The Role of Telavancin in Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

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Hospital-acquired pneumonia (HAP) due to gram-positive pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) continues to be a major cause of morbidity and death. Telavancin is a lipoglycopeptide antibiotic with potent in vitro activity against a range of gram-positive pathogens, including MRSA, methicillin-susceptible S. aureus, and Streptococcus species. In 2 phase 3 clinical trials, telavancin was noninferior to vancomycin in patients with HAP due to gram-positive pathogens. Clinically evaluable patients with S. aureus as the sole pathogen or S. aureus with a vancomycin minimum inhibitory concentration >1 µg/mL, however, had higher cure rates with telavancin than with vancomycin. In patients with bacteremic HAP, telavancin resulted in clearance of blood cultures. It was associated with increased serum creatinine levels and higher mortality rates in patients with moderate to severe renal impairment at baseline; however, on subsequent analysis, the outcomes seemed to have been at least partially affected by the adequacy of empiric gram-negative antimicrobial therapy. Thus, clinicians need to consider the risk-benefit balance when choosing telavancin in patients with severe renal impairment at baseline. Overall, these data support the use of telavancin in the treatment of HAP due to S. aureus, including MRSA and strains with elevated vancomycin minimum inhibitory concentrations, but clinicians should always weigh the risks and benefits of various treatment options.

Keywords. telavancin; vancomycin; hospital-acquired pneumonia; ventilator-associated pneumonia.
initially inappropriate therapy. Not surprisingly, the most important predictor of outcome in these diseases, and perhaps the only modifiable factor, is timely prescription of an appropriate initial antibiotic regimen against the causative pathogen [3].

Even though MRSA rates generally have been decreasing in the United States and across the globe, MRSA still remains a leading pathogen in both HAP and VAP [5]. Traditionally, only 2 agents active against gram-positive pathogens were approved for use in HAP and VAP: vancomycin and linezolid [2]. Telavancin, a novel lipoglycopeptide with bactericidal properties against S. aureus, including MRSA, was approved in the United States for use in HAP and VAP in 2013 [6]. (Note that telavancin is indicated in the European Union for the treatment of adults with nosocomial pneumonia, including VAP, known or suspected to be caused by MRSA, and it should be used only in situations where other alternatives are not suitable [7]). Clinicians need to understand this drug, particularly its unique in vitro potency and pharmacokinetics, and the clinical trials that led to its regulatory approval.

In this article, we will briefly discuss the in vitro and preclinical evidence that supported the evaluation of telavancin for treatment of HAP in 2 phase 3 trials. We will also examine the pharmacokinetic properties of telavancin as they relate to treatment of HAP. Finally, we review the clinical studies that supported the approval of telavancin for treatment of HAP, including post hoc analyses that provide further insights into the clinical use of this agent.

**PULMONARY PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF TELAVANCIN**

Gotfried et al studied whether potentially therapeutic concentrations of telavancin (10 mg/kg) were reached in the epithelial lining fluid (ELF) and alveolar macrophages of healthy subjects, following intravenous administration on 3 consecutive days [8]. The mean concentration of telavancin in the ELF was found to range from 1 to 4 µg/mL after the third dose and approximated free (unbound) plasma concentrations (Figure 1). In plasma, telavancin is primarily bound to albumin and albumin does not readily cross into ELF; therefore, these ELF concentrations approximate the free active fraction of telavancin within this compartmental space. In addition, very high concentrations were found in the alveolar macrophages (19–42 µg/mL). These concentrations far exceed the minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC90) for S. aureus, including MRSA, which is 0.06 µg/mL. In separate experiments, pulmonary surfactant was found to have no detectable effect on the in vitro activity of telavancin against MRSA or *Streptococcus pneumoniae*.

Many patients with HAP/VAP may have concomitant acute kidney injury with a diminished creatinine clearance (CrCl).

![Figure 1. Penetration of telavancin (10 mg/kg/d) into alveolar macrophages (AMs) and epithelial lining fluid (ELF) in 20 healthy subjects undergoing fiberoptic bronchoscopy. Values are expressed as mean and standard deviations. Reproduced with permission from Gotfried et al [8]. Abbreviation: MIC90, minimum inhibitory concentration required to inhibit the growth of 90% of organisms.](https://academic.oup.com/cid/article-abstract/61/suppl_2/S79/397344/397344)

The dose adjustment of telavancin in patients with renal impairment is supported by the findings of 2 independent phase 1 studies in subjects with varying degrees of renal impairment [9]. For patients with a CrCl of >50 mL/min, a telavancin dose 10 mg/kg every 24 hours is recommended, with dose adjustments of 7.5 mg/kg every 24 hours for patients with a CrCl 30–50 mL/min and 10 mg/kg every 48 hours for those with CrCl of 10–30 mL/min. The data on hemodialysis, peritoneal dialysis, and continuous renal replacement therapy are sparse. Approximately 6% of the telavancin dose was eliminated during a 4-hour hemodialysis session, but the calculated hemodialysis clearance is approximately 25% of total body clearance, suggesting that a longer duration of dialysis might clear a larger proportion of drug dose. Despite this process, the recommended dose of telavancin with renal replacement therapy is 10 mg/kg every 48 hours.

Lodise et al [10] used population modeling and Monte Carlo simulation to further determine the penetration of telavancin into ELF. Plasma and ELF pharmacokinetic data were used from the lung penetration study. Concentration-time profiles in plasma and ELF were simultaneously modeled using a 3-compartment model with zero-order infusion and first-order elimination and transfer. The median AUC_{ELF}/free AUC_{plasma} penetration ratio (where AUC indicates the area under the pharmacokinetic dosing curve for telavancin) was 0.73, suggesting that the lung penetration in healthy subjects would be
approximately 75% of the free AUCplasma. In summary, telavancin penetrates the pulmonary epithelium adequately and is not inactivated by lung surfactant, supporting its assessment in clinical trials of HAP and VAP.

IN VITRO AND PRECLINICAL STUDIES

In Vitro Data
Telavancin in vitro activity against gram-positive clinical isolates from US hospitals and from a worldwide collection has been revisited, applying the revised broth microdilution susceptibility testing method approved by the US Food and Drug Administration (FDA) [11, 12] (see the article by Karlowsky et al [13] in this supplement for revised minimum inhibitory concentration [MIC] testing method). Among 10,920 nonduplicate clinical isolates (24% from respiratory tract infections) from US hospitals and 12,436 nonduplicate clinical isolates (14.7% from HAP/VAP) from a worldwide collection, telavancin demonstrated bactericidal activity against all S. aureus isolates tested (all MRSA and methicillin-susceptible S. aureus [MSSA] 100% susceptible at the ≤0.12 μg/mL FDA break point for susceptibility) [11, 12]. In both studies, the telavancin MIC90 (0.06 μg/mL) against MRSA was 16–32-fold lower than that of vancomycin and linezolid (1 µg/mL) and 8-fold lower than that of daptomycin (0.5 μg/mL) [11]. All streptococcal isolates tested were also inhibited at telavancin concentrations of ≤0.12 μg/mL. Earlier investigations of telavancin activity against gram-positive bacteria isolated from respiratory tract sources [14, 15] found good activity against the isolates tested, but given that these data were generated with the old susceptibility testing method, the in vitro activity would be expected to be magnified. For further information on in vitro activity of telavancin, see the article by Karlowsky et al [13].

Telavancin seems to have antimicrobial activity against Staphylococcus spp. growing within biofilms. Telavancin inhibits S. aureus and other gram-positive pathogens embedded within biofilms at concentrations well below the MIC of planktonic cultures [4]. For more detailed information on the activity in biofilms, see Chan et al [16].

Animal and Cell-based Studies
The extracellular and intracellular activities of telavancin and vancomycin against strains of S. aureus with different resistance phenotypes (MSSA, MRSA, and vancomycin-resistant S. aureus) have been compared using both human and mouse-cultured macrophages [17]. Telavancin was rapidly bactericidal against extracellular and intraphagocytic bacteria at concentrations mimicking the human total maximum serum concentration, while retaining its bactericidal activity at MIC levels (Figure 2). In contrast, vancomycin displayed bactericidal activity against extracellular bacteria at concentrations at or above 10 times the MIC and only after 15–20 hours (Figure 2). Furthermore,
vancomycin was able to exert a bacteriostatic effect only against intracellular bacteria (Figure 2).

Telavancin activity has been evaluated in several studies using neutropenic murine models of pneumonia [18]. In a study of MRSA pneumonia in neutropenic mice, the bacterial burden in the lungs was compared among untreated control animals and animals treated with telavancin, vancomycin, or linezolid [19]. Telavancin treatment initiated 12 or 24 hours after inoculation resulted in significantly greater reductions in bacterial burden in the lungs than vancomycin or linezolid and significant improvements in survival compared with linezolid.

The effects of telavancin on MSSA pneumonia have also been tested in neutropenic mice [20]. In that study, telavancin treatment, compared with nafcillin, vancomycin, and linezolid, resulted in significantly greater reductions in bacterial titers in the lungs of infected animals.

Crandon et al [21] compared the efficacy of telavancin and vancomycin using human simulated exposures in a murine model of S. aureus pneumonia employing a variety of resistance phenotypes. The 2 drugs had similar activity against vancomycin-susceptible strains, including heteroresistant vancomycin-intermediate S. aureus, but telavancin displayed superior activity against vancomycin-intermediate S. aureus.

In summary, telavancin demonstrated bactericidal activity against both intracellular and extracellular forms of S. aureus in vitro as well as in neutropenic mouse models of pneumonia. Thus, given the challenge of eradicating infection in immunosuppressed animals, the potential efficacy of telavancin in human infection is supported by the experimental data.

**CLINICAL TRIALS OF TELAVANCIN FOR HAP**

**Phase 3 Clinical Trials**

The ATTAIN studies (Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia) were 2 identical, international, phase 3, double-blind, active-controlled trials (NCT00107952 and NCT00124020) comparing telavancin (10 mg/kg/24 h) and vancomycin (1 g/12 h) in the treatment of gram-positive HAP (including VAP) in 1503 randomized patients [22]. Vancomycin dose adjustment was permitted according to local standards of practice, based on weight, renal function, and serum level monitoring, as long as the study blind was maintained. The prespecified primary efficacy end point for these noninferiority studies was the clinical response at follow-up/test of cure in the all-treated (AT) and clinically evaluable populations, in which clinical cure was defined as improvement or no progression on radiographic findings at the end of treatment and resolution of signs/symptoms at follow-up/test of cure.

More than half of patients had only gram-positive pathogens isolated. In both studies, cure rates were similar for the telavancin and vancomycin groups in both the AT and clinically evaluable populations (Figure 3). In secondary outcome analyses, cure rates were higher for telavancin in patients with monomicrobial S. aureus infections, including MSSA and MRSA, as well as in patients infected with S. aureus with a vancomycin MIC $\geq$1 $\mu$g/mL (Figure 3). It was observed that lower cure rates with telavancin vs vancomycin occurred in patients with mixed (gram-positive/gram-negative) infections (66.2% vs 79.4%) [22]. As a result, the adequacy of initial gram-negative coverage was evaluated by blinded medical monitors as well as by an independent blinded panel of critical care physicians. In patients with only gram-positive pathogens or mixed infections that included adequately treated gram-negative pathogens, cure rates were higher in the telavancin group (61.4% [197 of 321] vs 58.4% [184 of 315]); however, these differences were not statistically significant [22]. Infections with multidrug-resistant gram-negative pathogens were disproportionately represented in the telavancin arms and may have confounded the results. These confounding factors and their impact on mortality are discussed in greater detail in the article by Lacy et al [23] in this supplement.

The overall incidence of adverse events (AEs) and the most common AEs (eg, anemia, abnormal serum potassium levels, and hepatic enzyme abnormalities) were similar in both treatment groups. Prolongation of the Frederica-corrected QT interval by $>60$ ms was also observed at similar and equally small proportions in the telavancin and vancomycin groups (8% and 7%, respectively). No arrhythmias due to QT prolongation were reported. Adverse renal events (summation of AEs with the following terms: renal failure, renal insufficiency, renal impairment, and creatinine increases) were observed slightly more frequently in the telavancin group than in the vancomycin group (10% vs 8%). Increases in serum creatinine (defined as a 50% increase from baseline and a maximum value $>1.5$ mg/dL) occurred more commonly with telavancin than with vancomycin (16% vs 10%) [22]. To our knowledge, telavancin has not been compared with linezolid, another antibiotic indicated for gram-positive HAP/VAP, in any clinical or observational studies to date.

**Post Hoc Analyses**

After the 2 ATTAIN studies were conducted, the FDA published draft guidance that proposed modified inclusion criteria for enrollment in phase 3 registration trials for HAP and VAP and also proposed that 28-day all-cause mortality, instead of clinical cure, serve as the primary end point for studies of HAP and VAP [24] (see article by Wenzler and Rodvold [25] in this supplement for commentary on the FDA recommendations). In the ATTAIN studies, patients with preexisting moderate to severe renal impairment (CrCl $\leq$50 mL/min) who were treated with telavancin for HAP/VAP had an increased mortality rate compared with patients in the vancomycin group [6].
a post hoc analysis of ATTAIN study data per the new FDA guidance, 1289 patients (86%) met the modified inclusion criteria [26]. Survival rates (Kaplan–Meier estimates) were lower for telavancin (59%) than for vancomycin (70%) in patients with moderate to severe renal impairment at baseline (CrCl, ≤ 50 mL/min). This difference was not statistically significant and was largely driven by the different survival rates in patients with severe renal impairment (CrCl, <30 mL/min): 47% for telavancin versus 61% for vancomycin. For patients with a CrCl >50 mL/min, the survival rates at 28 days were similar in the telavancin and vancomycin groups (84% and 81%, respectively) [26]. For more details on all-cause mortality analysis in the ATTAIN population see the article by Lacy et al. [23] in this supplement.

Bacteremia is an important potential complication in HAP and may result in increased mortality [27, 28]. Therefore, an analysis was conducted in patients with *S. aureus* bacteremia from ATTAIN [29]. Cure rates for telavancin and vancomycin were similar (41% and 40%, respectively) for the 53 patients with *S. aureus* bacteremic HAP, and the cure rate for MRSA infections favored telavancin (42% vs 33%), but this difference was not statistically significant. Only 2 patients from the telavancin group (both with MRSA) had persistently positive blood cultures after enrollment, compared with 6 from the vancomycin group (2 with MSSA and 4 with MRSA). None of these patients were cured of their pneumonia.

Approximately 30% of the AT population in the ATTAIN studies had VAP [22]. However, studies have suggested that non–ventilator-associated HAP is also associated with substantial mortality and may be associated with different causative pathogens compared with VAP [30–33]. Therefore, a post hoc analysis of ATTAIN study data was performed to examine the efficacy and safety of telavancin for non–ventilator-associated HAP [34]. A total of 1076 patients from ATTAIN were included.
DISCUSSION: CLINICAL ROLE FOR TELAVANCIN

The treatment options for MRSA HAP/VAP are limited. In addition to telavancin, only vancomycin and linezolid are approved by the FDA for this indication. The data reviewed in this article support the potential role for telavancin. Telavancin is indicated for use in HAP/VAP caused by S. aureus when alternative agents are not suitable, and caution should be taken in patients with pre-existing moderate to severe renal dysfunction that the perceived benefits outweigh the possible risks. (Note that in the European Union, telavancin is contraindicated in patients with acute renal failure [CrCl, <30 mL/min], including those undergoing hemodialysis [7]). Data are limited in renal replacement therapy, but a clear dose reduction is warranted in patients with a CrCl <50 mL/min. Certainly concerns about the impact of renal function on outcome must figure prominently in any assessment of risk and benefit. However, there are clear attributes of telavancin that make it appealing in certain situations.

First, approximately 15%–20% of patients with MRSA pneumonia are bacteremic. In this scenario, daptomycin is not likely to prove optimal given that it should not be used for respiratory infections [35]. Similarly, linezolid, because of its bacteriostatic activity, may not lead to rapid clearing of the bloodstream infection.

Second, linezolid may have clinical limitations if a more prolonged course of treatment is anticipated, when myelosuppression may become problematic [36]. Physicians caring for patients with significant thrombocytopenia or anemia may wish to avoid linezolid for this reason. In addition, owing to the ability of linezolid to inhibit monoamine oxidase, an interaction with selective serotonin reuptake inhibitors may lead to serotonin syndrome [37]. Although this syndrome is infrequently reported, clinicians may want an effective alternative when a patient has received a selective serotonin reuptake inhibitor in the prior 14 days.

Third, during the past decade we have witnessed a shift in the susceptibility of MRSA to vancomycin. Historically, MRSA had MICs for vancomycin in the 0.5–1-µg/mL range. More recently, there has been a creep upward in the MICs of vancomycin to MRSA (see article by Cardona and Wilson [38] in this supplement for a discussion on MIC “creep” and the article by Munita et al [39] for a commentary on evolving resistance among gram-positive pathogens). Concomitantly, findings of meta-analyses suggest that clinical outcomes are worse for patients treated with vancomycin when the MIC to vancomycin in MRSA is ≥1 µg/mL [40, 41]. A third, more recent meta-analysis suggests no association with MIC and outcomes, but definitions of elevated MICs differed among these studies [42].

Penetration into the ELF of the lungs represents an important measure of the potential efficacy of an antibiotic in treating pneumonia. For example, the therapeutic efficacy of vancomycin in the treatment of nosocomial pneumonia caused by S. aureus (especially MRSA) has been questioned owing to concerns that inadequate dosing leads to low concentrations of the drug in ELF [8, 11].

Assessments of the pharmacokinetic and pharmacodynamic characteristics of vancomycin suggest that achieving the desired pharmacokinetic target in pneumonia with vancomycin (AUC/MIC ratio, >400) is challenging if the MIC is >1 µg/mL [43]. This observation provides biologic plausibility to the notion that as the MIC of vancomycin to MRSA shifts up, clinicians need an alternative to this agent in deep-seated infections such as pneumonia. Given the more predictable pharmacokinetics of telavancin and the data from the ATTAIN studies, which underscore the efficacy of telavancin in these patients, telavancin should be considered when the clinician learns the results of microbiology testing in patients with MRSA pneumonia.

Biofilms on endotracheal tubes may complicate treatment of VAP; therefore, biofilm penetration and bacterial inhibition are potentially important considerations in determining a treatment strategy. Telavancin appears to have antimicrobial activity against S. aureus and coagulase-negative Staphylococcus spp. growing within biofilms at clinically relevant concentrations as well as at concentrations well below the MIC of planktonic cultures [4]. Vancomycin, by contrast, only inhibits biofilm formation at levels above the MIC. The larger clinical impact of biofilm penetration is unknown, but clinically attainable levels of telavancin, even below the level of the MIC, can inhibit the formation of biofilm on the endotracheal tubes.

Finally, the role of empiric S. aureus coverage in VAP, particularly in the critically ill, can present challenges for the clinician. Vancomycin has been associated with poor outcomes in MSSA VAP, particularly with bacteremia [44]. In contrast, telavancin outcomes in cases of MSSA pneumonia were numerically better than vancomycin outcomes; thus, during empiric therapy while MICs are pending, telavancin can provide adequate coverage for all strains of S. aureus.

CONCLUSION

Susceptibility data, pharmacokinetic and pharmacodynamic assessments, and preclinical studies all supported advancing
Telavancin into testing for treatment of HAP and VAP, and clinical studies subsequently provided evidence supporting its use for this indication. The ATTAIN studies have also provided insight enabling better assessment of the benefit-risk ratio associated with its use. Patients with HAP (including VAP) known or suspected to be caused by gram-positive pathogens such as MRSA are the most likely to benefit. Thus, telavancin should be considered for patients with HAP for whom other approved agents are not suitable, particularly those with MRSA strains exhibiting a vancomycin MIC ≥1 μg/mL. Risks can be mitigated by first considering alternative treatments in patients with moderate to severe renal impairment. In patients with normal renal function or mild renal impairment, telavancin has been shown to be effective and safe for the treatment of HAP and VAP. With appropriate cautions, telavancin should prove to be a useful therapeutic addition for the clinician.

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