Long-Acting Lipoglycopeptides and Infectious Complications of Injection Drug Use

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Student Name: Cameron T. Nutt, BA

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Mentor Name and Affiliations: Eugene Richardson, MD, PhD; Department of Global Health and Social Medicine, Harvard Medical School; Division of Global Health Equity, Brigham and Women's Hospital; Division of Infectious Diseases, Brigham and Women's Hospital

Study Type: Narrative Review

Abstract:
Purpose: People who inject drugs (PWID) are vulnerable to invasive bacterial infections of the heart valves, bones, and joints. These patients also have high rates of departing the hospital "against medical advice," placing them at high risk of recurrence, with important consequences for long-term morbidity and mortality. As current treatment modalities require patients to receive up to six weeks of intravenous antibiosis, new therapeutic options are needed. Novel long-acting lipoglycopeptide antibiotics dalbavancin and oritavancin may offer important alternatives for the right patient.

Methods: A focused literature review was performed utilizing search terms related to the lipoglycopeptide antibiotics, injection drug use, and Gram-positive bacterial infections to identify relevant article published between 2002 and 2019.

Findings: Many challenges to the successful completion of extended courses of parenteral antibiotics among PWID were identified. While harm reduction strategies and access to medication-assisted therapy remain critical to preventing severe bacterial infections in this population, there remains an important treatment gap that means a large proportion of PWID do not receive complete courses of therapy after developing one of these complications of injection drug use. Dalbavancin and oritavancin, novel antibiotics with excellent coverage of staphylococcal, streptococcal, and enterococcal organisms and with terminal half-lives over two weeks, have been used in a range of settings across Europe and the United States to bridge this gap. Early results are promising, though uncertainties regarding patient selection criteria, optimal dosing schedules, and the potential for resistance remain.

Conclusion: Off-label use of the lipoglycopeptides in PWID appears likely to be a safe and effective option in certain cases of endocarditis, septic arthritis, and osteomyelitis caused by Gram-positive organisms, and can be considered by clinicians who treat this population while further studies are conducted.

Glossary of Abbreviations:
AMA: against medical advice
IDSA: Infectious Diseases Society of America
MRSA: methicillin-resistant *staphylococcus aureus*
POET: Partial Oral Treatment of Endocarditis trial
PWID: people who inject drugs
OPAT: outpatient parenteral antibiotic therapy
OVIVA: Oral versus Intravenous Antibiotics for Bone and Joint Infection trial
SSTIs: skin and soft tissue structure infection

Statement Regarding Student Role:
During the course of two clinical infectious diseases rotations during my third and fourth years of medical school, I participated in decisions to treat several of my patients with the long-acting lipoglycopeptide dalbavancin. I was struck by the clinical and social justice issues posed by high rates of "discharge against medical advice" among patients with severe Gram-positive bacterial infections and ongoing intravenous drug use, and intrigued by our teams' off-label use of dalbavancin. When I later learned about our patients' clinical cures, I was motivated to learn more about this approach and its potential generalizability.

The absence of a detailed overview of the lipoglycopeptides' potential role for this population and the clinical issues salient to decisions about whether to use them for an individual patient appeared to be an important gap. I therefore undertook a focused review of the infectious diseases, microbiology, pharmacology, and addiction medicine literatures, and drafted a manuscript for eventual publication in a peer-reviewed infectious diseases journal. The draft in its current form is my own original work, and represents the final product of three months of part- time research on this topic.

Methods:
I searched PubMed and Google Scholar for publications with the terms "dalbavancin", "oritavancin", "lipoglycopeptide", "people who inject drugs", "injection drug use", "intravenous drug use", "intravenous drug abuse", "opioid use disorder", "outpatient parenteral antibiotic therapy", "endocarditis", "osteomyelitis", and "septic arthritis" in various combinations without language restrictions. The search covered the period from January 1, 2002, the year that the first phase I trials of dalbavancin were published, until January 31, 2019. Review articles were cited when appropriate. This narrative review focused on the drugs' potential role in the treatment of severe Gram-positive bacterial infections among people who inject drugs. As most clinical data regarding their use in this population comes from case reports rather than observational studies or randomized trials, and as retrospective cohorts are heterogenous with regards to infection sites, antimicrobial resistance patterns, and preceding antibiotic and surgical exposure, meta-analysis was not possible.

A Role for Long-Acting Lipoglycopeptides in Responding to the Opioid Crisis

As the nation responds to the growing opioid crisis, public health authorities have rightly focused on skyrocketing rates of opioid overdose across the United States and called attention to outbreaks of human immunodeficiency virus and hepatitis C associated with needle sharing among people who inject drugs. Also rising exponentially is the incidence of the severe Gram-positive bacterial complications of injection drug use such as infective endocarditis, septic arthritis, osteomyelitis, spinal epidural abscess, and skin and soft tissue structure infections (SSTIs), including necrotizing fasciitis.

National Trends in Infectious Complications of Injection Drug Use

While the increasing frequency of these infections among young people who inject drugs (PWID) is well-known to clinicians working in hospitals around the country, however, these trends have not yet occasioned the same alarm from the general public or the same policy response from health agencies. No studies have estimated the annual number of deaths attributable to these infections among PWID, but hospitalization data paints a worrisome picture. Taken together, they may constitute one of the leading threats to the health of this population, after overdose.

North Carolina, for instance, has seen a tenfold rise in admissions for infective endocarditis associated with injection drug use between 2013 and 2017.[1] In addition to a severe infection associated with high in-hospital mortality that requires between four and six weeks of antibiotic therapy, all such patients have co-existing opioid use disorder; many also have undertreated mental illness and face socioeconomic barriers to remaining engaged in care. Nearly one in seven of these patients left the hospital “against medical advice” (AMA), placing them at high risk of treatment failure, readmission, and death.[1] This concords with nationwide data suggesting that, despite ongoing severe illness, PWID have nearly three times higher risk of departing AMA than the rest of the hospitalized population.[2]

Treatment Challenges in People Who Inject Drugs

Lack of evidence-based inpatient opioid use disorder treatment with buprenorphine or methadone likely represents the single most important preventable cause of these AMA discharges.[3,4] Yet

even at hospitals where addiction medicine teams are now closely involved in the care of every patient with injection drug use-associated infections (including our own), rates of premature discharge remain elevated due to the many psychosocial stressors these patients face during prolonged hospitalizations.

Despite concerns that PWID might not be capable of successfully completing outpatient parenteral antibiotic therapy (OPAT), recent reviews have largely demonstrated high rates of retention and cure,[5] with some exceptions.[6] Outdated guidelines, bias by clinicians fearful of patients injecting through central lines despite the absence of evidence that line manipulation is widespread, high rates of non-insurance among PWID in many states, and the refusal of many skilled nursing facilities and home infusion services to accept PWID have all hindered more widespread use of OPAT, though this situation is slowly improving due to advocacy by infectious diseases and addiction specialists.

But what of the patient who suddenly leaves the hospital AMA in the midst of their acute illness and is not successfully enrolled in OPAT? Unless they are readmitted or manage to complete an oral regimen hastily prescribed before they departed, many will not receive a complete course of therapy for their life-threatening infection. Additionally, while the results of recent trials investigating prolonged courses of oral antibiotics for endocarditis (POET)[7] and bone and joint infections (OVIVA)[8] are highly encouraging, only 1.25% of POET participants reported injection drug use, and the OVIVA study did not include data on participants' substance use. While the pharmacology of oral antimicrobial therapy would of course not differ for people who inject drugs, those who depart AMA likely face more serious barriers to treatment adherence than either study's cohort. There remains an important gap in treatment options that contributes to poor outcomes in this growing population.[3]

Novel Long-Acting Lipoglycopeptides

In 2014, the Food and Drug Administration approved two novel antibiotics in the lipoglycopeptide class, a group of synthetic vancomycin derivatives. Both agents, dalbavancin and oritavancin, have been shown to be highly effective against the Gram-positive organisms most commonly implicated in the infectious complications of injection drug use, including methicillin-resistant

staphylococcus aureus (MRSA).(**Table 1**)[9,10] They also possess notable activity against vancomycin-resistant enterococci, though dalbavancin is ineffective against strains expressing *vanA* gene products.[9,10] Similar to vancomycin, each drug acts by binding to D-alanyl-D-alanine residues, inhibiting elongation of peptidoglycan chains in growing cell walls. Unlike vancomycin, they also act directly at the cytoplasmic membrane to disrupt its function, and kill stationary-phase biofilm-forming MRSA in vitro.[11,12]

While the lipoglycopeptides' excellent activity against important Gram-positive pathogens is encouraging research to explore their place in the treatment of severe drug-resistant nosocomial infections, perhaps their most significant advance over prior classes of antimicrobials is their extended elimination half-life, which averages over two weeks in healthy patients for both agents.(**Figure 1**) Lipophilic tails added to dalbavancin and oritavancin alter their pharmacokinetics dramatically in relation to the agents their chemical structures are derived from (teicoplanin and vancomycin, respectively). As a result, both drugs have a large distribution, are highly protein-bound, and are excreted very slowly by the kidneys (<5% per day). Each has excellent bone and joint penetration.[13,14]

New Tools for Complicated Gram-Positive Infections

In addition to offering new therapeutic options for severe infections caused by pathogens like vancomycin-resistant enterococci, then, the lipoglycopeptides might have an important role to play in improving outcomes for PWID deemed ineligible for OPAT or who likely face barriers to adherence to a prolonged oral regimen.

Both dalbavancin and oritavancin were initially studied in emergency department patients with acute SSTIs, where each was non-inferior to vancomycin when given in two once-weekly doses or as a single dose. These findings were consistent sub-group analyses of patients with confirmed MRSA.[15,16] While the oritavancin trials did not include sub-group analyses of PWID, dalbavancin was found to be non-inferior to dalbavancin in PWID.[15]

One Ukrainian trial has explored the use of dalbavancin for osteomyelitis in conjunction with surgical debridement and found it non-inferior to standard intravenous antibiotic therapy and

debridement, but included no PWID.[17] Similarly, one Austrian cohort of endocarditis patients treated with dalbavancin after clearance of blood cultures has been published; the clinical success rate was 92.6%, but no participants reported injection drug use.[18]

One early American trial of weekly dalbavancin for central line-associated bloodstream infection by Gram-positive organisms (mostly *staphylococcus aureus* and *s. epidermidis*) showed a significantly higher overall success rate compared to treatment with twice-daily vancomycin,[19] and a secondary analysis of bacteremic patients in a range of trials of dalbavancin for SSTIs reported similarly encouraging results;[20] no subgroup analyses on PWID were reported.

All data on their use in PWID with endocarditis or bone and joint infections to date is therefore observational, though available case series and cohort studies are highly encouraging.[21-26] Most notable is Bryson-Cahn and colleagues' comparative study from Seattle. Among 34 PWID treated for bacteremia, endocarditis, septic arthritis, or osteomyelitis between 2015 and 2016, rates of documented clinical cure more than doubled following implementation of a dalbavancin protocol (from 29.4% with standard anti-staphylococcal therapy to 64.7%) while rates of 30-day readmission fell from 29.4% to 0.0%.[21] Outcomes described in this group's larger case series of patients who received dalbavancin though late 2017 were less dramatic, but still encouraging. Among 32 patients received 13 days of parenteral antibiotics on average and had negative blood cultures prior to the first dose of dalbavancin, reported a confirmed clinical response in 53.1%, with 31.3% lost to follow-up, and 12.5% experiencing a documented treatment failure (only one of whom completed a full course of treatment).[22]

Barriers to Wider Adoption

Several issues have been raised about routine use of the lipoglycopeptides. While their long half-lives raise theoretical concern about extended hypersensitivity reactions, these have not been seen in trials and cohort studies to date; adverse effects consist mostly of nausea, vomiting, diarrhea, and headache. Prolonged exposure to subinhibitory concentrations following administration of the final dose also risks selection for resistant mutants if the infection is not eradicated, as demonstrated by two case reports of patients who developed cross-resistance to vancomycin after treatment with dalbavancin for complicated MRSA infections.[27,28] Limited animal model data

suggests that they do not cross the blood-brain barrier in rats,[29] and thus likely cannot be used for meningitis, spinal epidural abscess, or endocarditis with suspected septic emboli to the brain.

Manufacturers have set high price points for dalbavancin ($5,525 per 1500mg dose) and oritavancin ($3,584 per 1200mg dose), which they justify by citing evidence of reduced length-of-stay for SSTI patients. Compared to generic formulations of vancomycin or oral anti-MRSA agents, these prices may pose barriers to access among patients without health insurance, though an increasing number of hospitals have demonstrated willingness to add them to formularies in light of growing evidence of their cost-effectiveness (including in cohorts of PWID) and continuing shifts from fee-for-service to accountable care payment models.[30,31]

Additional data is warranted, yet only one prospective, randomized study is presently underway (investigating dalbavancin for septic arthritis and osteomyelitis).[32] Unfortunately, two phase 2 trials of dalbavancin for the treatment of osteomyelitis and endocarditis were cancelled by Allergan for unclear reasons.[33,34] Two dalbavancin shortages were reported in 2018, and the manufacturer does not appear to be pursuing additional FDA approvals beyond SSTIs.

Opportunities and Next Steps

Taken together, however, currently available data on dalbavancin and oritavancin indicate that they have an important off-label niche in the care of patients with Gram-positive endocarditis, septic arthritis, osteomyelitis, or SSTIs who are deemed ineligible for traditional OPAT programs and who are unable or unwilling to remain in an inpatient setting for the full duration of therapy. Each drug can be administered as a once-weekly infusion in the outpatient setting, or after transfer to a skilled nursing facility without a central venous catheter so long as the patient can be transported to an infusion center for doses each week. For select patients who have already received a partial course of definitive therapy intravenously, dalbavancin and oritavancin can also be given as a single-dose prior to discharge, without need for further antimicrobials.

Many hospitalists who care for such patients on a frequent basis are currently unfamiliar with these drugs. Furthermore, there is no formal guidance for infectious diseases consultants regarding appropriate patient selection criteria (including type of infection, specific pathogen, duration of

parenteral therapy already completed) or dosage schedules. When they are used, it is often in unstandardized fashion, sometimes in conjunction with ad-hoc oral regimens.

Yet long-acting lipoglycopeptides were not mentioned during a March 2018 National Academies of Sciences, Engineering, and Medicine workshop entitled, "Integrating Infectious Disease Considerations with Response to the Opioid Epidemic,"[35] or in a policy brief published the same month by the Infectious Diseases Society of America (IDSA).[36] Newly released IDSA OPAT guidance states only that "the role of these expensive agents, particularly in PWID, remains to be defined."[37] Formal clinical guidelines on the management of severe bacterial infections in PWID are needed, and should specifically reference the role of long-acting lipoglycopeptides, as well as clarify areas where more research is warranted.

Expanded use of and additional data on dalbavancin and oritavancin in this vulnerable population would help to improve outcomes and advance the infectious diseases community's response to this decade's leading public health crisis.

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Table 1. Minimum Inhibitory Concentrations of Vancomycin, Daptomycin, and Lipoglycopeptides Against Common Gram-Positive Pathogens

Organism	Vancomycin	Daptomycin	Dalbavancin	Oritavancin
MSSA	1	0.5	0.06	0.06
MRSA	1	0.5	0.06	0.06
VISA	8	4	0.12	2
CoNS	2	0.5	0.06 - 0.12	0.06
Viridans group streptococci	1	1	0.1016 - 0.03	0.03
E. faecalis	>16	1-2	0.015 - >32	0.03 - 0.5
E. faecium	>16	2	0.032 - >32	≤0.008 - 0.12

MSSA = methicillin-susceptible *staphylococcus aureus*; MRSA = methicillin-resistant *s. aureus*; VISA = vancomycin-intermediate *s. aureus*; CoNS = coagulase-negative s. aureus (*s. epidermidis*)

Figure 1. Plasma Concentrations of Dalbavancin and Vancomycin for Complicated Staphylococcal Infection (adapted from reference #20; data from reference #20)