Telavancin for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections

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Methicillin-resistant Staphylococcus aureus (MRSA) causes a wide range of infections, including skin and skin-structure infections, pneumonia, bloodstream infections, and endocarditis [1]. Staphylococci, including MRSA, are considered to be a leading cause of healthcare-associated infections [2]. Many of these infections can be life-threatening and cause sepsis and death. The Centers for Disease Control and Prevention estimate that 80 461 severe MRSA infections and 11 285 MRSA-related deaths occur each year in the United States [2]. The changing epidemiology and increasing prevalence of resistant phenotypes of S. aureus, including MRSA, heteroresistant vancomycin-intermediate S. aureus, vancomycin-intermediate S. aureus and, rarely, vancomycin-resistant S. aureus, have spurred the need for new antimicrobial agents to treat serious infections caused by these gram-positive pathogens.

Telavancin is a semisynthetic lipoglycopeptide antibacterial with potent bactericidal activity against a broad spectrum of these gram-positive organisms, including MRSA [3]. The recommended dosage regimen for telavancin is 10 mg/kg body weight intravenously infused over a 60-minute period every 24 hours in patients with normal renal function (creatinine clearance [CrCl], >50 mL/min). A dosage adjustment is required for patients with renal impairment (CrCl ≤50 mL/min). This supplement provides historical and current perspectives on the present roles of telavancin in clinical practice.

The first article in the supplement, which Eric Wen- zler and I coauthored, summarizes the discovery and development programs that allowed telavancin to become the first marketed semisynthetic lipoglycopeptide in 2009 [3]. Telavancin is commercially available again after a long and winding road involving regulatory decisions, manufacturing obstacles, and changes in commercialization partners. Importantly, telavancin continues to be supported by ongoing clinical research programs including the Telavancin Observational Use Registry (TOUR; NCT02288234) in the United States and an international phase 3, randomized trial comparing telavancin with standard intravenous antibiotic therapy for the treatment of patients with complicated S. aureus bacteremia, including right-sided endocarditis.

The dual mechanism of action and in vitro activity of telavancin against clinically significant wild-type and drug-resistant gram-positive pathogens are outlined in the article by Karlowsky and colleagues [4]. The Clinical and Laboratory Standards Institute revised the broth microdilution susceptibility testing of telavancin in 2014, which resulted in a more accurate method for determining minimum inhibitory concentration [5, 6]. The US Food and Drug Administration has also revised minimum inhibitory concentration interpretive break point criteria for susceptibility to telavancin for S. aureus (≤0.12 µg/mL), Streptococcus pyogenes (≤0.12 µg/mL), Streptococcus agalactiae (≤0.12 µg/mL), Streptococcus anginosus group (≤0.06 µg/mL), and Enterococcus faecalis (vancomycin susceptible, ≤0.25 µg/mL) [5, 6]. The recent in vitro activity of telavancin from 2 large surveillance
programs (2013 CANWARD and 2011–2013 SENTRY) is summarized, along with a discussion of mechanisms of vancomycin resistance.

There are several mechanisms of resistance to each of the various antibiotic classes used to treat gram-positive bacteria. Munita and colleagues [7] provide a thorough review of the resistance mechanisms commonly associated with β-lactams, glycopeptides, oxazolidinones, and daptomycin, with emphasis placed on clinically important gram-positive pathogens (eg, staphylococci, streptococci, and enterococci).

In the United States and Canada, telavancin is currently approved for the treatment of adult patients with complicated skin and skin-structure infections (cSSIs) caused by susceptible gram-positive pathogens. Cardona and Wilson [8] review the epidemiology, etiology, microbiology, and scoring system for complicated skin and soft-tissue infections. The results from the phase 2 and 3 clinical trials (FAST and ATLAS) of telavancin for cSSIs are summarized [9–12]. The role of telavancin in the treatment of cSSIs is discussed, and the updated (2014) practice guidelines of the Infectious Diseases Society of America for the diagnosis and management of skin and soft-tissue infections are outlined [13].

Until 2013, only 2 agents had been approved for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by MRSA: vancomycin and linezolid [14]. Telavancin has recently been approved in the United States for the treatment of HABP/VABP caused by susceptible isolates of S. aureus (methicillin-susceptible and MRSA isolates), reserved for use when alternative agents are not suitable. In the European Union, telavancin is also indicated for the treatment of adults with nosocomial pneumonia (including ventilator-associated pneumonia), known or suspected to be caused by MRSA, and should be used only in situations where it is known or suspected that alternative agents are not suitable. Sandrock and Shorr [15] briefly review the phase 3 clinical studies (ATTAIN), including the post hoc analysis of clinical response and 28-day survival [16, 17]. The clinical role of telavancin for treatment of HABP/VABP caused by MRSA is described based on the risks and benefits of the limited therapeutic options available.

One of the complex issues in understanding the efficacy of telavancin for the treatment of HABP/VABP is the increased 28-day all-cause mortality rates observed in patients with preexisting moderate to severe renal function (CrCl, ≤50 mL/min) [16, 17]. The all-cause mortality outcomes were evaluated in the group of patients who had ≥1 baseline gram-positive respiratory pathogen, and included those patients who had both gram-positive and gram-negative organisms (mixed infections). In their article, Lacy and colleagues [18] report a post hoc analysis exploring clinical efficacy and 28-day all-cause mortality of patients who received inadequate gram-negative therapy during the ATTAIN studies. The results suggest that differences in outcome did occur in patients with CrCl <30 mL/min if inadequate gram-negative therapy was administered to patients with only gram-negative organisms or mixed infections, as opposed to patients with pneumonia caused exclusively by gram-positive organisms. This post hoc analysis lends support to the previously reported clinical cure rates and 28-day mortality rates that favor telavancin compared with vancomycin in patients with HABP/VABP in whom S. aureus was the only baseline pathogen [16, 17].

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