}
   1. Reported rate of infection relapse as high as 40% in staphylococcal OM
   2. Success rate with debridement, antibiotics, and implant retention in PJI ranges from 31% to 82% in the literature (\textasciitilde55\% reported for staphylococcal PJI)

OUTPATIENT PARENTERAL ANTIMICROBIAL THERAPY (OPAT)

I. HISTORY\textsuperscript{9,25-26}
   A. First report of safety and efficacy of OPAT was published in 1974
      i. Described successful treatment of chronic bronchopulmonary infections in cystic fibrosis patients
      ii. Since the 1970’s OPAT use has expanded to many other patient populations
         1. Estimated 1 in 1000 Americans receives OPAT each year
         2. Patients in the US rarely stay admitted to the hospital solely to complete IV antibiotic course
   B. Potential benefits of OPAT

<table>
<thead>
<tr>
<th>To Healthcare System</th>
<th>To Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter hospital stays with same compensation</td>
<td>Less absentee time from school or work</td>
</tr>
<tr>
<td>Reduction or prevention of nosocomial infections</td>
<td>Resume daily activities with minimal interruption</td>
</tr>
<tr>
<td>Cost-savings</td>
<td>A sense of freedom, control, and/or satisfaction</td>
</tr>
</tbody>
</table>

II. MODELS OF DELIVERY\textsuperscript{25}
   A. Three basic models exist: (1) home-based, (2) infusion-center based, (3) skilled nursing facility (SNF)-based
   B. Each requires significant multidisciplinary communication and coordination

III. PATIENT SELECTION\textsuperscript{25}
   A. Afebrile with stable vital signs
   B. Infection stabilized and not progressive
   C. Appropriate home environment (running water, lights, refrigeration, etc.)
   D. Access to a working telephone and adequate transportation

IV. THERAPEUTIC CONSIDERATIONS\textsuperscript{25-26}
   A. Infections most commonly treated with OPAT include osteoarticular infections and bacteremia
   B. Virtually any infection can be treated with OPAT after stabilization of the patient in the hospital
   C. Refer to Appendix B for a comparison of GP agents used in OPAT

V. CONCERNS
   A. Potential line complications (infection, clotting, accidental removal, etc.) or pump malfunction (Appendix C)
   B. Reimbursement can be a challenge for some patients
   C. Not everyone is a candidate (history of IVDU, patients leaving AMA, homeless, etc.)

VI. ALTERNATIVES TO OPAT\textsuperscript{23,28}
   A. Remaining hospitalized to complete a long course of IV antibiotics is not practical or cost-effective
   B. Highly bioavailable oral (PO) antibiotics can be an acceptable OPAT alternative in bone and joint infections
      i. Select oral antibiotics are capable of achieving adequate levels in bone
         1. Most evidence is for fluoroquinolones ± rifampin
            a. Often with longer durations (12-16 weeks) and higher doses
            b. Most studies show cure rates of 60-80%
         2. Less evidence for other highly bioavailable oral agents
            a. Linezolid, trimethoprim-sulfamethoxazole, clindamycin, doxycycline, metronidazole, fosfomycin, fusidic acid
3. Even less evidence exists for the less bioavailable options like the oral beta-lactams
   ii. Oral versus intravenous antibiotics for bone and joint infection (OVIVA Trial), 2019
      1. Randomized controlled trial concluded noninferiority of PO vs IV antibiotics for OM
      2. No particular regimens were compared, though they were selected by ID specialist
         a. Large portion of patients in PO group received fluoroquinolones (36.5%)
         b. Small portion of patients in PO group received penicillins (15.9%)
      3. 94.9% of patients in this trial received surgical intervention
   iii. Use of highly bioavailable oral options frequently limited by pathogen susceptibility profiles as well as the various toxicities associated with currently available agents

CLINICAL QUESTION

Do long-acting lipoglycopeptides have a role in the clinical management of bone and joint infections, or should we stick to the labeled indication?

LONG-ACTING LIPOGLYCOPEPTIDES (LA-LGPs)

IV. History
   A. Dalbavancin (Dalvance®)
      i. Non-inferior to vancomycin (VAN) for treatment of acute bacterial skin and skin structure infections (ABSSSI) in DISCOVER 1 and DISCOVER 2
      ii. Approved by FDA May 23, 2014 for ABSSSIs due to susceptible GP organisms
      iii. First drug granted QIDP designation under the GAIN Act
   B. Oritavancin (Orbactiv®)
      i. Non-inferior to VAN for ABSSSI treatment in SOLO I and SOLO II
      ii. Approved by FDA August 6, 2014 for ABSSSIs due to susceptible GP organisms

<table>
<thead>
<tr>
<th>DALBAVANCIN (DAL)</th>
<th>ORITAVANCIN (ORI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A semisynthetic teicoplanin-derivative</td>
<td>A synthetic vancomycin analog</td>
</tr>
</tbody>
</table>

V. Mechanism of Action
   A. Cell wall synthesis inhibitors
      i. Heptapeptide core binds D-alanyl-D-alanine (D-ala-D-ala) at C-terminus of peptidoglycan precursors
      ii. Binding D-ala-D-ala prevents transglycosylation and transpeptidation
      iii. Ineffective polymerization and cross-linking → destabilization, osmotic damage, and cell death
   B. Structure activity relationship
      i. Modifications to the heptapeptide core enhance GP activity of DAL and ORI
      ii. Addition of long, lipophilic side chains to DAL and ORI
1. Significantly prolongs the half-life
2. Enhances D-ala-D-ala binding through dimerization and membrane anchoring
   iii. Additional side chain modifications in ORI increase bactericidal activity by disrupting cell membrane potential and increasing bacterial cell permeability

VI. Spectrum of Activity
A. Broad spectrum aerobic and anaerobic GP activity
   i. Potent activity against staphylococci, enterococci, and streptococci (Appendix D and Appendix E)
   ii. Excellent activity against Corynebacterium spp, Clostridium perfringens, and Peptostreptococcus spp
   iii. Unlike DAL, ORI maintains activity in the presence of the vanA gene, which causes high level vancomycin resistance in Enterococcus

B. No gram-negative activity due to inability to pass through outer membrane

VII. Resistance
A. Susceptibility testing
   i. Requires addition of 0.002% polysorbate 80 to testing media
   ii. Vancomycin can be considered a surrogate for in vitro susceptibility testing
   iii. Refer to Appendix F for staphylococci, streptococci, and enterococci susceptibility breakpoints

B. Mechanisms of resistance
   i. Target site modifications (D-ala-D-ala → D-ala-D-lactate or D-ala-D-serine)
   ii. Abnormal cell wall properties (production of excess cell wall material and altered autolysis)

C. Resistance selection studies suggest that DAL might have a higher barrier to resistance than VAN

D. Large antimicrobial surveillance studies do not suggest emerging resistance to DAL over the past 10 years, with MICs remaining consistent for GP cocci evaluated

VIII. Pharmacokinetics (PK) and Pharmacodynamics (PD) (Table 2)

Table 2. PKPD comparison of DAL and ORI

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>DALBAVANCIN (DAL)</th>
<th>ORITAVANCIN (ORI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor oral absorption, only available as IV</td>
<td>Poor oral absorption, only available as IV</td>
<td></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear PK properties</td>
<td>Linear PK properties</td>
<td></td>
</tr>
<tr>
<td>30-min infusion of 1500 mg dose</td>
<td>3-hr infusion of 1200 mg</td>
<td></td>
</tr>
<tr>
<td>o C&lt;sub&gt;max&lt;/sub&gt; = 423 µg/mL</td>
<td>o C&lt;sub&gt;max&lt;/sub&gt; = 138 µg/mL</td>
<td></td>
</tr>
<tr>
<td>o AUC&lt;sub&gt;0-24&lt;/sub&gt; = 4837 µg•h/mL</td>
<td>o AUC&lt;sub&gt;0-24&lt;/sub&gt; = 1110 µg•h/mL</td>
<td></td>
</tr>
<tr>
<td>Highly protein bound (93%)</td>
<td>Highly protein bound (85%)</td>
<td></td>
</tr>
<tr>
<td>Extensive tissue distribution &amp; moderate accumulation within macrophages, but poor CSF penetration</td>
<td>Extensive tissue distribution &amp; accumulation within macrophages, but poor CSF penetration</td>
<td></td>
</tr>
<tr>
<td>o V&lt;sub&gt;d&lt;/sub&gt; = 7-13 L</td>
<td>o V&lt;sub&gt;d&lt;/sub&gt; = 87 L</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not a CYP450 substrate, inhibitor, or inducer</td>
<td>Weak inducer of CYP3A4 and CYP2D6</td>
<td></td>
</tr>
<tr>
<td>Weak inhibitor of CYP2C19 and CYP2C9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-compartment model, extensive elimination phase</td>
<td>Complex multiexponential elimination phase</td>
<td></td>
</tr>
<tr>
<td>o Terminal t&lt;sub&gt;1/2&lt;/sub&gt; = 204 hrs</td>
<td>o Terminal t&lt;sub&gt;1/2&lt;/sub&gt; = 245 hrs</td>
<td></td>
</tr>
<tr>
<td>35% eliminated unchanged in urine, 20% in feces</td>
<td>Excreted slowly, unchanged in the urine and feces</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration-dependent killing</td>
<td>Concentration-dependent killing</td>
<td></td>
</tr>
<tr>
<td>AUC/MIC ratio correlates best with efficacy</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;/MIC ratio correlates best with efficacy</td>
<td></td>
</tr>
<tr>
<td>Requires ~24 hrs to achieve 3-log bactericidal kill</td>
<td>Exhibits rapid bactericidal activity</td>
<td></td>
</tr>
<tr>
<td>May be efficacious in biofilms</td>
<td>May be bactericidal against nondividing bacteria</td>
<td></td>
</tr>
</tbody>
</table>
A. Dosing and Administration\textsuperscript{29,31,34,37}
   i. Administering higher doses less frequently optimizes AUC/MIC and $C_{\text{max}}$/AUC ratios
   ii. FDA-labeled dosing recommendations (ABSSSI)\textsuperscript{31,34,37}

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>DAL</th>
<th>ORI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCl $\geq$ 30 mL/min</strong></td>
<td>1500 mg single dose, or 1000 mg day 1 and 500 mg day 8</td>
<td>1200 mg single dose</td>
</tr>
<tr>
<td><strong>CrCl $&lt; 30$ mL/min</strong></td>
<td>1125 mg single dose, or 750 mg day 1 and 375 mg day 8</td>
<td>Not evaluated</td>
</tr>
<tr>
<td><strong>Hemodialysis (HD)</strong></td>
<td>No dose adjustments Given without regard to HD timing</td>
<td>Not evaluated Not cleared by HD</td>
</tr>
</tbody>
</table>

iii. Minimal data available regarding dosing in obesity
   1. One ORI population PK study suggested patients $>110$ kg may require 50% dose increase to maintain same steady-state AUC; however, this study was looking at daily administration\textsuperscript{43}
   2. PK study of DAL extended-interval ABSSSI dosing suggests dose adjustment not necessary\textsuperscript{44}
      a. Variables analyzed included weight ranging from 42.8 to 320 kg, body surface area (BSA) ranging from 1.36 to 4.00 m\textsuperscript{2} and CrCl ranging from 26 to 436 mL/min
      b. Increased weight and BSA associated with lower $C_{\text{max}}$ but within 20-30% of normal

B. Drug-Drug and Drug-Lab Interactions\textsuperscript{29}
   i. DAL has minimal potential for drug interactions as it is not a CYP450 substrate, inducer, or inhibitor
   ii. ORI has been shown to increase warfarin AUC by 31%
   iii. ORI artificially prolongs PT and INR for up to 24 hours and aPTT for up to 48 hours
      1. Binds to and prevents phospholipid reagents from activating coagulation
      2. Use of heparin is contraindicated for 48 hours after ORI administration

IX. Adverse Effects\textsuperscript{29,31,34,37}
   A. Both DAL and ORI appear to be well-tolerated
   B. Most commonly reported side effects in clinical trials were gastrointestinal in nature
   C. OM observed more frequently with ORI in SOLO II trial
      i. 5 patients developed OM in the ORI group vs 0 patients in the VAN group
      ii. All events occurred within 1-9 days of study initiation

X. Clinical Uses
   A. DAL and ORI are only FDA-approved for the treatment of ABSSSI
   B. Off-label use may be occurring more frequently than use for ABSSSI
      i. Multicenter, retrospective study of DAL as targeted therapy for GP infections\textsuperscript{45}
         1. Reported an 89% clinical success rate among 101 patients
         2. Indications included PJI (31%), OM (29%), endocarditis (25%), and ABSSSI (12%)
      ii. Retrospective cohort of patients receiving 2 to 18 doses of ORI for complicated GP infections\textsuperscript{46}
         1. All 17 patients achieved clinical success or saw clinical improvement
         2. Less than half were treated for ABSSSI
      iii. Case series of 10 patients receiving ORI for invasive GP infections\textsuperscript{47}
         1. Reported clinical success rate of 70%
         2. Indications included bacteremia, ABSSSI, OM, and endocarditis
         3. Reasons for ORI use included OPAT refusal or noncompliance, IVDU, or drug allergies
      iv. Two retrospective studies evaluated DAL and ORI as effective, safe, cost-saving options for vulnerable patient populations such as IVDU\textsuperscript{48,49}
         1. 13%-15% of patients experienced clinical failure
         2. 18%-31% were lost to follow-up
   C. Retrospective cohort study of 59 patients receiving DAL or ORI for definitive therapy for GP infections estimated a reduction in hospital days of 514 and healthcare savings of $963,456.72 ($17,204.58/person)\textsuperscript{50}

XI. Summary
   A. DAL and ORI are important additions to our GP armamentarium
i. DAL may be associated with higher barrier to resistance than VAN
ii. Both are highly effective against MRSA and demonstrate activity against VISA
iii. ORI may have activity against non-dividing bacteria in biofilms and against VRSA and VRE

B. PK/PD properties allow for extended dosing regimens with numerous potential benefits
i. Reducing hospital length of stay or avoiding a hospital admission
ii. Potential role in OPAT therapy, avoiding central line placement and associated morbidity
iii. More convenient one-time, weekly or biweekly (every other week) dosing schedules

C. Both agents have cost-savings potential for healthcare systems and patients
i. High acquisition cost, but patients require fewer doses
ii. Likely less expensive than hospital admission, extended stay in a SNF, or even OPAT in most cases

D. Many recent case reports, case series, and retrospective studies have been published documenting successes with LA-LGPs for a variety of off-label indications, including bone and joint infections

UTILIZATION OF LA-LGPs FOR BONE AND JOINT INFECTIONS

I. Phase I studies and animal models
A. Phase I bone penetration and extended-duration study in healthy subjects
i. DAL levels measured in bone calculated to be similar to simultaneous free DAL serum concentrations
ii. PK modeling predicts DAL exposure ≥ 0.12 µg/mL in bone for entire 8-week treatment duration after giving two IV 1500 mg doses administered one week apart

B. Rabbit model demonstrated better bone penetration with ORI compared to previous studies of linezolid, vancomycin, teicoplanin, and even DAL

C. DAL demonstrated efficacy in treatment of MRSA sternal osteomyelitis in rat model
i. Clinical MRSA isolate from infected human sternal bone (DAL MIC 0.06 mg/L, VAN MIC 1 mg/L)
ii. DAL treatment effect similar to VAN at 7 days and 14 days

II. Multiple case reports describe success with use of ORI for treatment of complex osteomyelitis cases
A. Indications included hardware-associated OM of the femur, tibia, or spine, and native vertebral OM (NVO)
B. ORI dosing regimens varied (800-1200 mg every 1-2 weeks for up to 8 weeks) with concomitant ampicillin used in one case
C. Organisms treated included 2 cases of daptomycin nonsusceptible VRE, MRSA in an immunosuppressed patient with history of leaving against medical advice, and MSSA in the setting of multiple drug allergies

III. Case series of 9 patients receiving ≥2 doses of ORI for chronic OM of a lower extremity
A. All doses of ORI were 1200 mg (number of doses up to physician discretion, ranged from 2 to 6)
B. 67% received no prior antibiotics, 44% had diabetes, and 56% of cases were due to MRSA
C. 100% of patients achieved clinical cure at 6 months
D. 3/12 patients originally evaluated were excluded for only getting 1 dose, but all achieved cure at 6 months
E. Supports a potential role for ORI in treatment of chronic lower extremity OM

IV. Retrospective studies (Table 3 and Table 4)
V. Prospective randomized trial (Table 5)

Table 3. Morata, et al. (2019)

<table>
<thead>
<tr>
<th>Objective</th>
<th>To review the clinical characteristics, outcome, and adverse events observed in patients with bone and joint infections treated with at least one dose of dalbavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective, observational chart review including 30 institutions in Spain</td>
</tr>
<tr>
<td>Population</td>
<td>All patients with bone or joint infections from Mar 2016 to Nov 2017 treated with ≥ 1 dose of DAL</td>
</tr>
</tbody>
</table>
| Groups    | Orthopedic implant associated infections (n=45)  
|           | Hip (29%) > spine (24%) > knee (22%) > long bone (11%) > shoulder (7%) = other (7%)  
|           | Bone or joint infections (n=19) |

Table 3. Morata, et al. (2019)
Outcomes

- Primary endpoint: Clinical outcome at the time of latest medical visit

Clinical outcome definitions

- **Success** – no evidence of infection at latest visit and no need for additional surgery or antibiotic treatment for same infection during or after DAL treatment
- **Improved** – no evidence of infection at latest visit but suppressive antibiotic therapy was initiated after DAL treatment
- **Failure** – persistent or reappearing signs of infection, need for additional surgery after starting DAL, occurrence of adverse events requiring DAL discontinuation, or infection-related death

Microbial Etiology

<table>
<thead>
<tr>
<th>Microorganism, n (%)</th>
<th>Implant-associated infection (n=45)</th>
<th>Bone or joint infection (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoNS</td>
<td>29 (64.3)</td>
<td>4 (21)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4 (8.9)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
<td>1 (2.2)</td>
<td>3 (15.7)</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>7 (15.5)</td>
<td>2 (10.4)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>2 (4.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (19.9)</td>
<td>5 (26.1)</td>
</tr>
</tbody>
</table>

- 93.3% (28/30) S. epidermidis isolates and 64.3% (9/14) S. aureus isolates were methicillin-resistant
- All enterococci were susceptible to VAN

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Implant-associated infection (n=45)</th>
<th>Bone or joint infection (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>64 (15.0)</td>
<td>61 (17.5)</td>
</tr>
<tr>
<td>Diabetes mellites, n (%)</td>
<td>7 (15.5)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>5 (11.1)</td>
<td>1 (5.2)</td>
</tr>
<tr>
<td>Days of antibiotic therapy prior to DAL treatment, median (IQR)</td>
<td>41 (21-87)</td>
<td>32 (21-46)</td>
</tr>
<tr>
<td>No. of DAL doses, median (IQR)</td>
<td>5 (3-8)</td>
<td>2 (2-4)</td>
</tr>
<tr>
<td>Reason for starting DAL, n (%)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Failure on prior antibiotic</td>
<td>12 (26.6)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Simplification</td>
<td>23 (51.1)</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Toxicity to prior antibiotic</td>
<td>10 (22.2)</td>
<td>6 (31.5)</td>
</tr>
<tr>
<td>Concomitant antibiotics, n (%)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Rifampin</td>
<td>8 (17.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (15.5)</td>
<td>6 (31.5)</td>
</tr>
</tbody>
</table>

- DAL dosing strategies were highly variable
  - First dose: 1500 mg (19%), 1000 mg (78%), 750 mg (1.5%), 500 mg (1.5%)
  - Followed by a median of 5 weekly 500 mg doses in 84% of patients
  - 9 patients only received the first dose and 1 patient received 4 biweekly doses of 1500 mg
- Seven documented adverse events, none of which led to treatment discontinuation

Primary Endpoint

<table>
<thead>
<tr>
<th>Variable</th>
<th>Implant-associated infection (n=44)</th>
<th>Bone or joint infection (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant retention, no. (%)</td>
<td>23 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>15 (65.2)</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>8 (34.8)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Implant removal, no. (%)</td>
<td>21 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>16 (76.2)</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>4 (19.0)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>1 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Death, no. (%)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Days of follow-up, median (IQR)</td>
<td>157 (75.5-273.5)</td>
<td></td>
</tr>
</tbody>
</table>

- 14 (73.6)
- 3 (15.7)
- 2 (10.5)
- 3 (15.7)
- 164 (93-262.5)
Success rate >50% among patients initiated on DAL after failing a different antibiotic agent

Using ≥2 doses of DAL is safe for treating bone and joint infections, and appears to demonstrate an acceptable success rate that should be confirmed with prospective studies

S. epidermidis and S. aureus were most common organisms, with high methicillin-resistance rates

Retrospective design, conducted only in Spain

Reported reasons for initiating off-label DAL use

Not defined which bones or joints were involved in non-implant-associated group

Documented different dosing strategies employed

Variable DAL dosing regimens

Evaluated safety of prolonged DAL use (≥2 doses)

DAL may not have been dosed high enough

Heterogeneity regarding infection type makes more generalizable to all types of osteoarticular infections

Most patients received long durations of IV therapy with other antibiotics prior to starting DAL

Concomitant therapy with other agents was allowed, but specific agents other than rifampin not disclosed

No information on surgical interventions or vascular status

Relatively short follow-up period

Multiple (≥2) weekly or biweekly doses of DAL appear safe, no treatment-altering adverse effects

Success rates of 65.2-76.2% support use of DAL as sequential therapy in osteoarticular infections

DAL doses were lower than those more recently used in the OM literature

DAL may have a therapeutic role in sequential or salvage therapy of bone and joint infections

Table 4. Almangour, et al. [2019]60

| Dalbavancin for the management of gram-positive osteomyelitis: Effectiveness and potential utility |
|---|---|
| **Objective** | To describe the effectiveness and tolerability of dalbavancin in the treatment of OM |
| **Methods** | |
| **Design** | Retrospective chart review conducted at 3 sites (Texas, Washington, and North Carolina) |
| | Evaluated at start of DAL, while on DAL, at the end of DAL therapy, and for ≥3 months after |
| **Population** | Adults admitted with confirmed osteomyelitis from January 1, 2015 to January 31, 2018 |
| | Adults ≥18 years with confirmed GP OM |
| | Treated with ≥1 dose of DAL, even if DAL started later to complete course |
| | Lost to follow-up (n=3) |
| | Lacking data to evaluate clinical outcome (n=2) |
| **Intervention** | Doses and durations of DAL were variable (n=31) |
| | 1500 mg weekly x 2 (n=7) |
| | 1000 mg weekly x 1 followed by 500 mg weekly (total 2-14 weeks) (n=15) |
| | 1500 mg weekly x 1 followed by 500 mg weekly (total 2-4 weeks) (n=3) |
| | 1500 mg x 1 (n=6) |
| **Endpoints** | **Primary Endpoint** |
| | Clinical success at end of DAL treatment, defined as resolution of signs and no requirement for additional surgical intervention or change in antibiotic |
| | Continuous clinical success at 3-months post-DAL |
| | Safety outcomes |
| | Hospital length of stay (HLOS) |
| | Projected cost savings |
| **Statistics** | Mean and standard deviation or median and interquartile range were used for descriptive analysis |
| **Results** | |
| **Baseline Characteristics** | **Variable** | **Value, no. (%)** |
| | Age, mean (SD) | 50 (14) |
| | Diabetes | 10 (32) |
| | IVDU | 10 (32) |
| | Current smoker | 8 (26) |
| | Previous OM at same site | 5 (16) |
| | Orthopedic hardware | 4 (13) |
| | Current immunosuppressive therapy | 1 (3) |
| | Peripheral arterial disease | 0 (0) |
| | Source of infection | ---- |
| | Contiguous | 18 (58) |
| | Hematogenous | 10 (32) |
Table 5. Rappo, et al. (2018)\textsuperscript{21}

<table>
<thead>
<tr>
<th><strong>Dalbavancin for the treatment of osteomyelitis in adult patients:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A randomized clinical trial of efficacy and safety</strong></td>
</tr>
</tbody>
</table>

**Objective**
- To describe efficacy and safety of dalbavancin for the first episode of OM known or suspected to be caused by GP pathogens in adults

**Methods**
- **Design**
  - Phase II, single-center, randomized, open-label, comparator-controlled, parallel-group trial
  - Conducted March 2016 through December 2017
  - Randomized 7:1 to DAL vs SOC
    - Aztreonam allowed at randomization for presumed GN coinfection

**Population**
- 860-bed tertiary teaching hospital with large orthopedic referral center in Cherkasy, Ukraine
• Age ≥ 18 years
• First episode of OM, acute or chronic
• >24 hr IV antibiotics within 96 hr of randomization
• Prosthetics at infection site at study initiation
• Infection associated with burn, sacral decubitus ulcer, multiple sites, noncontiguous septic arthritis, GN bacteremia, or concomitant endocarditis or necrotizing fasciitis

Groups
• DAL (n=70): 1500 mg IV as 30-minute infusion on day 1 and day 8
  o DAL dose adjusted to 1000 mg for patients not on dialysis with CrCl < 30 mL/min
• SOC (n=10): antibiotic choice based on investigator judgment and continued for 4-6 weeks
  o Most commonly IV VAN (n=3) or IV VAN with a switch to either IV LZD or IV LVX (n=4)

Endpoints
<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
</table>
| Clinical response at day 42 in the CE population, defined as recovery without need for additional antibiotic therapy | Early clinical improvement at day 21 and day 28
| Clinical failure at day 42 | Clinical response at day 180 and day 365
| Safety data collected at baseline and days 1, 8, 21, 28, 42, and 6 months |

Statistics
• Fisher’s exact used for categorical data and Wilcoxon rank-sum test for continuous data
• mITT population – excludes patients with only GN pathogens isolated
• CE population – subset of mITT receiving ≥ 1 dose DAL or ≥ 2 wks SOC and ≤ 1 dose of non-study antibiotic with activity against causative pathogen for an indication other than OM
• Microbiological-mITT population – subset of mITT with GP pathogen isolated from blood and/or bone

Results
Baseline Characteristics
• More men in the DAL group vs SOC group, 59/70 (84.3%) vs 5/10 (50%) (p=0.024)
• Fewer patients with diabetes in the DAL vs SOC group, 10/70 (14.3%) vs 5/10 (50%) (p=0.017)
• Low incidence of DFI overall, 4/70 (5.7%) in DAL group vs 1/10 (10%) in SOC group
• Four patients in the DAL group were bacteremic at baseline (2 MSSA, 2 CoNS)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DAL (n=70)</th>
<th>SOC (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD; range) years</td>
<td>49.2 (13.3; 26-79)</td>
<td>54.4 (15.3; 29-79)</td>
</tr>
<tr>
<td>Prior fracture and surgical repair, n (%)</td>
<td>33 (47.1)</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Debridement and open biopsy, n (%)</td>
<td>70 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Baseline histology showing necrotic bone, n (%)</td>
<td>43 (61.4)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Site of OM, n (%)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Tibia</td>
<td>27 (38.6)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Foot</td>
<td>17 (24.3)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Femur</td>
<td>11 (15.7)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (21.4)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Baseline pathogen in bone, n (%)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>MSSA</td>
<td>38 (54.3)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>MRSA</td>
<td>4 (5.7)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>CoNS</td>
<td>14 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>8 (11.4)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

Primary Endpoint
<table>
<thead>
<tr>
<th>Group (CE and mITT)</th>
<th>Clinical cure at day 42 n (%) [95% CI]</th>
<th>Clinical failure at day 42 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAL (n = 67)</td>
<td>65 (97) [89.6-99.6]</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SOC (n = 8)</td>
<td>7 (88) [47.3-99.7]</td>
<td>1 (12)</td>
</tr>
</tbody>
</table>

• 2 patients in DAL group were indeterminate due to loss to follow-up prior to day 21

Secondary Endpoints
<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical improvement at day 21 n (%)</th>
<th>Clinical cure at day 180 and day 365 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAL (n=67)</td>
<td>63 (94)</td>
<td>63 (94)</td>
</tr>
<tr>
<td>SOC (n=8)</td>
<td>5 (63)</td>
<td>7 (88)</td>
</tr>
</tbody>
</table>
CONCLUSIONS

I. LA-LGPs are only FDA-approved for treatment of ABSSSI, but due to cost, short required duration of treatment and plenty of effective oral options, use for this indication is not always practical unless it prevents hospital admission

II. Potent GP activity makes the LA-LGPs promising alternatives for treatment of invasive GP infections
   A. Case reports, series, and retrospective cohort studies support use of LA-LGPs in bone and joint infections
   B. Recent randomized controlled trial confirmed 2-dose DAL regimen as effective OM treatment option
   C. DAL appears to have a relatively high barrier to resistance
   D. ORI maintains activity against VRE harboring vanA

III. LA-LGPs penetrate well into bone and synovial fluid and appear to be well-tolerated, even after multiple doses

IV. PK/PD properties make LA-LGPs well-suited OPAT alternatives for infections requiring long treatment durations

Legend: IV=intravenous; DAL=dalbavancin; SOC=standard of care; VAN=vancomycin; LZD=linezolid; LVX=levofloxacin; mITT=modified intention-to-treat; CE=clinically evaluable; DFI=diabetic foot infection; CI=confidence interval; LOS=length of stay; TEAE=treatment-emergent adverse event; MIC=minimum inhibitory concentration; CFZ=cefazolin; BSI=bloodstream infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>DAL (n=67)</th>
<th>SOC (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital LOS (days), mean ± SD</td>
<td>15.8 ± 7.1</td>
<td>33.3 ± 14.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Days of IV antibiotics, mean ± SD</td>
<td>2.0 ± 0.0</td>
<td>31.6 ± 7.0</td>
<td>--</td>
</tr>
</tbody>
</table>

| Author’s Conclusions | • High microbiologic potency and prolonged tissue exposure with a 2-dose regimen providing 6 weeks of antibiotic coverage make DAL a convenient alternative for osteomyelitis treatment  
|                      | • High clinical cure rates observed make DAL an effective alternative for osteomyelitis treatment |

<table>
<thead>
<tr>
<th>Reviewer’s Critique</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| DAL 1500 mg IV administered on day 1 and day 8 appears to be a safe and effective treatment option for native osteomyelitis after surgical debridement and open biopsy and may prove to be a convenient and cost-saving treatment option  
| • Randomized design with SOC comparator  
| • Consistent DAL dosing regimen  
| • Relatively long study follow-up (12 months)  
| • Reported isolated pathogens and some MIC ranges  
| • Included patients who were bacteremic at baseline  
| • Included both acute and chronic osteomyelitis  
| • Low rate of TEAEs and no DAL discontinuations  
| • Included hospital LOS as a secondary endpoint | • Open-label, single-center study conducted only in the Ukraine  
| | • Large orthopedic referral center may limit generalizability  
| | • Small sample size in the SOC comparator group  
| | • Small number of infections due to MRSA  
| | • ≥50% of isolates were MSSA, but DAL compared to VAN  
| | • No information about how VAN was dosed  
| | • Significantly fewer diabetic patients in DAL group  
| | • Small number of DFIs included  
| | • Excluded those with prosthetics at site of infection  
| | • Frequent follow-up may not reflect reality in clinical practice |

| Overall Conclusions | • Few cases of DFI in DAL group, but all 4 experienced clinical cures at day 42, 6 months and 1 year providing limited evidence that DAL can be effective  
|                     | • Few cases of bacteremia in DAL group, but all 4 patients (2 MSSA, 2 CoNS) cleared bacteremia within 2-3 days, providing limited evidence that DAL may be an option in BSI management  
|                     | • It is encouraging that none of the organisms isolated were non-susceptible to DAL  
| | • DAL appears to have a relatively high barrier to resistance  
| | • DAL 1500 mg IV administered on day 1 and day 8 appears to be a safe and effective treatment option for native osteomyelitis after surgical debridement and open biopsy and may prove to be a convenient and cost-saving treatment option  
| | • Few cases of DFI in DAL group, but all 4 experienced clinical cures at day 42, 6 months and 1 year providing limited evidence that DAL can be effective  
| | • Few cases of bacteremia in DAL group, but all 4 patients (2 MSSA, 2 CoNS) cleared bacteremia within 2-3 days, providing limited evidence that DAL may be an option in BSI management  
| | • It is encouraging that none of the organisms isolated were non-susceptible to DAL  
| | • DAL appears to have a relatively high barrier to resistance  
| | • DAL 1500 mg IV administered on day 1 and day 8 appears to be a safe and effective treatment option for native osteomyelitis after surgical debridement and open biopsy and may prove to be a convenient and cost-saving treatment option  

4 patients in the DAL group did not meet criteria for clinical cure at 6-mo and 1-yr follow-up  
| • 2 were indeterminate due to loss to follow-up  
| • 1 died from underlying medical condition ~5 months after DAL use, deemed unrelated to DAL  
| • 1 required additional antibiotics ~4 months after DAL use and underwent debridement of soft tissue but had no signs of inflammation in bone and no growth from repeat site cultures  
| • All baseline GP isolates were susceptible to DAL and VAN  
| • In the microbiological-ITT group 96.8% in DAL and 87.5% in SOC were clinical cures at day 42  

Improved patient satisfaction and quality of life
RECOMMENDATIONS

I. LA-LGPs are a reasonable treatment option for BJIs due to GP organisms
II. DAL should be considered the preferred LA-LGP in BJIs (Table 6)
   A. More evidence compared to ORI
   B. Dosing regimen evaluated in randomized clinical trial (1500 mg on day 1 and day 8)
   C. Treatment of PJI may require additional doses (Infectious Diseases consult highly recommended)
III. ORI might be preferred in certain cases involving VRE, but no clear dosing strategy
IV. When susceptibility testing is unavailable, VAN susceptibilities should be used as a surrogate
   A. VAN MIC ≤ 2 for Staphylococcus spp and ≤ 1 for Streptococcus spp are LA-LGP susceptible
   B. VAN MIC > 4 for Enterococcus spp would require further testing to confirm LA-LGP resistance

Table 6. When to consider DAL for the treatment of BJIs

<table>
<thead>
<tr>
<th>Ideal Characteristics</th>
<th>Clinical Grey Areas</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection characteristics</td>
<td>• Culture negative BJI</td>
<td>• Empiric therapy for BJI</td>
</tr>
<tr>
<td>o BJI secondary to VAN susceptible GP pathogen</td>
<td>• No surgical debridement or intervention</td>
<td>• Concomitant</td>
</tr>
<tr>
<td>o Non-susceptible to highly bioavailable oral options</td>
<td>• Concomitant uncomplicated BSI</td>
<td>o Endocarditis</td>
</tr>
<tr>
<td>o Adequate surgical debridement or intervention</td>
<td>o Not MSSA, where cefazolin or an anti-staphylococcal penicillin are preferred</td>
<td>o Complicated BSI</td>
</tr>
<tr>
<td>• Patient characteristics</td>
<td>• Salvage therapy</td>
<td>o Uncomplicated MSSA BSI</td>
</tr>
<tr>
<td>o Not good candidate for OPAT or oral antibiotics</td>
<td>• Obesity</td>
<td>• PJI without an Infectious Diseases consult</td>
</tr>
<tr>
<td>o Allergy or toxicity concerns with first-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Leaving against medical advice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FUTURE DIRECTIONS

I. Randomized controlled trial evaluating efficacy of a pharmacokinetically optimized dose of oritavancin in BJI
II. Randomized controlled trials are needed to evaluate other off-label indications requiring long-term treatment
   A. Complicated bloodstream infections
   B. Endocarditis
   C. Prosthetic joint infections
III. Pharmacokinetic studies evaluating extended dosing of DAL and ORI in obese and morbidly obese patients
IV. Randomized controlled trials comparing LA-LGPs to antistaphylococcal penicillins or cefazolin for MSSA

REFERENCES


APPENDICES

Appendix A. IDSA guideline-recommended antibiotic treatment of bone and joint infections in adults20,22

<table>
<thead>
<tr>
<th>Microorganism isolated</th>
<th>Primary Regimen(s)</th>
<th>Alternative Regimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-susceptible S. aureus</td>
<td>Nafcillin or Oxacillin IV 12g daily Cefazolin IV 6g daily Ceftriaxone IV 2g q24h</td>
<td>Vancomycin IV 15-20mg/kg q12h Daptomycin IV 6-8mg/kg q24h Linezolid IV/PO 600mg q12h Levofloxacin PO 500-750mg + rifampin PO 600mg q24h Clindamycin IV 600-900mg q8h</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus</td>
<td>Vancomycin IV 15-20mg/kg q12h</td>
<td>Daptomycin IV 6-8mg/kg q24h Linezolid IV/PO 600mg q12h Levofloxacin PO 500-750mg + rifampin PO 600mg q24h</td>
</tr>
<tr>
<td>β-hemolytic streptococci</td>
<td>Penicillin G 20-24 million units daily Ceftriaxone 2g q24h</td>
<td>Vancomycin IV 15-20mg/kg q12h</td>
</tr>
<tr>
<td>Enterococci, penicillin susceptible</td>
<td>Penicillin G 20-24 million units daily Ampicillin 12g daily</td>
<td>Vancomycin IV 15-20mg/kg q12h</td>
</tr>
<tr>
<td>Enterococci, penicillin resistant</td>
<td>Vancomycin IV 15-20mg/kg q12h</td>
<td>Daptomycin IV 6-8mg/kg q24h Linezolid IV/PO 600mg q12h</td>
</tr>
</tbody>
</table>

Appendix B. A comparison of GP agents used in OPAT26-27

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Doses per day</th>
<th>Infusion time</th>
<th>Most common potentially serious ADRs</th>
<th>Other Comments</th>
<th>Average Wholesale Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin (CFZ)</td>
<td>3-4*</td>
<td>3-5 min push or 30-60 min</td>
<td>Hypersensitivity</td>
<td>Dialysis-only dosing possible</td>
<td>$41.19 per day</td>
</tr>
<tr>
<td>Ceftraroline (CPT)</td>
<td>2-3*</td>
<td>5 min push or 5-60 min</td>
<td>Hypersensitivity</td>
<td></td>
<td>$461.08 per day</td>
</tr>
<tr>
<td>Daptomycin (DAP)</td>
<td>1</td>
<td>2 min push or 30 min</td>
<td>Myopathy, rhabdomyolysis</td>
<td>Baseline and weekly CK</td>
<td>$1,069.16 per day</td>
</tr>
<tr>
<td>Dalbavancin (DAL)</td>
<td>Once per week</td>
<td>30 min</td>
<td>Hypersensitivity</td>
<td></td>
<td>$5,524.92 per dose</td>
</tr>
<tr>
<td>Nafcillin (NAF)</td>
<td>4-6*</td>
<td>30-60 min</td>
<td>Hypersensitivity, cytopenias, transaminits</td>
<td>Central line preferred</td>
<td>$214.02 per day</td>
</tr>
</tbody>
</table>
### Appendix C. Local OPAT complication rates compared to those found in the literature²⁶,⁶²

<table>
<thead>
<tr>
<th>Complication</th>
<th>South Texas VA (2018)</th>
<th>Previously Reported in the Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital readmission during OPAT (%)</td>
<td>18.7%</td>
<td>12.5% - 20.0%</td>
</tr>
<tr>
<td>Adverse Drug Events (%)</td>
<td>9.0%</td>
<td>10.2% - 63.2%</td>
</tr>
<tr>
<td>PICC line-related adverse events (%)</td>
<td>21.9%</td>
<td>6.4% - 17.9%</td>
</tr>
</tbody>
</table>

### Appendix D. Definitions related to antibiotic susceptibility testing, antibiotic resistance, and PD parameters⁶³

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the curve (AUC)</td>
<td>A PK measure indicating exposure to a drug during the full dosing interval</td>
</tr>
<tr>
<td>Breakpoint</td>
<td>Concentration of antibiotic that defines whether a species is susceptible or resistant</td>
</tr>
<tr>
<td>Maximal concentration (C&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>Occurs when rate of drug entering plasma equals rate of drug leaving from plasma</td>
</tr>
<tr>
<td>Concentration-dependent killing</td>
<td>Efficacy increased by maximizing AUC and C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Minimum inhibitory concentration (MIC)</td>
<td>Lowest antibiotic concentration that prevents visible growth of a bacteria at 24 hours</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Antibiotic concentration required to inhibit growth of 50% of a population of bacteria</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>Antibiotic concentration required to inhibit growth of 90% of a population of bacteria</td>
</tr>
<tr>
<td>Time-dependent killing</td>
<td>Efficacy increased by maximizing the duration of drug exposure above the MIC</td>
</tr>
</tbody>
</table>

### Appendix E. In vitro activity of DAL, ORI, and VAN against select gram-positive organisms²⁹

<table>
<thead>
<tr>
<th>Organism</th>
<th>DAL MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>DAL MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>ORI MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>ORI MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>VAN MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>VAN MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-susceptible S. aureus</td>
<td>≤ 0.25</td>
<td>≤ 0.12</td>
<td>≤ 0.008</td>
<td>≤ 0.008</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus</td>
<td>0.06</td>
<td>0.06</td>
<td>0.03</td>
<td>0.06</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Coagulase negative staphylococci</td>
<td>≤ 0.03</td>
<td>0.06</td>
<td>0.03</td>
<td>0.06</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>VAN susceptible</td>
<td>≤ 0.03</td>
<td>0.06</td>
<td>0.015</td>
<td>0.03</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>vanA</td>
<td>&gt; 4</td>
<td>&gt; 4</td>
<td>0.25</td>
<td>0.5</td>
<td>&gt; 16</td>
<td>&gt; 16</td>
</tr>
<tr>
<td>E. faecium</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>VAN susceptible</td>
<td>0.06</td>
<td>0.12</td>
<td>≤ 0.008</td>
<td>≤ 0.008</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>vanA</td>
<td>&gt; 4</td>
<td>&gt; 4</td>
<td>0.03</td>
<td>0.12</td>
<td>&gt; 16</td>
<td>&gt; 16</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>≤ 0.03</td>
<td>≤ 0.03</td>
<td>≤ 0.008</td>
<td>≤ 0.008</td>
<td>≤ 1</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td>≤ 0.03</td>
<td>0.06</td>
<td>≤ 0.008</td>
<td>0.06</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Group A streptococci</td>
<td>≤ 0.03</td>
<td>≤ 0.03</td>
<td>0.03</td>
<td>0.12</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>≤ 0.03</td>
<td>0.12</td>
<td>0.03</td>
<td>0.12</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Appendix F. Available CLSI breakpoints of DAL, ORI, and VAN⁶⁴

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptibility Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAL</td>
</tr>
<tr>
<td>S. aureus (including MRSA)</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td>E. faecalis (VAN-susceptible)</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>≤ 0.25</td>
</tr>
</tbody>
</table>