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REVIEW

Telavancin for the treatment of nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA)

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Abstract: Telavancin is a bactericidal lipoglycopeptide antibiotic that is structurally related to vancomycin. It demonstrates in vitro activity against a variety of Gram-positive pathogens including, but not limited to, methicillin-resistant *Staphylococcus aureus* (MRSA). Telavancin is currently FDA-approved for the treatment of complicated skin and skin-structure infections. Recently, two randomized clinical trials demonstrated the efficacy and safety of telavancin compared to vancomycin for the treatment of nosocomial pneumonia. Overall, telavancin has a favorable safety profile. However, mild gastrointestinal disturbances and reversible increases in serum creatinine were observed in clinical studies. Additional clinical studies are needed to evaluate telavancin's efficacy and safety in comparison to other antistaphylococcal agents for the treatment of infections such as bacteremia and endocarditis.

Keywords: telavancin, MRSA, hospital-acquired pneumonia, health care-associated pneumonia, ventilator-associated pneumonia, nosocomial pneumonia

Introduction

Nosocomial pneumonia describes hospital-acquired pneumonia (HAP), health care-associated pneumonia (HCAP), or ventilator-associated pneumonia (VAP); all of which are delineated primarily based on the time of onset and etiology of infection. HAP, pneumonia that occurs greater than 48 hours after admission, is the second most common nosocomial infection in the United States (US).[1] HCAP refers to pneumonia acquired outside of the hospital by patients with certain risk factors for infection by pathogens of a nosocomial origin. These risk factors include hospitalization in an acute care facility for two or more days in the previous 90 days; residence in a nursing home or long-term care facility; previous intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or hemodialysis in the hospital or clinic. In contrast, VAP is pneumonia that occurs at least 48 hours after endotracheal intubation.[1] Both HAP and VAP remain contributors to poor patient outcomes despite advances in antibiotic therapy and the implementation of preventative measures.[1] HAP has an average incidence of 5 to 10 cases per 1000 hospitalized patients, and an estimated attributable mortality of up to 50%.[1,2] A HAP diagnosis increases the length of hospitalization by an average of 7 to 9 days per patient, costing a reported excess of US$40,000 per patient.[3,4]

HAP can be caused by a variety of organisms including aerobic Gram-negative bacilli and Gram-positive cocci, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2] HAP caused by *S. aureus* has become a major epidemiological focal point, considering the rapid emergence of resistant strains with limited treatment

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options and their impact on mortality. In an analysis of a large US inpatient database, *S. aureus* was found to be the only pathogen among those causing nosocomial pneumonia to be associated with a significant increase in mortality.[2] The same study showed that patients infected with MRSA were more likely to receive inappropriate antibiotic therapy.[2] Inadequate therapy is associated with both an increase in pneumonia treatment failure rates and mortality.[1]

Risk factors for HAP have primarily been extrapolated from patients diagnosed with VAP. These risk factors are categorized as modifiable and nonmodifiable (Table 1).[1,5,6] Identifying and addressing modifiable risk factors could potentially aid in HAP management. These risk factors may also be important to consider when selecting antimicrobial therapy. The time of onset of clinical signs of pneumonia serves as a helpful indicator in determining likely pathogens and potential patient outcomes associated with HAP. Early-onset HAP (occurring within the first 4 days of hospital admission) is more likely to be caused by pathogens susceptible to antimicrobial therapy.[1] In comparison, late-onset HAP (occurring 5 days or more within current hospitalization) is more likely due to multidrug-resistant (MDR) pathogens.[1] Late-onset HAP and VAP caused by MDR pathogens is associated with increased morbidity and mortality.[1]

Consequences of HAP are further compounded by the limited antimicrobial treatment options available to combat this growing health care problem. Currently, vancomycin and linezolid are the only recommended therapies for HAP caused by MRSA.[1] Even more concerning is that recent evidence suggests that MRSA isolates with a minimum inhibitory concentration (MIC) of 2 μg/mL do not respond as well to vancomycin as those isolates with an MIC of ≤ 0.5 μg/mL.[7] The serious consequences of HAP coupled with limited treatment options emphasize the need for more available antistaphylococcal agents for the treatment of this infection.

Table 1 Risk factors for hospital-acquired pneumonia[1,5,6]

Modifiable risk factors	Nonmodifiable risk factors
• Intubation	• Extremes of age
• Duration of mechanical ventilation	• Chronic lung disease (especially bronchitis, chronic obstructive pulmonary disease and asthma)
• Aspiration	• Abdominal or thoracic surgery
• Body position (supine versus semi-recumbent)	• Intubation
• Enteral feeding	• Duration of mechanical ventilation
• Modulation of colonization (eg, decontamination)	• Immunosuppression
• Stress ulcer prophylaxis	• Prior antimicrobial use
• Transfusions	
• Hyperglycemia	

This article provides an overview of telavancin, including its clinical efficacy and safety profile, and evaluates its potential role in the treatment of nosocomial pneumonia caused by MRSA.

Overview of telavancin

Telavancin (Vibativ™; Theravance, San Francisco, CA, USA) is a bactericidal, lipoglycopeptide antibiotic that is structurally related to vancomycin.[8] It is an intravenous, semi-synthetic product with concentration-dependent, antimicrobial activity against Gram-positive aerobic and anaerobic bacteria.[9] Telavancin's mechanism of action is twofold.[10] It inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan. Also, telavancin binds to the bacterial membrane and disrupts membrane barrier function. Telavancin has been associated with a tenfold greater peptidoglycan synthesis inhibitory activity in intact MRSA cells compared to vancomycin.[11] In initial clinical trials and surveillance studies, telavancin demonstrated in vitro activity against organisms that commonly cause skin and skin-structure infections and Gram-positive bacteria that cause pneumonia, including *Staphylococcus* spp., *Streptococcus* spp., and some *Enterococcus* spp.[12] Telavancin does not exhibit appreciable activity against the most common type of vancomycin-resistant enterococci, Van A-producing strains.[12–14] However, telavancin may have some activity against Van B- and Van C-producing strains, depending on the free drug concentrations achieved.[12–14] Currently telavancin is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with complicated skin and skin-structure infections (cSSSI) caused by susceptible Gram-positive bacteria. A summary of telavancin dosing recommendations, considerations in special populations, and potential interactions is provided in Table 2.

Activity against *Staphylococcus aureus*

Telavancin demonstrated in vitro bactericidal activity against methicillin-susceptible *S. aureus* (MSSA) with an MIC_{90} (minimum inhibitory concentration required to inhibit the growth of 90% of organisms) of 0.12–1 μg/mL compared to 1–2 μg/mL for vancomycin.[10,15] Similar in vitro activity against MRSA was also observed with an MIC_{90} of 0.25–1 μg/mL compared to 1–2 μg/mL for vancomycin.[9,10,16] Currently, the Clinical and Laboratory Standards Institute (CLSI) has not published susceptibility breakpoints for telavancin. However, the FDA-approved MIC breakpoint for *S. aureus*, including MRSA, is ≤1 μg/mL using the broth dilution method. Although intermediate and resistant

Table 2 Telavancin dosing, use in special populations, and interactions[17,19,30,41–46]

Dosing

Recommended dosing in normal renal function:

10 mg/kg intravenously (IV) every 24 hours administered as a 1-hour infusion

Recommended dosing modification in renal impairment:

Creatinine clearance (Cl_{Cr})	**Recommended dosage adjustment**
30–49 mL/min	Administer 7.5 mg/kg IV every 24 hours
10–29 mL/min	Administer 10 mg/kg IV every 48 hours
<10 mL/min	Dosing recommendation not available
Hemodialysis	Dosing recommendation not available; about 6% of drug removed during four-hour session

Special populations

Sex and age: No clinical impact on the pharmacokinetic disposition of telavancin

Pregnancy: FDA pregnancy category C

Black box warning for potential risk of abnormal fetal development (ie, reports of increased rates of digit and limb malformations in animal offspring) Prescribers encouraged to register pregnant women receiving telavancin or women may enroll themselves into a pregnancy exposure registry created by Theravance

Interactions

Drug–drug Interactions: No clinically significant interactions have been reported with the concomitant use of telavancin and other drugs

Drug–laboratory test interactions:

Coagulation tests affected	**Coagulation tests not affected**
• INR (International Normalized Ratio)	• Fibrinogen level
• PT (Prothrombin time)	• Thrombin time
• aPTT (activated partial thromboplastin time)	• Heparin level
• ACT (Activated Clotting time)	• D-dimer

breakpoints have not been established, the manufacturer recommends that isolates yielding results other than susceptible be subjected to additional testing.[17]

Pharmacokinetics

In healthy young adults, telavancin demonstrated linear pharmacokinetics following the IV administration of single doses ranging from 5 to 12.5 mg/kg and multiple doses ranging from 7.5 to 15 mg/kg once daily for up to 7 days.[18] Steady-state concentrations were achieved by the third daily dose. At 24 hours post-infusion, serum concentrations from subjects given telavancin exceeded the MIC_{90} for MRSA and penicillin-resistant *Streptococcus pneumoniae* strains, suggesting that telavancin is an effective once-daily antibacterial agent.

Telavancin has a small volume of distribution (0.115 L/kg), with approximately 90 to 95% of the drug being bound to albumin. In pharmacokinetic studies, its elimination half-life ($t_{1/2}$) was 7.5 hours in healthy adults who received a single dose and 9.11 hours in adults who received multiple doses, respectively.[11,19] Telavancin primarily undergoes renal elimination and 65% to 72% of the drug is excreted unchanged after several doses.[18]

Though controversial, drug concentrations in epithelial lining fluid (ELF) have been used to evaluate drug penetration into the pulmonary tissues.[20] The intrapulmonary distribution of telavancin (10 mg/kg IV every 24 hours) was evaluated in 20 healthy individuals.[21] Throughout the dosing interval, telavancin achieved concentrations up to eightfold and 85-fold in ELF and alveolar macrophages, respectively, above the MIC_{90} for MRSA (0.5 μg/mL). It was also noted that pulmonary surfactant did not affect the in vitro antibacterial activity of telavancin. Using these 20 subjects, Monte Carlo simulation and population pharmacokinetic modeling were performed to evaluate telavancin's penetration into ELF. Investigators reported a median ELF area under the curve (AUC) that was approximately 75% of the free plasma AUC.[22] In comparison, vancomycin concentrations in lung tissue ranges from 5% to 41% of serum concentrations.[23–25] Epithelial lining fluid penetration in critically injured patients was highly variable, with an overall serum to ELF ratio of 6:1.[26] These observations suggest that penetration of vancomycin into pulmonary tissue and ELF is poor.[25,26]

Pharmacodynamics

Against *S. aureus*, telavancin exhibits concentration-dependent bactericidal activity with a post-antibiotic effect of 1 to 4 hours.[12,27,28] The AUC/MIC ratio has been identified as the pharmacodynamic marker correlating to the drug's efficacy against *S. aureus*.[21] An in vitro study demonstrated that the maximal killing against *S. aureus* was achieved at an AUC/MIC ratio of 404.[29] Alternatively, the lowest AUC/MIC ratio yielding no bacterial regrowth was 50. In order to

minimize the emergence of resistance, it has been suggested that the telavancin AUC/MIC ratio remain above 50.[30]

Animal models of pneumonia

The efficacy of telavancin and vancomycin against MRSA strains with vancomycin MICs ≥ 1 μg/mL was compared in a neutropenic murine model of pneumonia.[31] Mice were administered antibiotic doses designed to simulate the area under the concentration-time curve (AUC) observed in humans given telavancin 10 mg/kg IV every 24 hours or vancomycin 1 g IV every 12 hours. Thirteen clinical MRSA isolates (one vancomycin-susceptible, two vancomycin-heteroresistant, and four vancomycin-intermediate) were tested after 24 hours and seven isolates (one vancomycin-heteroresistant, and four vancomycin-intermediate) were tested after 48 hours of exposure to the drug. Efficacy was expressed as the 24 or 48 hour change in lung bacterial density from pretreatment counts. During both time points, similar colony-forming unit (CFU) reductions were demonstrated for telavancin and vancomycin against MRSA isolates with vancomycin MICs of 2 μg/mL or less. Both telavancin and vancomycin demonstrated similar efficacy following 24 and 48 hours of exposure against the vancomycin-heteroresistant strains tested. Against vancomycin-intermediate isolates, telavancin reduced bacterial burdens more than vancomycin for one of four isolates after 24 hours and for three of four isolates after 48 hours.

Another study compared telavancin to vancomycin and linezolid in a neutropenic murine model of MRSA pneumonia.[32] The MICs of telavancin, vancomycin, and linezolid against MRSA were 0.5, 1, and 1 μg/mL, respectively. Mice were administered antibiotic doses that closely approximated human exposures at doses of 5 and 10 mg/kg IV for telavancin, 1 g IV every 12 hours for vancomycin, and 600 mg IV every 12 hours for linezolid.[32,33] Mice treated with telavancin demonstrated a significantly greater reduction in lung bacterial titers at 48 hours compared to the mice treated with vancomycin or linezolid.

Clinical studies: ATTAIN 1 and ATTAIN 2

The efficacy of telavancin for the treatment of HAP, HCAP, and VAP due to Gram-positive pathogens, specifically MRSA, was evaluated in two identical randomized, multinational, noninferiority trials.[34] Eligible patients were adult nonpregnant females or males who showed clinical signs and symptoms consistent with nosocomial pneumonia. Patients were required to have specific signs and symptoms of pneumonia, radiographic findings consistent with pneumonia, and a sufficient respiratory specimen for microbiologic evaluation. Exclusion criteria included prior receipt of potentially effective antibiotic therapy for Gram-positive pneumonia, Gram stain or culture revealing only Gram-negative bacteria, presence of certain pulmonary diseases (lung cancer, active tuberculosis, cystic fibrosis, or granulomatous disease), uncompensated heart failure, absolute neutrophil count < 500 cells/mm^3, and baseline QTc interval greater than 500 milliseconds.

Patients were randomized in a 1:1 fashion to receive either telavancin, 10 mg/kg IV every 24 hours, or vancomycin, 1 g IV every 12 hours, for 7 to 21 days. Telavancin dosage adjustments were permitted in patients with creatinine clearance (Cl_{Cr}) of 50 mL/min or less. Vancomycin regimens were monitored and adjusted according to institutional policy at each site. The primary end point was clinical response (cure or failure) at follow-up/test-of-cure visit in the all-treated (AT) and clinically-evaluable (CE) populations, with a prespecified noninferiority margin of 20%. The AT population included patients who were randomized and received at least one dose of the study drug. The CE population included patients in the AT population who were protocol-adherent or who died from the HAP episode after study day 3. Results of the two identical studies were pooled for analysis. Secondary outcomes such as clinical response rate by identified pathogen, mortality, and safety parameters were also evaluated.

Of the 1532 patients randomized, 1,503 received at least one dose of the study drug (telavancin, n = 749; vancomycin, n = 754; AT population). A total of 654 patients were included in the CE population (telavancin, n = 312; vancomycin, n = 342). Patients in both groups were comparable in terms of baseline and demographic variables. More than half of the patients in both groups were aged 65 years or older and more than half of the patients were in the intensive care unit at baseline. About 25% of patients in both groups had APACHE II scores greater than 20. Common comorbidities included diabetes, chronic obstructive pulmonary disease, and renal failure (acute and/or chronic). About one-third of patients in both groups had a Cl_{Cr} of 50 mL/min or less. More than half of the patients in both groups received previous antibiotics for greater than 24 hours.

Monomicrobial pneumonia caused by *S. aureus* was present in a total of 298 patients, and MRSA was the major (60%) pathogen isolated from the respiratory tract. Mixed (Gram-positive and Gram-negative) infections were present in 27% of patients. Bacteremia was diagnosed in approximately six percent of patients. The MIC_{90} for

both MSSA and MRSA was 0.5 μg/mL for telavancin and 1 μg/mL for vancomycin. In those patients for which vancomycin serum concentration monitoring was performed (n = 226), the mean trough was ≥5 μg/mL in 94% of patients and ≥10 μg/mL in 66% of patients.

In the AT population, cure rates were 58.9% for telavancin and 59.5% for vancomycin (95% confidence interval [CI]: −5.6% to 4.3%). In the CE population, cure rates were 82.4% for telavancin and 80.7% for vancomycin (95% CI: −4.3% to 7.7%). Based on these results, telavancin's noninferiority to vancomycin was demonstrated.

In secondary analysis, clinical response in patients with pneumonia due to MRSA with or without other pathogens was also similar between the two treatment groups. However, treatment with telavancin was associated with higher cure rates in patients with MSSA (87.9% versus 75%; 95% CI: −4.2% to 28.8%) and monomicrobial MRSA infection (81.8% versus 74.1%; 95% CI: −3.5% to 19.3%). Similarly, higher cure rates with telavancin were observed among patients infected with *S. aureus* with a vancomycin MIC ≥ 1 μg/mL (87.1% versus 74.3%; $P = 0.03$). Cure rates were lower for telavancin in patients with mixed infections (66.2% versus 79.4%; 95% CI: −26.9% to 3.2%). However, cure rates were similar between treatment groups in patients with mixed infections who received adequate Gram-negative antimicrobial coverage (63.2% versus 66.7%; 95% CI: −28.9% to 25.7%). There were no significant differences in mortality between treatment groups (20% for telavancin versus 18.6% for vancomycin, 95% CI: −2.6% to 5.3%).

Safety

More patients experienced serious adverse events that lead to drug discontinuation in the telavancin group compared to the vancomycin group (8% versus 5%). The most common adverse effects reported were nausea, anemia, hypokalemia, diarrhea, and constipation. Clinically significant increases in serum creatinine were more frequent among the telavancin group compared to the vancomycin group (16% versus 10%). Drug-related increases in serum creatinine associated with telavancin were mild and reversible after drug discontinuation. Prolongation of the QTc interval > 60 milliseconds occurred in 8% of telavancin-treated patients and 7% of vancomycin-treated patients. A maximum QTc interval > 500 milliseconds occurred in 2% of patients in each group, and no patients experienced arrhythmias attributable to a prolonged QTc interval.

Limitations of the ATTAIN studies

Due to variations by country in the standard of care for pneumonia diagnosis, a limited number of patients in the ATTAIN studies underwent semi-invasive procedures such as bronchoalveolar lavage (BAL). Therefore, determination of the exact microbial pathogen in these studies may be less reliable. Respiratory tract samples (invasive or noninvasive) were obtained in approximately 30% of patients overall.

Authors reported that the majority of patients achieved "adequate" mean vancomycin serum concentrations (5–15 μg/mL). However, for the treatment of health care-associated pneumonia (including HAP and VAP), the recommended trough goal is 15–20 μg/mL.[1,35,36] This trough goal should be considered for invasive infections such as HAP, and may increase the likelihood of achieving the target AUC/MIC ratio of 400 (when the MRSA MIC is < 2 μg/mL).[35] Furthermore, since vancomycin troughs <10 μg/mL have been associated with the emergence of resistance, this should generally be avoided.[35,37] In the ATTAIN studies, telavancin was likely compared to suboptimal vancomycin therapy suboptimal vancomycin therapy as evidenced by only evidenced by only 66% of patients with a trough ≥10 μg/mL. A comparison of telavancin to dose-optimized vancomycin could serve to further validate the findings of the ATTAIN studies.

Clinical utility of telavancin

Telavancin provides advantages in the treatment of nosocomial pneumonia due to MRSA compared to other antistaphylococcal agents. It exhibits rapid bactericidal activity, whereas vancomycin demonstrates relatively slow bactericidal activity. Additional advantages over vancomycin include once-daily dosing, the lack of serum concentration monitoring, and a low incidence of infusion-related reactions. Telavancin lacks clinically relevant drug interactions, which may be an advantage over linezolid. However, telavancin is available only as an intravenous preparation. Also, telavancin has demonstrated in vitro and clinical efficacy in the treatment of pneumonia, an advantage over daptomycin.

Higher vancomycin MICs in MRSA are correlated with a greater likelihood of treatment failure.[23,35,36] The fact that MICs have continued to increase in *S. aureus* strains highlights the need for additional effective antibacterial agents.[34] Though a secondary outcome in the ATTAIN studies, higher cure rates with telavancin were observed in patients

infected with MRSA with a vancomycin MIC ≥ 1 μg/mL. This preliminary evidence suggests that telavancin may play a role in treating this subset of patients. However, this requires further study.

Results of two retrospective analyses and one prospective study suggest that linezolid is superior to vancomycin for the treatment of MRSA nosocomial pneumonia.[38,39] In light of these findings, subsequent studies should evaluate the efficacy of telavancin compared to linezolid for MRSA nosocomial pneumonia. Furthermore, comparing telavancin, linezolid, and dose-optimized vancomycin simultaneously may provide additional insight into the agent of choice for this indication.

Though there are benefits to telavancin use, additional research is necessary in some areas. At the present time evidence does not support the use of telavancin in patients with severe renal insufficiency, therefore limiting its use to patients with a Cl_{Cr} > 10 mL/min. The acquisition cost of telavancin may limit its use in health care facilities. Although pharmacoeconomic analysis is not yet available, the reported average wholesale price of telavancin is approximately $150 per day compared to $20 per day for vancomycin.[40] Additional clinical studies are needed to evaluate the efficacy of telavancin for the treatment of other serious Gram-positive infections, such as bacteremia and endocarditis, as well.

Conclusion

In the setting of limited options for the treatment of nosocomial pneumonia due to MRSA, telavancin represents an effective alternative to standard therapy. Telavancin was associated with higher cure rates among MRSA strains with a vancomycin MIC ≥ 1 μg/mL, providing a potential role to be further explored. Overall, telavancin is well tolerated, with the most commonly experienced side effects being gastrointestinal intolerance and mild, reversible elevations in serum creatinine.

Disclosure

The authors report no conflicts of interest in this work.

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