

Telavancin in the treatment of invasive Gram-positive infections

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Abstract: Telavancin is a newer once-daily lipoglycopeptide with activity against Gram-positive bacteria, including those that are resistant to conventional antibiotics like beta-lactams. The results of recent clinical trials led to registration of telavancin for use in skin and skin structure infections in the US and Canada and for nosocomial pneumonia in Europe, based primarily on the favorable results of clinical trials. We review the evidence for use of telavancin in Gram-positive intravascular infections, focusing on bacteremic subpopulations in the large clinical trials as well as anecdotal evidence for use of the drug in the setting of infective endocarditis.

Keywords: telavancin, Gram-positive bacteria, skin infections, infective endocarditis

Introduction

Gram-positive bacteria are common causes of both community-acquired and nosocomial invasive infections, and are a leading cause of bloodstream infections. *Staphylococcus aureus* is a leading cause of bacteremia, and has become more common in recent years with the increase in invasive procedures, indwelling catheters, and prosthetic devices, as well as the aging population. These infections are associated with substantial morbidity, complications, and mortality. The increase in methicillin-resistant *S. aureus* (MRSA) both in the health care setting and the recent explosive rise in community-acquired MRSA has further complicated the management of patients with staphylococcal bacteremia, increasing the duration of hospital stay and decreasing the availability of clinically effective therapeutic agents, and has been accompanied by increased costs of hospital stay and patient management.¹⁻⁴

Telavancin is an intravenous lipoglycopeptide agent, with an improved tissue distribution profile supporting once-daily dosing without the need for serum concentration monitoring.⁵ Telavancin is a 14 times more potent inhibitor of peptidoglycan synthesis than vancomycin. In addition, telavancin has an additional mechanism of action that sets it apart from other glycopeptide derivatives, namely, it interacts selectively with the bacterial cell membrane, leading to an increase in membrane permeability with ensuing efflux of intracellular ATP and potassium, and the ability to abolish the cell membrane potential.^{6,7,9} In vitro, telavancin is rapidly bactericidal against clinically important Gram-positive bacteria,^{11,12} including MRSA, vancomycin-intermediate and vancomycin-resistant *S. aureus*, and penicillin-resistant *Streptococcus pneumoniae*. It is also active against beta-hemolytic streptococci, *Listeria monocytogenes*, *Bacillus anthracis*, and *Corynebacterium* spp.^{8-13,16-19} In addition, telavancin maintains

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antibacterial activity against various anaerobic Gram-positive organisms, such as lactobacilli, actinomycetes, clostridia, and *Propionibacterium* spp.^{8,13,16} In addition, telavancin retains bactericidal activity against vancomycin-tolerant¹³ and vancomycin-intermediate^{10,12,14,16,18} strains. Moreover, telavancin has been shown to possess a 2–4-fold greater antistaphylococcal potency compared with vancomycin, a 4–8-fold greater potency than linezolid, and is 2-fold more potent than daptomycin against *S. aureus*.^{13,14,19} Its potency is similar to oxacillin against methicillin-susceptible strains.

Telavancin is approved in the US and Canada for the treatment of adult patients with complicated skin and skin structure infections due to susceptible-Gram-positive pathogens.²⁰ It is being evaluated in the US currently for registration in the management of Gram-positive nosocomial pneumonia. In Europe, telavancin has been approved for use in nosocomial pneumonia (including ventilator-associated pneumonia) caused by *S. aureus*. The role of *S. aureus* in hospital-acquired pneumonia, and specifically the fact that over 60% of isolates from US hospitals are resistant to methicillin and therapy is initiated prior to microbiological diagnosis, necessitates the use of antimicrobials with anti-MRSA activity prior to microbiological identification of the causative organism implicated in the pneumonia.^{21–26} Vancomycin and linezolid are recommended in current guidelines but have limitations,^{25,26} while tigecycline is not indicated in ventilator-associated pneumonia and daptomycin is not indicated for hospital-acquired pneumonia.^{22,26} Recently, the results of the ATAIN (Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia) studies were reported.^{25,28} These studies were international, randomized, double-blind, parallel-group Phase III trials investigating the efficacy and safety of telavancin in the treatment of hospital-acquired pneumonia caused by Gram-positive pathogens in adults. *S. aureus* was the most commonly isolated organism; two thirds of such isolates in the study were MRSA, reflecting the widespread occurrence of this organism globally. Comparison of telavancin with vancomycin yielded similar cure rates for pooled analysis. Telavancin was superior to vancomycin in patients with monomicrobial pneumonia due to *S. aureus* and in the subgroup of patients infected with *S. aureus* and a vancomycin minimum inhibitory concentration ≥ 1 $\mu\text{g/mL}$ and trended towards superiority for monomicrobial MRSA pneumonia. The evidence for the role of telavancin in the

treatment of Gram-positive bloodstream and intravascular infections is the focus of this review.

Telavancin for treatment of bacteremia

Telavancin has theoretical advantages compared with vancomycin. It is more rapidly bactericidal and has more potent activity against Gram-positive organisms, including MRSA and glycopeptide-intermediate *S. aureus* D, E-1. Because vancomycin is only slowly bactericidal against methicillin-sensitive *S. aureus* and linezolid is only bacteriostatic, telavancin and daptomycin remain the only options for reliable treatment of methicillin-sensitive *S. aureus* bacteremia in individuals who are allergic to beta-lactam antibiotics and those with MRSA bacteremia. These salutary effects of telavancin may be attributed to the dual action of the drug. In mouse models of heteroresistant vancomycin-intermediate and glycopeptide-intermediate *S. aureus* infection, telavancin has been shown to possess an 8–16-fold greater potency than vancomycin for different resistant strains.^{15,17,27,30,31,38} In a model using immunocompromised mice inoculated intraperitoneally with MRSA and treated with two subcutaneous doses (once every 12 hours) of vehicle or test compound, equivalent exposure to vancomycin and telavancin was ensured based on murine pharmacokinetic data. Telavancin produced significantly greater reductions in bacterial load compared with vancomycin in the blood and spleen. This reduction translated into significantly decreased mortality, from 100% in animals treated with vehicle and vancomycin to 7% in telavancin-treated animals.²⁹

The ATLAS (Assessment of Telavancin in Complicated Skin and Skin Structure Infections) trials randomized 1867 patients with skin and skin structure infections to receive either vancomycin or telavancin. In the clinically evaluable population, microbiological and clinical success rates were similar for the two drugs at 7–14 days after the last antibiotic dose. A single causative pathogen was isolated in nearly 80% of participants and, of the isolated bacteria, *S. aureus* was the most common, accounting for 83% of monomicrobial infections. Although 56 patients in the ATLAS study had bacteremia (36 in the telavancin-treated group and 20 in the vancomycin-treated group) and *S. aureus* accounted for 34 cases, no separate analysis was reported for these bacteremic cases.^{20,32}

In a post hoc analysis of the ATAIN studies, bacteremic hospital-acquired pneumonia was diagnosed based on the presence of a negative respiratory culture and recovery of a respiratory pathogen on baseline blood cultures, or in the

setting where the same micro-organism, sharing the same antimicrobial susceptibility profile, was identified from both respiratory and blood samples at baseline. Seventy-three cases of bacteremia (6.7% of cases) were identified, comprising 34 in the telavancin group and 39 in the vancomycin group. Gram-positive pathogens were isolated from nearly 80% of patients and Gram-negative pathogens from roughly 25%. *S. aureus* was the most frequent isolate, recovered from 72.6% of patients, with nearly two thirds being MRSA. The overall outcome at the test of cure assessment and pathogen eradication rates was similar. In the 33 patients with monomicrobial *S. aureus* infection, cure rates for telavancin and vancomycin patients were 60% and 33%, respectively (Stryjewski, unpublished data, 2012).

Telavancin for treatment of endocarditis

S. aureus is the most common micro-organism associated with infective endocarditis, and due to an increase in the prevalence of MRSA, vancomycin is frequently used, despite its high rates of persistent bacteremia and failure.^{33,34} Evidence from in vitro and a rabbit model of aortic valve endocarditis comparing the activity of telavancin and vancomycin against methicillin-resistant and vancomycin-intermediate *S. aureus* strains provided some encouraging results. Telavancin was bactericidal in time-kill studies at a concentration of 5 µg/mL against both strains. Vancomycin was only bacteriostatic at the same concentration and bactericidal at 10 µg/mL against an MRSA strain, and was bacteriostatic at 10 µg/mL against the vancomycin-intermediate *S. aureus* strain. Compared with untreated control rabbits, a twice-daily regimen of telavancin 30 mg/kg reduced mean aortic valve vegetation titers of the MRSA strain after 4 days of therapy and sterilized six of 11 vegetations, compared with a lower reduction of colony-forming units and clearance of organisms from three of 10 vegetations on a regimen of twice-daily vancomycin 30 mg/kg. Telavancin was significantly more effective than vancomycin in the vancomycin-intermediate *S. aureus* model, producing greater reduction versus no reduction in number of colony-forming units with vancomycin.¹⁸ Added to the potential for superior potency of telavancin in the setting of infection caused by Gram-positive pathogens, several lines of evidence point to an advantage in the context of biofilm-producing organisms. Telavancin has been shown to be more effective than vancomycin against biofilm-forming *S. aureus* in a pharmacokinetic filter model³⁵ as well as in an in vitro biofilm activity assay.³⁶ La Plante et al studied biofilm-

producing reference strains of *S. aureus*, *Staphylococcus epidermidis*, and *Enterococcus faecalis* as well as biofilm-producing clinical isolates obtained from proven catheter-related bloodstream infections. Vancomycin demonstrated no activity against bacteria embedded in a biofilm produced by *S. aureus* in contrast with telavancin that was shown to be active against these bacteria with a low minimum eradication concentration of 0.125 to 2 µg/mL for biofilm-embedded organisms, a concentration that is attainable with doses used clinically. They demonstrated the ability of telavancin to inhibit biofilm formation at concentrations below the respective minimum inhibitory concentration of each isolate. In contrast, vancomycin inhibited biofilm formation at concentrations only at or above the respective minimum inhibitory concentration of each isolate.³⁶ Similarly, an in vivo rabbit model demonstrated that therapeutic doses of telavancin were superior to vancomycin for prevention of subcutaneous implant colonization and infection by *S. aureus*. The effect was concentration-dependent.³⁷

In another animal model, telavancin was able to achieve a larger reduction in bacterial vegetation load, but the difference between vancomycin and telavancin failed to reach statistical significance.³⁸ The first report of use of telavancin in right-sided MRSA endocarditis (vancomycin minimum inhibitory concentration ≤ 0.5 mg/L, daptomycin minimum inhibitory concentration ≤ 1 mg/L) described a patient in whom, despite a vancomycin dose of 15 mg/kg every 12 hours and trough levels of 15–20 mg/dL, blood cultures remained positive through 8 days of treatment. Treatment was then switched to telavancin intravenously every 24 hours with abrupt clearance of the bacteremia and a favorable outcome.³⁹ A subsequent case report of vancomycin-intermediate *S. aureus* pacemaker lead endocarditis, that was initially daptomycin susceptible became resistant while on daptomycin (minimum inhibitory concentration initially 0.5 µg/mL, increasing to 2.0 µg/mL). Treatment with telavancin resulted in rapid clearance of bacteremia within one day of initiation of telavancin and a favorable outcome.⁴⁰ A similar case of telavancin use following unsuccessful treatment of *S. aureus* endocarditis has been reported.⁴¹ A case of failure of daptomycin to cure *S. aureus* endocarditis of the mitral valve was cured with subsequent telavancin and linezolid therapy,⁴¹ attesting to the utility of telavancin in severe infections.

Summary

Telavancin is a new addition to the treatment armamentarium for Gram-positive bacteria, with documented efficacy

in skin and skin structure infections as well as in the setting of nosocomial pneumonia. *S. aureus* is a common cause of skin and skin structure infections and pneumonia, and is a leading cause of bacteremia and endocarditis. The rise in MRSA and its dissemination in the community, along with slow bactericidal activity of vancomycin, highlight the need for additional antimicrobial agents. Telavancin is one such antimicrobial agent, possessing theoretical benefits over vancomycin, both in terms of pharmacokinetics and in vitro data, particularly in the presence of a creeping vancomycin minimum inhibitory concentration. In addition, it has the potential for superior activity when biofilm formation is involved, such as that occurring in staphylococcal endocarditis. Analysis of the subsets of patients with bacteremia from the major trials leading to licensing of telavancin suggests that this drug is as effective as vancomycin, with potential superiority in the monomicrobial infections included in the ATTAIN trial. Experience with the use of telavancin for treatment of staphylococcal endocarditis is limited to a few case reports, but is promising given the demonstrated effect in biofilm models. Use of telavancin for the treatment of enterococcal infections remains to be determined, given that this organism is not one of the common culprits causing skin or pulmonary infections.

Disclosure

The authors report no conflicts of interest in this work.

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