New Drug Review

Beyond Vancomycin: The Tail of the Lipoglycopeptides

Kenneth P. Klinker, PharmD[1]; and Samuel J. Borgert, PharmD[2]

[1]*University of Florida, College of Pharmacy, Gainesville, Florida; and* [2]*Department of Pharmacy, University of Florida Health Shands Hospital, Gainesville, Florida*

ABSTRACT

Purpose: The purpose of this comparative review is to provide clinical information on the semisynthetic lipoglycopeptides (telavancin, oritavancin, and dalbavancin) for the management of gram-positive infections.

Methods: A PubMed search was conducted using the following terms: *telavancin*, *dalbavancin*, and *oritavancin*. Clinical trials evaluating pharmacokinetic properties, pharmacodynamic properties, clinical efficacy, and safety profiles were included in the review.

Findings: The lipoglycopeptides are approximately 4- to 8-fold more potent than vancomycin against gram-positive organisms, including activity against vancomycin-intermediate or vancomycin-resistant strains of *Staphylococcus* and *Enterococcus* species. In addition, oritavancin maintains activity against *Enterococcus* species harboring vanA operon. Clinical trial data revealed equal efficacy to vancomycin in the management of acute bacterial skin and skin structure infections and, in the case of telavancin, hospital-acquired pneumonia. A benefit of oritavancin and dalbavancin is that a full course of therapy consists of a single- or 2-dose regimen, respectively. These agents are well tolerated with similar adverse event rates to vancomycin. Telavancin requires a thorough assessment before initiation of therapy to minimize the risk of acute kidney injury and teratogenicity.

Implications: The lipoglycopeptides enhance the antibiotic gram-positive armamentarium at a time when methicillin-resistant *Staphylococcus aureus* prevalence and overall resistance is at an all-time high. These agents serve to fill different clinical roles in the management of gram-positive infections. On the basis of the available data, telavancin should be considered a plausible agent for the management of gram-positive organisms when patients do not respond or develop adverse effects to vancomycin. Dalbavancin and oritavancin are new therapeutic options, and their potency and pharmacokinetic properties may provide benefit over existing therapies. Clinical trial data indicate that patients with signs or symptoms of skin and skin structure infections may be successfully treated using 1 or 2 doses of these agents. Eliminating the need for inpatient admission, central catheter placement, and/or daily outpatient parenteral antibiotic therapy is a major advance in treatment of skin and skin structure infections. This strategy may reduce costs associated with resource utilization and iatrogenic morbidity, resulting in overall improvements in care. (*Clin Ther.* 2015;37:2619–2636) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: acute bacterial skin and skin structure infections, dalbavancin, oritavancin, telavancin.

INTRODUCTION

A common challenge for health care professionals is maintaining antimicrobial efficacy in the setting of rapidly changing susceptibility patterns. Although the development of bacterial resistance is complex, overprescribing of antimicrobial agents remains a common thread. After the introduction of new antimicrobials, broad use often results in the presence of clinically relevant resistance.[1] The rapidity with which resistance develops has increased in the past decades, with some resistant isolates being identified shortly after product launch.[1] This event is concerning because the pipeline for new antimicrobials active against these strains is often limited.

A prototypical organism with rapid development of resistance is *Staphylococcus aureus*. Methicillin-resistant *S aureus* (MRSA) was identified within 2 years of the introduction of methicillin into clinical

Accepted for publication November 13, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.11.007
0149-2918/$ - see front matter

© 2015 Elsevier HS Journals, Inc. All rights reserved.

practice.[2] Similar results were seen with linezolid and daptomycin.[3,4] These data highlight Mother Nature's ability to outpace product development and preserve species survival. *S aureus* has unique properties that allow it to evade eradication. Adapting to harsh environmental conditions (including antimicrobial exposure), establishing asymptomatic carriage, and expressing multiple virulence factors, the organism has survived most control efforts.[5] The ability to adapt allowed MRSA to effectively integrate into health care and community settings, resulting in high morbidity, mortality, and resource utilization.[6] From 1999 through 2005, hospitalizations involving infections with MRSA increased 62%, and the rate of *S aureus*–related diagnoses per 1000 admissions increased 50%.[7] During the same period, skin and soft-tissue infections (SSTIs) (cellulitis and abscesses) increased >4-fold.[7]

To combat the trend, health care organizations in the United States have implemented infection prevention and antimicrobial stewardship strategies to reduce the incidence of MRSA infections.[8] However, MRSA remains a common pathogen in patients presenting with acute bacterial skin and skin structure infections (ABSSSIs) and central catheter, surgical site, or ventilator-associated infections.[9,10] Therefore, it is paramount to develop and implement effective treatment strategies.

For decades, vancomycin has been viewed as the gold standard for managing MRSA infections. In review of available prospective data, vancomycin remains equivalent to newer agents for the management of complex infections (eg, pneumonia, ABSSSI), with a relatively low incidence of vancomycin resistance among MRSA isolates.[11–13] These data have resulted in vancomycin remaining a first-line agent for managing complicated MRSA infections.[14] Despite these data, there are several challenges. Vancomycin has poor penetration into key tissues (ie, lung) and slow bactericidal activity.[15] Variability in the pharmacokinetic properties of vancomycin makes it difficult for clinicians to attain therapeutic concentrations in most patients, even using standardized protocols.[16] Multiple reports reveal increased frequency of treatment failure associated with MICs in the range of 1.5 and 2 μg/mL.[17,18] Although controversy exists regarding reasons for vancomycin treatment failures, consideration of using newer agents on various strains of MRSA may be necessary.[5,19] In addition, concerns exist for the development of heteroresistant vancomycin-intermediate *S aureus* (hVISA), vancomycin-intermediate *S aureus* (VISA), and vancomycin-resistant *S aureus* (VRSA) strains, which may elude detection.[20] Lastly, vancomycin-related adverse events, in particular nephrotoxicity, may result in increased morbidity and resource utilization.[21,22] Together these data highlight a need for continued development of agents that have excellent activity against gram-positive organisms, are clinically effective, and have an acceptable safety profile. The purpose of this comparative review is to provide clinical information on the semisynthetic lipoglycopeptides (telavancin, oritavancin, and dalbavancin) for the management of gram-positive infections.

METHODS

A PubMed search was conducted with the following terms: *telavancin*, *dalbavancin*, *BI397*, *oritavancin*, and *LY33328*. Clinical trials evaluating pharmacokinetic properties, pharmacodynamic properties, clinical efficacy, and safety profiles were included in the review. Primary literature and data available from the Interscience Conference on Antimicrobial Agents and Chemotherapy, the annual meeting of the Infectious Diseases Society of America, and the European Congress of Clinical Microbiology and Infectious Diseases were incorporated.

RESULTS

Chemical Structure

Consistent among glycopeptide and lipoglycopeptide antimicrobials is a heptapeptide core, which interferes with cell wall synthesis by binding to the D-alanyl-D-alanine (D-ala-D-ala) terminus of peptidoglycan precursors (Figure 1).[23] The interaction results in ineffective peptidoglycan polymerization and cross-linking. Further modifications to the heptapeptide core result in alterations in spectrum of activity and pharmacokinetic parameters.

Telavancin is a semisynthetic derivative of vancomycin that differs by the presence of a hydrophobic decylaminoethyl side chain and a hydrophilic phosphonomethylaminomethyl group.[24,25] The addition of a hydrophobic side chain strengthens the bond with bacterial cell membranes and D-ala-D-ala targets, thus improving activity against MRSA phenotypes and vanB enterococci.[25] In addition, binding to the cell membrane disrupts membrane potential and increases permeability, thus enhancing activity.[25] The addition

Download English Version:

https://daneshyari.com/en/article/5824687

Download Persian Version:

https://daneshyari.com/article/5824687

Daneshyari.com