Telavancin: The Long and Winding Road From Discovery to Food and Drug Administration Approvals and Future Directions

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Telavancin (TD-6424) was discovered in 2000 and became the first marketed semisynthetic lipoglycopeptide in 2009. This parenteral antibacterial agent has a dual mechanism of action and potent in vitro activity against gram-positive pathogens, including methicillin-resistant Staphylococcus aureus and isolates with reduced vancomycin susceptibility. Pharmacokinetic and pharmacodynamic analyses support the concentration-dependent activity and once-daily dosing regimen of telavancin. A changing regulatory approval process, manufacturing obstacles, and the termination of a commercialization partnership have challenged the development and marketing of telavancin. The commercial operations for telavancin have been restored, a new manufacturer has been secured, and reliable product supplies are available for clinical use. In addition, telavancin continues to be supported by ongoing clinical research with the recent launch of the Telavancin Observational Use Registry (TOUR; NCT02288234) in the United States and an international phase 3, randomized trial comparing telavancin with standard therapy for the treatment of patients with complicated S. aureus bacteremia, including endocarditis (NCT02208063).

**Keywords.** telavancin; lipoglycopeptide; methicillin-resistant Staphylococcus aureus; drug development; pharmacology.

Staphylococcus aureus remains a major public health threat worldwide and represents a tremendous burden for both patients and clinicians [1]. The increasing prevalence of resistant phenotypes of S. aureus, including methicillin-resistant S. aureus (MRSA), vancomycin-intermediate S. aureus (VISA), heteroresistant VISA (hVISA), and, rarely, vancomycin-resistant S. aureus (VRSA), has spurred the need for new antimicrobial agents to treat serious infections caused by these gram-positive pathogens. Several antibiotics have recently become available to address the declining utility of vancomycin as a first-line agent for the treatment of acute bacterial skin and skin-structure infections caused by MRSA. In addition, several agents are considered alternative treatment options for serious MRSA infections, such as nosocomial pneumonia and bacteremia [2]. Although a number of agents with potent in vitro activity against MRSA have now come to fruition, their pathway from drug discovery to subsequent approval by the US Food and Drug Administration (FDA) was a long and winding road. This article provides a historical perspective on the drug development program for telavancin and reviews the current and potential roles of telavancin for the treatment of MRSA infections.

**DISCOVERY**

Advances in medicinal and organic chemistry have afforded innovative modifications of the vancomycin backbone to yield novel glycopeptides that are highly active against MRSA. Two such highly successful approaches to improving the activity of vancomycin without directly altering peptidoglycan binding have been
N-alkyl modifications of the amino sugars and/or alteration of the terminal carboxyl group by amide derivatization [3]. Several attempts have also been made to attach hydrophobic substituents to vancomycin to improve its antimicrobial efficacy, including adding vancomycin-resistant enterococci activity. However, this change often imparts unfavorable pharmacokinetic properties. Scientists used the concept of adding hydrophobic substituents to candidate molecules along with a hydrophilic group to allow for the restoration of the advantageous pharmacokinetic properties of vancomycin while improving the in vitro potency and enhancing the rapid bactericidal activity.

The discovery of telavancin and other derivatives has been reviewed in detail by Leadbetter and colleagues [4]. Briefly, telavancin was derived from N-decylaminoethylvancomycin (THRX-689909) by regioselective reductive alkylation of the vancosamine nitrogen (Figure 1) [4, 5]. Positively charged, negatively charged, and neutral hydrophilic groups were appended to assess the effect on antibacterial activity and pharmacokinetic properties. A negatively charged β-alanine at the C position (Figure 1) of the vancomycin derivative showed improved in vitro activity against staphylococci and VanA vancomycin-resistant enterococci, but this increasing net negative charge had a substantial deleterious impact on distribution. Altering the compound to obtain a zero net charge at physiological pH demonstrated urinary recovery equivalent to that of vancomycin, indicating that decreasing the net positive charge was critical to improving the clearance and distribution properties. This discovery allowed preparation of new analogs with negatively charged groups at the C and R positions.

The in vitro potency of these new compounds remained similar with slightly less activity against VanA enterococci. The addition of a phosphonic acid at the R position showed a substantial increase in urinary clearance and decrease in kidney and liver distribution compared with the original vancomycin derivative. The addition of a negatively charged auxiliary hydrophilic group improved both the antibacterial activity and distribution. A further substitution at the resorcinol position via Mannich reaction yielded TD-6424. In vitro data also demonstrated rapid bactericidal activity against methicillin-susceptible S. aureus (MSSA), MRSA, and VISA [6]. Through this discovery process, TD-6424 emerged as the lead candidate for development and was subsequently advanced to experimental models of infection and human clinical trials as telavancin.

**DEVELOPMENT**

**Pharmacodynamics**

In vitro and animal pharmacodynamic models are commonly used tools to understand the relationship between drug exposure and microbiological activity. During the development of telavancin, pharmacodynamic studies were performed with the older methods for determining the minimum inhibitory concentration (MIC). However, a newer MIC testing method and revised telavancin MIC interpretive break points were introduced in 2014 (see the article by Karlowsky et al [7] in this supplement). This revised methodology for testing MIC values for telavancin should be considered when interpreting the results of the following studies.

**In Vitro Models**

The in vitro killing rates of telavancin have been examined extensively in time-kill assays against resistant phenotypes of multiple gram-positive pathogens. Telavancin has demonstrated
concentration-dependent bactericidal activity against VISA and VRSA at 4–8 times the MIC, for which there are few other remaining treatment options [8]. The ratio of area under the concentration-time curve (AUC) to MIC for unbound telavancin plasma concentrations (fAUC/MIC) required for 90% maximum antibacterial effect is >40 and >70 for vancomycin-susceptible S. aureus and enterococci, respectively [9]. Given the free-drug AUC of approximately 50–100 mg·h/L observed in healthy volunteers administered 10 mg/kg of telavancin, antibacterial efficacy for staphylococci and enterococci could be reasonably expected up to a MIC of 1 mg/L [9]. Against the more common phenotype hVISA, telavancin was bactericidal at both peak and trough concentrations and at low and high in-ocula [10].

Animal Models
The efficacy of telavancin in experimental animal models of gram-positive infections has been appraised in detail in an expert review by Hegde and Janc [11]. Briefly, in the neutropenic mouse thigh model, the total daily dose of telavancin, and not the frequency, was directly proportional to the decrease in colony-forming units (CFUs) per gram of tissue, whereas fAUC/MIC was the best predictor of antibacterial efficacy [12]. The pharmacodynamic target associated with a 1-log10 reduction in CFU count from stasis was a total AUC/MIC of 219 [13]. In MRSA bacteremia models, telavancin was able to sterilize the blood in as early as 28 hours after only 2 doses, compared with modest reductions in bacterial titers by vancomycin [14]. In MRSA/VISA and daptomycin-nonsusceptible endocarditis, telavancin sterilized 55% and 87% of rabbit cardiac vegetations, respectively, with no difference in efficacy between the humanized 7.5- and 12.5-mg/kg doses [15, 16]. In neutropenic pneumonia models, telavancin achieved a significantly greater reduction in MSSA burden than nafcillin or linezolid. A ≥1-log10 reduction in CFU count was observed 48 hours after administration of telavancin in mice with hVISA or VISA pneumonia [17,18].

Despite the low level of penetration into inflamed meninges (approximately 2%), telavancin sterilized the cerebrospinal fluid of 6 of 10 rabbits with penicillin-resistant Streptococcus pneumoniae and MSSA meningitis [19]. The concentration of telavancin in infected left tibal bone matrix was 0.27 µg/g in rabbits with MRSA-induced osteomyelitis. At 56 days after infection, 3 of 15 rabbits (20%) treated with telavancin had MRSA-positive tibal cultures, compared with 9 of 15 (60%) in the control group [20]. In rabbits with MSSA-inoculated vascular catheters implanted subcutaneously, the rate of infection was 5 of 54 (9%) and 6 of 54 (11%) for doses of 30 and 45 mg/kg, respectively, given preoperatively. All control devices were both colonized and infected, along with 52% of the devices in rabbits given vancomycin [21].

Pharmacokinetics
In healthy subjects, total exposure to telavancin increased proportionally with dose, demonstrating maximum and minimum plasma concentrations of 186 and 16 mg/L, respectively, for the 15-mg/kg dose, and 88 and 6 mg/L, respectively, for the 7.5-mg/kg dose. The steady-state AUC was also approximately 2-fold higher for the 15-mg/kg dose than for the 7.5-mg/kg dose—1282 versus 599 mg·h/L [22]. Telavancin was primarily eliminated from the body by the kidney. The overall dose recovery in the urine through 216 hours was 76.3%, with negligible fecal excretion at 0.7%. Only 17% of the total administered dose of telavancin was excreted in the urine as any of the 3 inactive metabolites [23]. Accumulation was not observed over 7 days, and the serum of subjects produced significant bactericidal titers against MRSA at 24 hours after dosing even though telavancin was 93% protein bound, primarily to albumin [24].

A population pharmacokinetic model of telavancin was developed using data from healthy subjects, 513 patients with complicated skin and skin-structure infections (cSSSIs), and 197 with hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) [25]. The final pharmacokinetic models included approximately 5259 observations from 710 patients, and select pharmacokinetic parameters are shown in Table 1, stratified by degree of renal impairment. In patients with cSSSI, clearance was approximately 10% higher in male than in female patients, and the AUC was approximately 11% higher in patients aged ≥75 years. The median AUC was 34% higher in obese patients (body mass index, ≥35 kg/m2) despite a 50% increase in dose, whereas median clearance was 24% higher. In patients with HABP, AUC decreased by 6% in patients aged ≥75 years and increased only 18% in obese patients, whereas clearance was 27% higher. The linear relationship between weight and clearance of telavancin has supported dosing based on body weight (in milligrams per kilogram). Some questions remain regarding creatinine clearance (CrCl) estimates, AUC values, and dosing of telavancin based on total body weight (in milligrams per kilogram) in obese patients [26].

Renal Impairment
Pharmacokinetic parameters in plasma for subjects with normal renal function and various degrees of severe renal impairment, hemodialysis, and end-stage renal function are presented in Table 2 [27–30]. Protein binding was approximately 87%, with no differences observed between groups. Although there are no specific dosing recommendations provided for patients receiving intermittent hemodialysis in the package insert for telavancin [31], these data support the dosing regimen of 10 mg/kg every 48 hours given to patients receiving dialysis in the phase 3 studies [27].

Individual pharmacokinetic profiles have been generated for 10 260 subjects using Monte Carlo simulation with dosing
regimens of 10 mg/kg/d for individuals with CrCl >50 mL/min, every 48 hours for CrCl <30 mL/min, and 7.5 mg/kg/d for individuals with CrCl 30–50 mL/min. There were no marked differences in simulated maximum or minimum plasma concentrations between patients with normal renal function and those with impairment. A probability of target attainment of 93% for an AUC/MIC of 219 was obtained for all MIC values up to 2 mg/L in all patients for daily partitioned AUC values. This analysis helped solidify the renal dose adjustments suggested by Monte Carlo simulations performed from phase 1 study data and confirmed the lack of difference in exposure profiles of telavancin across varying degrees of renal impairment [32].

The mean maximum serum inhibitory titers in subjects given a single 7.5-mg/kg dose of telavancin were slightly higher in subjects with renal impairment than in those with normal renal function (367 and 302 for severe impairment and dialysis, respectively vs 290 for normal function) [28]. The respective mean 48-hour area under the inhibitory curve (AUIC₄₈) values (eg, minimum serum inhibitory titers) were 3192 and 3450 in subjects with severe renal impairment and dialysis compared with 1668 in those with normal renal function. For the subjects with renal impairment, the 1.9- and 2.1-fold higher AUIC₄₈ values were similar to the 2.1- and 2.5-fold higher AUC₄₈ values based on plasma telavancin concentrations. Bactericidal titers were potent and prolonged in all patients, and no difference was seen in those with renal impairment. This study provides evidence that the biological activity of telavancin is not impaired in patients with poor renal function.

Table 2. Plasma Pharmacokinetic Parameters in Healthy Subjects and Various Degrees of Renal Impairment

<table>
<thead>
<tr>
<th>Subjects/Patients</th>
<th>Dose, mg/kg</th>
<th>Cmax, µg/mL</th>
<th>AUC₀₋∞, µg·h/mL</th>
<th>t₁/₂, h</th>
<th>CL, mL/h</th>
<th>Vss, mL/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchin et al [27]</td>
<td>7.5 (single)</td>
<td>70.6 (11.2)</td>
<td>568 (97)</td>
<td>8.1 (0.7)</td>
<td>14 (2)</td>
<td>139 (14)</td>
</tr>
<tr>
<td>Hemodialysis (n = 6)</td>
<td>7.5 (single)</td>
<td>52.1 (10.1)</td>
<td>1147 (441)</td>
<td>19.7 (4.9)</td>
<td>7 (3)</td>
<td>189 (26)</td>
</tr>
<tr>
<td>Barriere et al [28]</td>
<td>7.5 (single)</td>
<td>76 (12)</td>
<td>541 (58)</td>
<td>5.2 (0.8)</td>
<td>1.27 (0.24)</td>
<td>9.5 (1.9)</td>
</tr>
<tr>
<td>Severe renal impairment (n = 15)</td>
<td>7.5 (single)</td>
<td>109 (109)</td>
<td>1366 (345)</td>
<td>18.6 (6.5)</td>
<td>0.49 (0.14)</td>
<td>11.5 (3.5)</td>
</tr>
<tr>
<td>ESRD (n = 14)</td>
<td>7.5 (single)</td>
<td>111 (127)</td>
<td>1651 (461)</td>
<td>15.1 (8.9)</td>
<td>0.44 (0.17)</td>
<td>8.3 (3.8)</td>
</tr>
<tr>
<td>Sun et al [29]: healthy subjects (n = 8)</td>
<td>7.5 (multiple)</td>
<td>84.8 (5.3)</td>
<td>604 (83)</td>
<td>6.3 (0.8)</td>
<td>11.8 (2.1)</td>
<td>98 (15)</td>
</tr>
<tr>
<td>Gottfried et al [30]: healthy subjects (n = 20)</td>
<td>10 (multiple)</td>
<td>116 (30)</td>
<td>785 (111)</td>
<td>7.4 (1.1)</td>
<td>13.0 (1.9)</td>
<td>122 (22)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC₀₋∞, area under the concentration-time curve from 0 extrapolated to infinity; CL, clearance; Cmax, maximum plasma concentration; ESRD, end-stage renal disease; multiple, total of 3 doses; single, single dose; t₁/₂, elimination half-life; Vss, apparent volume of distribution at steady state.

a Except for doses, values are given as mean (SD).

b Values given in liters per hour.

c Values given in liters.

d AUC₀₋∞, area under the concentration-time curve at steady state.
Continuous Renal Replacement Therapy

The mean total body clearance of telavancin during continuous renal replacement therapy at ultrafiltration or dialysate flow rates of 3 L/h equated to that observed in healthy subjects (12–18 mL/min) at a dose of 7.5 mg/kg [33]. When flow rates were increased to 6 L/h, the clearance of telavancin exceeded that observed in healthy subjects. An increase in dose and/or frequency of administration of telavancin may be needed in patients receiving continuous renal replacement therapy at these higher ultrafiltration or dialysate flow rates.

Telavancin is formulated with hydroxypropyl-β-cyclodextrin, a renally eliminated solubilizer that has been associated with liver necrosis and renal tubular obstruction in animals if accumulation occurs [34]. Transmembrane clearance of hydroxypropyl-β-cyclodextrin approached ultrafiltration or dialysate flow rates, making accumulation unlikely in patients receiving continuous renal replacement therapy.

Body Fluid Penetration and Cellular Activity

Telavancin has demonstrated adequate penetration into blister fluid with an average ratio of AUC relative to plasma of 40.3% [29]. In addition, rapid bactericidal activity against MSSA has been observed within human macrophages [35]. The observed potent intra- and extracellular activity of telavancin against S. aureus indicates that telavancin may be effective at decreasing persistence and recurrence, 2 challenging features of serious staphylococcal infections. Intrapulmonary pharmacokinetic studies in healthy adult subjects have revealed an epithelial lining fluid AUC to plasma AUC penetration ratio of approximately 75% along with extensive alveolar macrophage dispersion [30,36]. The pulmonary penetration and distribution of telavancin will be discussed further by Sandrock and Shorr in this supplement [37].

REGULATORY REVIEW PROCESS AND MANUFACTURING ISSUES

The past decade has been filled with significant changes in the drug regulatory approval process and study design requirements for the development of new antimicrobial agents. These issues, along with a change in product manufacturer, led to a rather lengthy progression between the discovery of TD-6424 in 2000 and the clinical development and distribution of telavancin (Figure 2). The path to approval required years of commitment and considerable resource, which in turn significantly affected the commercialization of telavancin.

Findings in cSSSI Studies

In October 2007, the US FDA issued an approvable letter for telavancin for the treatment of cSSSI caused by S. aureus (including MRSA), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group, and Enterococcus faecalis [38]. Additional preclinical and clinical data as well as additional analysis focused on both the primary efficacy end point and subgroup analyses of the phase 3 cSSSI studies were submitted by the sponsor as requested by the FDA. In September 2009, telavancin was approved in the United States and Canada for the treatment of adult patients with cSSSI caused by susceptible gram-positive pathogens [31]. Several postmarketing commitments were requested by the FDA and completed by the sponsor, including a prospective study [39] (see pharmacokinetic parameters in Renal Impairment above) to determine the effect of renal function on the biological activity of telavancin due to the decreased clinical cure rates in telavancin-treated patients with baseline CrCl ≤ 50 mL/min in a subgroup analysis of the pooled cSSSI trials [28].

HABP and VABP

Two randomized, double-blind, phase 3 trials (ATTAIN) were conducted between 2005 and mid-2007 to compare telavancin
and vancomycin for the treatment of hospital-acquired pneumonia [40]. The primary efficacy analysis for these identically designed studies was a previously agreed-on noninferiority margin of 20% for clinical response at the test-of-cure assessment. However, before the new drug application submission in January 2009 [41], the FDA presented in July 2008 an approach to justify a noninferiority margin for the indication of nosocomial pneumonia based on 28-day all-cause mortality [42]. A subsequent workshop held in March and April 2009 focused on study design features and end points for registration trials of antimicrobials in the treatment of HABP and VABP [43–45]. Consequently, the FDA evaluated the ATTAIN trials using the 28-day all-cause mortality end point and concluded that the study populations differed substantially between the 2 trials with respect to demographics that could affect the risk for mortality, and that the inclusion criteria for these trials were not consistent with the recommendations in the 1998 FDA draft guidance nor the guidelines of the Infectious Diseases Society of America for diagnosis of nosocomial pneumonia [38, 46]. The application was resubmitted [39, 41] but was subsequently rejected because the FDA concluded that both trials did not provide sufficient evidence of noninferiority compared with vancomycin using a 10% margin for mortality in the population of patients with nosocomial pneumonia caused by gram-positive bacteria, as suggested in the FDA’s new 2010 draft guidance [47].

An appeal was made to the FDA in mid-2011 regarding multifaceted concerns surrounding appropriate study design and lack of finalized guidance for acceptable end points in nosocomial pneumonia trials [41]. In response to a formal dispute resolution at the end of 2011, the FDA requested a new drug application resubmission for review and reconsideration of the complex historical and scientific issues associated with evaluating these trials and also requested that an Anti-Infective Drug Advisory Committee (AIDAC) meeting be held to discuss the revised application. Based on the supplemental new drug application resubmission and recommendations from that committee, on 21 June 2013, telavancin was approved in the United States for the treatment of adults with HABP/VABP caused by susceptible isolates of S. aureus when alternative treatment agents are not suitable [31].

Manufacturing Issues and Commercialization Changes

In November 2005, a collaborative arrangement was established between Theravance and Astellas Pharma for the development and commercialization of telavancin, with worldwide marketing rights eventually extended to Astellas in July 2006. At that time, a single-source supplier was responsible for manufacturing telavancin drug product during the development program. During audits and on-site inspections conducted by the FDA at this supplier site in 2007 and 2008, deficiencies in quality and laboratory systems were noted with regard to sterility of drug products, but these were not specifically related to the manufacturing of telavancin.

In October 2007, the FDA issued an approvable letter for telavancin that included unresolved regulatory compliance issues at the manufacturing facility. These issues were addressed and found acceptable by the Chemistry and Manufacturing Controls Division of the FDA, and telavancin subsequently became available for distribution in the United States in August 2013.

In October 2008, Astellas Pharma Europe formally notified the European Medicines Agency (EMA) of its decision to withdraw the application for centralized marketing authorization of telavancin for the treatment of cSSSI [48]. In 2012, EMA suspended a previously granted marketing authorization for telavancin in the treatment of nosocomial pneumonia due to deficiencies in Good Manufacturing Practices at the pharmaceutical supplier. As noted above, a new manufacturing site was established in 2013, and EMA authorized marketing of telavancin in March 2014 for the treatment of adults with nosocomial pneumonia, including ventilator-associated pneumonia, known or suspected to be caused by MRSA; telavancin should be used only in situations where it is known or suspected that other alternatives are not suitable [49].

CLINICAL EXPERIENCE AND FUTURE DIRECTIONS

Clinical Experience

Currently, a limited number of published reports have evaluated the safety and efficacy of telavancin in clinical situations outside the FDA-approved labeled indications. The majority of these publications have focused on the clinical experiences of telavancin for the treatment of bacteremia and/or infective endocarditis caused by gram-positive organisms, especially MRSA. Corey and colleagues [50] have recently provided a critical evaluation of these experiences along with a review of the in vitro and experimental animal data that support the potential role of telavancin to treat S. aureus bacteremia or infective endocarditis. In addition to these data and the previously discussed preclinical data, the evidence supporting the use of telavancin in this role has been limited to: case reports of patients with complicated infections involving pathogens resistant to, or lacking response to, vancomycin and/or daptomycin therapy [51–55], results from a phase 2, randomized, double-blind controlled trial (ASSURE study) comparing telavancin with standard therapy in adult patients with uncomplicated S. aureus bacteremia [56], and a post hoc subgroup analysis comparing the efficacy and safety of telavancin with that of vancomycin in patients with HABP and S. aureus bacteremia [57].

Additional case series and case reports on the clinical use of telavancin have involved patients with osteomyelitis and abscesses treated successfully with telavancin and source control...
The majority of these patients tolerated extended courses of telavancin without serious adverse events. These reports highlight the potential use of telavancin as salvage monotherapy after standard therapy has failed in serious infections caused by S. aureus. Clinical outcomes with telavancin as part of combination therapy are lacking despite high rates of in vitro synergy and improved bactericidal activity demonstrated with aminoglycosides, β-lactams, and rifampin [60, 61].

Telavancin Observational Use Registry
An observational use registry has recently been established to assess the clinical use of telavancin in various institutional settings [62]. Telavancin Observational Use Registry (TOUR) is a multicenter, observational, prospective study designed to enroll approximately 1000 patients from 50–60 hospital sites or outpatient infusion centers in the United States throughout an 18-month period (NCT02288234). The registry began in November 2014 and is expected to be complete in December 2016 [63].

Phase 3 Bacteremia Trial
A phase 3 randomized clinical trial is being conducted to compare telavancin with standard intravenous therapy (vancomycin or daptomycin for MRSA or an antistaphylococcal penicillin or cefazolin for MSSA) for the treatment of patients with complicated S. aureus bacteremia, including endocarditis [64]. This international, registrational trial began in February 2015 and is aiming to enroll 248 patients before completion in approximately 2 years (NCT02208063). This phase 3 trial will also use rapid diagnostic technologies to identify S. aureus from blood cultures for subjects enrolled in the trial.

Antimicrobial Stewardship Perspective
Telavancin has several attractive qualities as a treatment option for serious gram-positive infections, particularly for MRSA. Microbiological characteristics of telavancin include a dual mechanism of action, concentration-dependent bactericidal activity, and a superior in vitro spectrum of activity compared with vancomycin against resistant phenotypes of S. aureus [65, 66]. Recent modifications of in vitro susceptibility testing ensure a reliable determination of MIC values to support the amended FDA-approved break point for S. aureus (≤0.12 µg/mL) [67, 68]. The pharmacokinetic-pharmacodynamic profile of telavancin allows for once-daily dosing with adequate penetration into the skin and lungs and no requirement for monitoring serum drug concentrations. The change in manufacturing process has reestablished a reliable supply of telavancin for both inpatient and outpatient parenteral antimicrobial therapy.

Data from the ATTAIN trials have demonstrated that the cure rates were significantly improved for telavancin compared with vancomycin in the microbiologically evaluable patients with monomicrobial S. aureus pneumonia and a vancomycin MIC value ≥1 µg/mL [40]. These results suggest a potential role for telavancin as empiric therapy in clinical settings with a high prevalence of MRSA isolates with MIC values ≥1 µg/mL. A recently published algorithm, based on the European approval of telavancin for nosocomial pneumonia caused by MRSA, may serve as a good starting point for positioning the clinical use of telavancin [69].

The evidence for telavancin as empiric or definitive therapy for patients with known or suspected S. aureus bacteremia has demonstrated promise [50] and suggests that telavancin could potentially be used in place of combination therapy with vancomycin and a β-lactam antibiotic given its rapid and potent bactericidal activity. Telavancin could also be considered as a preferred alternative to vancomycin for the treatment of MSSA bacteremia if β-lactams are contraindicated. Limited clinical experiences suggest telavancin is an effective therapeutic option in patients with persistent S. aureus bacteremia who fail or are intolerant to standard therapy or who have VISA, hVISA, or VRSA.

As with any therapy, the potential benefits and roles of telavancin must be balanced with the known adverse events and precautions accompanying its use. The most common adverse events observed during phase 3 clinical trials included diarrhea in patients treated for HABP/VABP, and nausea, vomiting, taste disturbances, and foamy urine in patients treated for cSSSI. Although telavancin has been well tolerated, nephrotoxicity and worsening renal impairment have occurred during telavancin therapy [70]. Renal adverse events have been more frequently reported in patients with baseline comorbid conditions and/or in patients taking concomitant medications known to predispose them to renal dysfunction. Renal function should be monitored in all patients receiving telavancin, and dosage adjustments are required in patients whose CrCl is ≤50 mL/min. Warnings and precautions have been advised for patients with moderate to severe renal impairment (CrCl ≤50 mL/min) because of the observed increased mortality rates in HABP/VABP and decreased clinical response in cSSSI with telavancin compared with vancomycin.

Adverse developmental outcomes in animal species suggest that telavancin should be avoided during pregnancy unless the potential benefit outweighs the potential risk to the fetus. A serum pregnancy test should be performed before telavancin is administered to women with childbearing potential and the medication guide should be provided to patients or their caregivers as part of the FDA-required Risk Evaluation and Mitigation Strategies program. Although telavancin does not directly alter blood coagulation, telavancin does interfere with the phospholipid-based reagents used for certain coagulation tests including prothrombin/international normalized ratio, activated partial thromboplastin times, activated clotting time, and factor X activity assays. Monitoring of coagulation tests should be performed no earlier than 18 hours after a dose of telavancin to.
minimize the effect on coagulation parameters, with the exception of activated partial thromboplastin time levels during unfractionated heparin use, because concomitant therapy with telavancin is now contraindicated [31, 71].

CONCLUSION

The discovery of telavancin represents an important step forward in the fight against gram-positive bacteria with ever-increasing resistance profiles. Telavancin has excellent bactericidal activity against multiple resistant phenotypes of S. aureus and has demonstrated promising efficacy in diverse animal models of difficult-to-treat gram-positive infections, such as pneumonia, bacteremia, and endocarditis. These in vitro and in vivo activities have translated well to the clinical cure rates observed during phase 3 clinical trials for the treatment of cSSSI and HABP/VABP. Telavancin is commercially available again after a long and winding road of historical hurdles involving regulatory approvals and manufacturing issues. Clinicians and antimicrobial stewardship teams will need to evaluate the risks and benefits of telavancin compared with alternative agents for the treatment of patients with cSSSI and HABP/VABP caused by susceptible gram-positive pathogens, including MRSA. The use and role of telavancin will continue to be delineated as the prevalence of patients with serious gram-positive infections continues to rise, including those with bacteremia or resistant phenotypes of MRSA (eg, hVISA or MRSA with a vancomycin MIC of ≥1 µg/mL). The ongoing observational use registry (TOUR) and the phase 3 clinical trials in patients with complicated S. aureus bacteremia and endocarditis should offer valuable information about real-world clinical experiences and potentially establish roles for telavancin in the future.

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