Lipoglycopeptide Antibiotics: Reliable Fighters Against Gram-Positive Pathogens

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Abstract

Multi-drug resistant (MDR) strains of staphylococci are usually difficult to treat. Vancomycin has had a time-honored niche in treating MDR Staphylococcus strains; however, during recent years, many clinical failures have been reported worldwide. Since 2014, new semisynthetic lipoglycopeptides antibiotics have been introduced to combat methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-intermediate Staphylococcus aureus (VISA), vancomycin-resistant Staphylococcus aureus (VRSA), and vancomycin-resistant enterococci (VRE). They include dalbavancin, oritavancin, and telavancin. These semisynthetic lipoglycopeptides have a considerable efficacy against MDR Staphylococcus strains. Due to the presence of a lipid side chain, the half-life is prolonged and it enables them to anchor the cell membrane of a pathogen. Lipoglycopeptides display a greater potency and more consistent activity against all species of staphylococci than vancomycin. Among them, oritavancin is active against MRSA, VISA, and VRSA. However, dalbavancin and telavancin have activities against MRSA and VISA. Dalbavancin is used once weekly, telavancin is used daily, and oritavancin is usually administered one dose per treatment. Compared to vancomycin, these semisynthetic lipoglycopeptides have longer half-lives with a lower minimum inhibitory concentration (MIC) and rapid bactericidal activity. In addition, lipoglycopeptides have concentration-dependent effects in vivo and in vitro. In the present paper, we review the structure, mechanism of action, microbiology, indications, safety, and important interactions of dalbavancin, oritavancin, and telavancin.

Keywords: Skin Infections, Antibiotic, Lipoglycopeptide, Resistance

1. Literature Search

A literature search was done on Medline and EMBASE using relevant keywords like lipoglycopeptides, vancomycin, telavancin, dalbavancin, oritavancin, MRSA, VRSA, pneumonia, and skin infection in keywords, title, or abstract. Additional references were found from bibliographies of the selected papers. Relevant medical texts were checked when required. Randomized controlled trials and other types of studies were considered.

1.1. Structure

Glycopeptides have a common heptapeptide core, which enables them to inhibit the cell wall synthesis (1). The peptide backbone of glycopeptides forms the D-alanyl-D-alanine binding site that is important for their antimicrobial activity (2). Glycopeptides can bind to C-terminal D-alanyl-D-alanine (D-Ala-D-Ala) of cell wall precursor units and disrupt the polymerization of N-acetyl Glucomamine and N-acetylmuramic acid. Because of their large molecular size, they are unable to penetrate the outer membrane of Gram-negative bacteria (3). All three lipoglycopeptides contain lipophilic side chains, which prolong their half-lives and increase their activities against Gram-positive cocci (4). The length of the lipophilic side chain is important; an increase in the chain length increases the activity of the agent against enterococci but it reduces the activity against MRSA (5, 6). Dalbavancin is a semisynthetic derivative of teicoplanin. Modifications include the removal or substitution of sugars and derivatization of the functional groups such as the carboxy group of amino acid 7 (the C-terminus of the peptide), the N-terminus of the peptide, and different hydroxy groups. All modifications are at sites that do not directly affect the D-alanyl-D-alanine binding pocket (7). Oritavancin is a synthetic derivative of naturally occurring glycopeptides chloroeremomycin. N-Alkyl-p-chlorophenyl benzyl substituent improves the activity of oritavancin against both vancomycin-susceptible enteroc-