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EXPERT REVIEW

Telavancin: A Review of its Use in Treating Gram-Positive Infections

Sian V. Coggle[1] and M. Estée Török[2]

[1]Cambridge University Hospitals NHS Foundation Trust, Department of Infectious Diseases, Box 25, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom. [2]University of Cambridge, Department of Medicine, Box 157, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom.
Corresponding author email: estee.torok@addenbrookes.nhs.uk

Abstract: Telavancin is a lipoglycopeptide antibiotic with a dual mechanism of action; it disrupts both cell wall synthesis and cell membrane integrity resulting in rapid bactericidal activity. It is active against a wide range of Gram-positive organisms, including methicillin-resistant, vancomycin-intermediate, linezolid-resistant and daptomycin-resistant *Staphylococcus aureus* strains. Resistance is uncommon and only occurs in vancomycin-resistant organisms of the VanA type. Its pharmacokinetic profile enables once daily administration, making it potentially suitable for use in the outpatient setting. Telavancin is renally excreted and requires dose adjustment in renal impairment. Clinical trials have demonstrated efficacy in the treatment of complicated skin and skin structure infections and nosocomial pneumonia caused by Gram-positive pathogens. This review outlines the mechanisms of action, antimicrobial spectrum, pharmacokinetics, clinical use and safety aspects of telavancin, and discusses its potential role in the antimicrobial armamentarium.

Keywords: telavancin, methicillin-resistant *Staphylococcus aureus*, skin and skin structure infection, hospital-acquired pneumonia

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Introduction

Gram-positive organisms are important pathogens in infections such as complicated skin and skin structure infections (cSSSI) and in nosocomial infections. Over the last two decades there has been a change in the epidemiology of such infections with antibiotic-resistant organisms playing a more prominent role and posing therapeutic challenges. Methicillin-resistant *Staphylococcus aureus* (MRSA) with rising minimum inhibitory concentrations (MIC) to vancomycin,[1] vancomycin-intermediate *Staphylococcus aureus* (VISA) and heteroresistant strains (hVISA)[2] are becoming more prevalent and eleven cases of vancomycin-resistant *Staphylococcus aureus* (VRSA) have been reported since 2002.[3] Recent evidence suggests that even among vancomycin-susceptible MRSA, isolates with MICs of 1–2 μg/mL do not respond as well to treatment as isolates with MICs of ≤0.5 μg/mL.[4] Concerns about increasing antimicrobial resistance in Gram-positive pathogens have led to the development of new antimicrobials with activity against these organisms; these include linezolid, daptomycin, tigecycline, and telavancin. Worryingly, resistance to daptomycin and linezolid has already emerged in MRSA and vancomycin resistant enterococci (VRE).[5,6]

Telavancin is a novel semi-synthetic derivative of the glycopeptide vancomycin.[7] It has a dual mechanism of action and disrupts both cell wall synthesis and cell membrane integrity.[8] Telavancin has antimicrobial activity against a wide range of Gram-positive organisms including MRSA and some VRE[9–11] and has been used to treat patients with cSSSIs,[12–14] hospital-acquired pneumonia and ventilator-associated pneumonia.[15] In this review we will outline the mechanisms of action, antimicrobial spectrum, pharmacokinetics, clinical use and safety aspects of telavancin, and discuss its potential role in the antimicrobial armamentarium.

Mechanism of Action

Telavancin is a semi-synthetic derivative of vancomycin, which has a hydrophobic (decylaminoethyl) side chain added to the vancosamine sugar and a hydrophilic [(phosphonomethyl) aminomethyl] group attached to the resorcinol-like 4′ position of amino acid 7 (Fig. 1).[8] Telavancin has superior *in vitro* activity compared to vancomycin and has rapid concentration-dependent bactericidal activity against glycopeptide-susceptible organisms and those with intermediate glycopeptide sensitivity.

The glycopeptide core of telavancin causes inhibition of cell wall synthesis in a mechanism similar to vancomycin, namely the binding of the D-Ala-D-Ala containing peptidoglycan precursor which inhibits the peptidoglycan polymerization (transglycosylation) and subsequent cross-linking (transpeptidation) steps. The hydrophobic (decylaminoethyl) side chain promotes the interaction with the cell membrane which provides improved binding affinity of the glycopeptide core for D-Ala-D-Ala containing peptidoglycan intermediates by localising the molecule to the bacterial surface. This is likely to account for the 10-fold greater potency in inhibition of peptidoglycan synthesis of telavancin compared to vancomycin, despite a lower calculated affinity relative to vancomycin for binding a D-Ala-D-Ala containing target in solution.[8] A study by Lunde and colleagues used fluorescence microscopy to demonstrate that telavancin showed enhanced binding to the division septum compared with vancomycin.[16]

If inhibition of cell wall synthesis was the only mechanism of action for telavancin then it would be expected to have a slow bactericidal effect. Time-kill studies, however, have demonstrated rapid, concentration-dependent bactericidal activity.[10] It has also been demonstrated that telavancin triggers concentration-dependent dissipation of cell membrane potential within 15 minutes.[8] Such depolarization was only detected at concentrations ten-fold higher than minimum inhibitory concentration (MIC), but there was a direct correlation between membrane potential and viability. The mechanism of action seemed to be dependent upon interaction with peptidoglycan intermediates.

Another study demonstrated the role of Lipid II in the mechanism of action of telavancin.[17] Lipid II is essential for cell wall synthesis and this seems to play a key role in the telavancin-induced depolarization of cell membrane. This interaction between telavancin and lipid II disrupts both peptidoglycan synthesis and membrane barrier function. The interaction seems to rely on the lipophilic side chain which increases the membrane anchoring properties of telavancin and increased affinity to lipid II. This observation may explain the difference between telavancin and vancomycin.

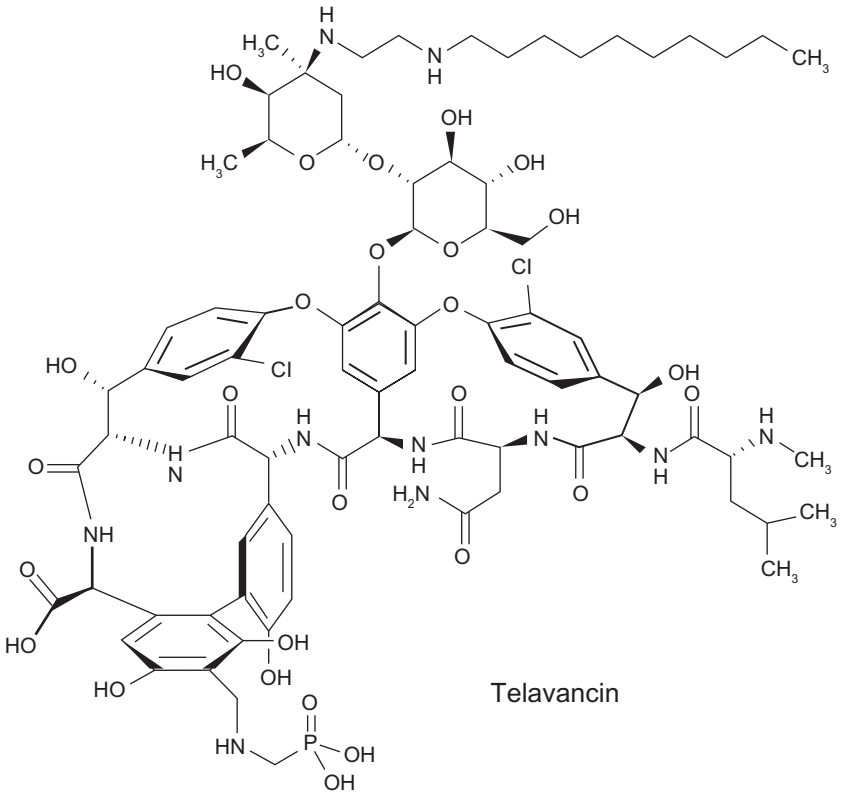

Figure 1. Chemical structure of telavancin.

It has been suggested that cell membrane permeability precedes membrane depolarization and cell killing. It also occurs at concentrations much closer to the MIC (two- to four-fold higher). When Higgins et al used radiolabelled compounds and cell fractionation it was discovered that the majority of telavancin was associated with the cell membrane compared to vancomycin; again suggesting a multi-functional anti-microbial agent. The temporal association between membrane depolarization and cell killing suggested a novel mode of action to explain the differences between telavancin and glycopeptides.[8]

The only known resistance mechanism that affects telavancin is the VanA type vancomycin resistance. Non-VanA type vancomycin-resistant organisms are typically susceptible to telavancin.[9,18,19] There is no known cross-resistance between telavancin and other antibiotics. *In vitro* experiments have failed to generate resistance and there are no clinical reports of telavancin resistance.[20]

Spectrum of Activity

Telavancin has been shown to be effective against Gram-positive organisms in vitro including those which are resistant to other antibiotics, such as methicillin-resistant, linezolid-resistant, daptomycin-resistant, vancomycin-intermediate, and vancomycin-heterogeneous *S. aureus* strains.[18,21,22] It also has activity against Gram-positive anaerobes including clostridia, *Propionibacterium* spp., *Lactobacillus* spp., *Peptostreptococcus* spp., and *Corynebacterium* spp.[23]

Another potentially significant difference is the ability of telavancin to penetrate biofilms and prevent their formation. Biofilm-producing strains of staphylococci and enterococci represent a risk to hospital patients with indwelling prosthetic devices making these infections more difficult to treat. A comparison of the *in vitro* activity of telavancin and vancomycin against biofilm producing strains of *S. aureus, S. epidermidis* and *E. faecalis* found that at clinically achievable concentrations telavancin was active against embedded bacteria (minimal biofilm eradication concentration [MBEC] 0.125–2 μg/mL).[11] For vancomycin to produce the same effect, a MBEC ≥ 512 μg/mL was required, a concentration which is not achievable in clinical practice. At concentrations below those required for MIC telavancin inhibited biofilm formation. This suggests

that telavancin may be useful in treating patients with device-related infections.

Pharmacokinetic Profile

The pharmacokinetic profile of telavancin has been elucidated by Phase I clinical trials in healthy subjects and in selected people with renal and hepatic impairment.[24,25] Telavancin has a linear profile when infused over 30 to 120 minutes at a dose range of 7.5 to 15 mg/kg. It takes three to four days to achieve a steady state and there is no evidence of tissue accumulation. Telavancin is highly protein bound with 90% of the drug being bound to serum albumin.

Telavancin has both a long half-life (7 to 9 hours) and post-antibiotic effect (4 to 6 hrs) and these allow for a once-daily dosing regimen.[26] The metabolic pathway of telavancin has not been determined but in vitro studies using human liver microsomal enzymes resulted in no metabolites.[20] Telavancin is primarily excreted by the kidneys at doses ≥5 mg/kg. Dose adjustment is, therefore, necessary in patients with reduced creatinine clearance. A dose of 10 mg/kg daily is recommended for patients with a creatinine clearance of ≥50 mL/min. If creatinine clearance is 30 to 50 mL/min the dose should be reduced to 7.5 mg/kg once daily; if creatinine clearance is <30 mL/min the dose interval is increased to 48 hourly. Telavancin is not recommended in patients on haemodialysis. There are no requirements to alter dosing in hepatic impairment[27] or the elderly.[28]

The impact of telavancin on the pharmacokinetics of midazolam,[29] aztreonam and piperacillin-tazobactam[30] have been studied in healthy volunteers and no significant interactions have been found.

Preliminary Studies

Telavancin is licensed for use in complex skin and skin structure infections (SSSIs). In one study[31] an acantharidan-induced skin blister model was used to mimic infected skin and determine plasma and blister fluid concentrations of telavancin in healthy individuals. Telavancin was administered at a dose of 7.5 mg/kg daily for three days and blisters were formed 14 hours prior to starting the final dose. The study demonstrated adequate concentration in plasma and blister fluid, above the MIC for common cSSSI pathogens, including methicillin-sensitive *S. aureus*, MRSA and streptococci. The area under the curve to MIC ratio (AUC/MIC) was considered high enough for the eradication of bacteria.

Another study[32] examined the distribution of telavancin in pulmonary epithelial lining fluid and alveolar macrophages in healthy individuals treated with intravenous telavancin at a dose of 10 mg/kg daily over three days. Bronchoalveolar lavages were performed on five of the subjects at 1, 2, 3, 4, 8 and 12 hours after the last antibiotic dose. Over the whole dosing interval, telavancin remained at eight-fold above the MIC90 for MRSA in pulmonary epithelial lining fluid and 85-fold over MIC in alveolar macrophages. Unlike, daptomycin, telavancin is not affected by surfactant.

A third study investigated the antimicrobial activity of telavancin against 2,279 clinical isolates obtained from patients with HAP in 87 hospitals as part of the international telavancin surveillance programme in 2007 to 2008[33] Telavancin was highly active against staphylococci (MIC90, 0.25 mg/L), *Streptococcus pneumoniae* (MIC90, 0.03 mg/L), viridans group streptococci (MIC90, 0.06 mg/L; 100% susceptible), β-haemolytic streptococci (MIC90, 03.06 mg/L; 100% susceptible) and vancomycin-susceptible enterococci (MIC90, 0.5 mg/L; 100% susceptible). Telavancin also inhibited all staphylococci at MIC ≤ 0.5 mg/L. However, amongst enterococci that are not susceptible to vancomycin (eg, *Enterococcus faecium*) telavancin was only fully active against those exhibiting the *vanB* phenotype (MIC90, 0.06–0.12 mg/L) and was considerably less potent against *vanA* strains (MIC ≥ 2 mg/L). These results were equal or superior to those of comparator drugs such as vancomycin, teicoplanin, daptomycin, linezolid and quinupristin/dalfoprisitin suggesting that telavancin may have a role to play in treatment of HAP/VAP caused by Gram-positive organisms (with the exception of some enterococci), especially those resistant to current therapies.

Clinical Trials

Clinical trials have demonstrated that telavancin has an important role to play in the treatment of cSSSI and HAP/VAP (Table 1). These studies represent the largest clinical trials of MRSA cSSSI and HAP conducted to date. A randomised, controlled phase 2 clinical trial compared telavancin (7.5 mg/kg once daily intravenously)

Table 1. Clinical trials of telavancin.

Clinical trial	Study design	Patient population	Interventions	Main findings
Stryjewski et al[12] FAST study	Phase 2, randomised double-blind, active control, parallel group	cSSSI 167 subjects 48 subjects MRSA infected	Telavancin 7.5 mg/kg/day versus anti-staphylococcal penicillin* or vancomcyin 1 g twice daily	AT population cured 79% (TLV) versus 80% (STD) CE population cured 92% (TLV) versus 96% (STD) ME population cured 93% (TLV) versus 95% (STD) *S. aureus* infected cured 80% (TLV) versus 77% (STD) MRSA infected cured 82% (TLV) versus 69% (STD) ~5% of patients stopped treatment
Stryjewski et al[13] FAST 2 study	Phase 2, randomised, double-blind, active control, parallel group	cSSSI 195 subjects 54 subjects MRSA infected	Telavancin 10 mg/kg/day versus anti-staphlococcal penicillin* or vancomycin1 g twice daily	AT population cured 82% (TLV) versus 85% (STD) CE population cured 96% (TLV) versus 94% (STD) ME population cured 97% (TLV) versus 93% (STD) *S. aureus* infected cured 96% (TLV) versus 90% (STD) MRSA infected cured 96% (TLV) versus 90% (STD) MRSA eradication 92% (TLV) versus 68% (STD), $P = 0.04$ Proportion of patients stopped treatment 6% (TLV) versus 3% (STD)
Stryjewski et al[14] ATLAS studies 0017 and 0018	Phase 3, two randomised, double-blind, active-controlled, parallel group trials	cSSSI 1867 subjects 719 MRSA infected	Telavancin 10 mg/kg/day versus vancomycin 1 g twice daily for 7 to 14 days	AT population cured 77% (TLV) versus 75.3% (VAN) CE population cured 88.3% (TLV) versus 87.1% (VAN) CE population MRSA infected cured 90.6% (TLV) versus 84.4% (VAN) Median duration of treatment one day shorter in TLV group ME population MRSA eradication 89.9% (TLV) versus 85.4% (VAN) Proportion of patients stopped treatment 8% (TLV) versus 6% (VAN)
Rubinstein et al[15] ATTAIN studies 0015 and 0019	Phase 3, two randomised, double-blind, active-controlled, parallel group	HAP 1503 subjects 290 subjects MRSA in respiratory specimens 15 subjects MRSA bacteraemia	Telavancin 10 mg/kg/day versus vancomycin 1 g twice daily for 7 to 14 days	AT population cured 58.9% (TLV) versus 59.5% (VAN) CE population cured 82.4% (TLV) versus 80.7% (VAN) ME population cured 79% (TLV) versus 76.8% (VAN) Cure rate in MRSA infection 74.8% (TLV) versus 74.7% (VAN) Cure rate in monomicrobial *S.aureus* infection 84.2% (TLV) versus 74.3% (VAN) Cure rate in mixed Gram-positive and Gram-negative infection 66.2% (TLV) versus 79.4% (VAN) Mortality 20% (TLV) versus 18.6% (VAN) Serious adverse event 31% (TLV) versus 26% (VAN) Proportion of patients stopped treatment 8% (TLV) versus 5% (VAN) Increase in serum creatinine more common in TLV group (16% versus 10%)

Note: *Anti-staphylococcal therapy was with nafcillin 2 g 6-hourly or oxacillin 2 g 6-hourly or cloxacillin 0.5–1 g 6-hourly.
Abbreviations: cSSSI, complicated skin and skin structure infection; HAP, hospital acquired pneumonia; AT, all treated; CE, clinically evaluable; ME, microbiologically evaluable; TLV, telavancin; VAN, vancomycin; STD, standard therapy.

to standard therapy (vancomycin 1 g twice daily or nafcillin or oxacillin 2 g every six hours or cloxacillin 0.5–1 g every six hours) in 167 patients, aged over 18 years who were diagnosed with cSSSI caused by suspected or confirmed Gram-positive organisms.[12] Treatment was given for 4 to 14 days and the cure rate was 79% for the telavancin group (n = 84) and 80% for the standard therapy group (n = 83). Amongst those patients who were clinically evaluable, 92% and 96% of the telavancin and standard therapy respectively were cured. In the microbiologically evaluable patients, the cure rates were 93% and 95%, respectively in patients where *S. aureus* was isolated, cure was achieved in 80% of telavancin and 77% of the standard therapy group. In patients where MRSA was isolated the cure rates were 82% and 69%, respectively. At test-of-cure, eradication of the organisms was seen in 80% (telavancin group) and 82% (standard therapy group) of patients. In MRSA-infected patients eradication was achieved in 84% and 74% of telavancin and standard therapy groups respectively.

A parallel randomised, controlled phase II clinical trial compared telavancin versus standard therapy in 195 adults with cSSSI caused by suspected or confirmed Gram-positive organisms.[13] Participants were randomised to receive telavancin (n = 100, dose 10 mg/kg once daily) or standard therapy (n = 95, vancomycin 1 g every 12 hours or an anti-staphylococcal penicillin every six hours). Clinical success rates were similar between the two groups: 82% of telavancin group versus 85% of the standard group ($P = 0.37$). In the patients who were clinically evaluable, 96% and 94% of patients in telavancin and standard group were cured respectively ($P = 0.53$). In the microbiologically evaluable population, the cure rate was 97% and 93% respectively ($P = 0.37$). In patients in whom *S. aureus* was isolated 96% of telavancin patients were cured compared to 90% of those on standard therapy ($P = 0.36$). These rates were replicated in those with MRSA ($P = 0.42$). Telavancin was more successful at eradicating *S. aureus* at test-of-cure than standard therapy, 92% compared to 78% ($P = 0.07$). Telavancin was also more successful at eradicating MRSA than the standard therapy, 92% compared to 68% ($P = 0.04$) and in pathogen eradication overall, 94% compared to 83% ($P = 0.06$).

The ATLAS study (Assessment of TeLAvancin in Skin and skin structure infections) was a combined analysis of two identical parallel, randomized, double-blind, active-controlled Phase 3 clinical studies with a pre-specified pooled analysis design conducted in 21 countries.[14] 1,867 men and non-pregnant women over the age of 18 years diagnosed with cSSSI that required more than seven days of parenteral antibacterial therapy were randomised to receive either telavancin (10 mg/kg daily) or vancomycin (1 g every 12 hours). The telavancin dose was adjusted according to renal function ie, if creatinine-clearance 30–50 mL/min then dose of 7.5 mg/kg daily and creatinine-clearance <30 mL/min a dose of 10 mg/kg every 48 hours. Those randomised received at least one dose of study medication, 928 received telavancin and 939 patients received vancomycin. The data was pooled after the 95% confidence intervals (CI) of the treatment differences between the two regimens were examined and found to overlap. In patients who were clinically evaluable, the clinical cure rates were 88.3% for the telavancin group and 87.1% for vancomycin group (95% CI for differences in cure rate −2.1, 4.6). Of the clinically evaluable patients with MRSA isolated, 90.6% and 86.4% of patients were cured respectively (95% CI for the difference in cure rates −1.1, 9.3). In microbiologically evaluable patients, *S. aureus* was eradicated in 89.3% and 87.3% respectively (95% CI for the difference in cure rates, −1.4, 6.2) and MRSA was eradicated in 89.9% and 85.4% (95% CI for the difference in cure rates, −0.9, 9.8). Overall patients were cured and pathogens eradicated in 88.6% of those on telavancin and 86.2% on vancomycin (95% CI for the difference in the cure rate, −1.6, 6.4). The median duration in therapy was approximately one day shorter for those on telavancin. In the 579 patients who were clinically evaluable, and had MRSA isolated at baseline, the overall therapeutic response was higher in the telavancin group 89.9% compared to 84.7% (95% CI for difference in cure rate, −0.3, 10.50).

Wilson et al used the data from the ATLAS study to compare the results of telavancin versus vancomycin when treating patients with post-surgical cSSSIs, especially those infected with MRSA.[34] Of the original study population of 1,867 randomised patients, 194 had cSSSI related to a recent surgical procedure (101 in the telavancin arm and 93 in the vancomycin arm). In these patients 49% had *S. aureus* isolated from their wound at baseline; 28% had MSSA and

22% had MRSA. There was no statistical difference between the two treatment groups in terms of cure rates or mean or median duration of treatment, although there was a trend towards benefit with telavancin, especially in MRSA and MSSA subgroups.

There have not yet been any clinical trials into the role of telavancin in the treatment of biofilm infection although the in vitro evidence suggests this maybe an important area of development.[11]

The ATTAIN study (Assessment of Telavancin for Treatment of hospital Acquired pNeumonia) combined two methodologically identical phase 3 randomised controlled trials (study 0015 and study 0019) of 1,503 patients with HAP due to Gram-positive organisms.[15] Participants were randomised to receive either telavancin (10 mg/kg daily) or vancomycin (1 g every 12 hours) for 7 to 21 days. In the pooled population, cure rates were similar in the telavancin and vancomycin groups respectively (58.9% versus 59.5%, 95% CI for the difference in cure, −5.6%, 4.3%). In the 654 clinically evaluable patients, cure rates were also similar in the two groups (82.4% versus 80.7%, 95% CI for the difference in cure rate −4.3, 7.7). In patients with monomicrobial *S. aureus* infections, including MRSA, telavancin achieved higher cure rates than vancomycin (84.2% versus 74.3%). In patients with mixed infections caused by Gram-positive and Gram-negative organisms, however, the cure rates were higher in the vancomycin group (79.4%) than the telavancin group (66.2%). Overall mortality rates were similar in the two arms (20% versus 18.6%). This study demonstrated that telavancin was non-inferior to vancomycin in treating HAP caused by Gram-positive organisms, but appeared to be inferior in HAP caused by mixed Gram-positive and Gram-negative organisms. This could be a result of inadequate gram-negative therapy in patients treated with telavancin alone, and is supported by the finding that, in the subset of patients with mixed infections who received adequate gram-negative coverage, cure rates were similar in the two treatment groups.

Safety Profile

In the FAST study adverse events were reported in 56% of patients in the telavancin group compared with 60% of patients in the standard therapy groups.[12] Adverse events possibly or probably related to therapy were 32% versus 29% in the telavancin and standard therapy groups, respectively. However, fewer patients in telavancin group experienced severe adverse effects (4% versus 7%) but a similar proportion discontinued therapy in each group (6% versus 5%). The frequency of each adverse event was similarly distributed in each group. A rise in serum creatinine occurred in two patients treated with telavancin compared to one patient in the standard treatment group. These creatinine rises were reversible and did not require cessation of treatment. Microalbuminuria was also more frequent in the telavancin group. Telavancin was associated with a mild decrease in platelet count (7%) compared to standard therapy (0%). There was also an increase in the QT interval by 6.4 msec in the telavancin group, with no clinical sequelae.

The FAST 2 study also reported similar frequencies of adverse effects in the telavancin group (56%) and the standard therapy group (57%).[13] In contrast, the proportion of adverse events possibly or probably related to therapy was higher in the telavancin group (73% versus 59%, $P = 0.16$). The frequency of severe adverse events was similar between the two groups (6% versus 4%) as were the number of patients who withdrew from the study (6% versus 3%). An increase in serum creatinine was observed in 5 patients in the telavancin group and hypokalaemia also occurred more frequently in the telavancin group. The frequency of hypomagnesaemia and microalbuminuria were similar between the two groups. Prolongation of the QT interval was observed more frequently in the telavancin group but there were no clinical symptoms. Mild transient nausea, insomnia, headache and taste alterations were more common in the telavancin group. Also reported in this group were disseminated intravascular coagulopathy, atrial fibrillation, lobar pneumonia, gastrointestinal bleeds, wound infection, abscess, myositis, suicidal ideation, renal failure, ileostomy and hypotension. The standard therapy group reported multi-organ failure, liver failure, bacteraemia, renal failure, atelectasis, respiratory failure and sepsis. Only two patients both in the telavancin group developed a rash resulting in withdrawal of treatment.

In the ATLAS study the frequency of adverse events was similar in the telavancin and standard therapy groups (79% versus 72%).[14] However, the frequency of serious adverse events was higher in the telavancin group (7% versus 4%) and slightly more patients discontinued telavancin than vancomycin

(8% versus 6%). In general, the adverse events were similar in nature and severity between the two groups, except for the following: a temporary soapy/metallic taste disturbance (33% versus 7%), mild nausea (27% versus 15%), and foaming urine (13% versus 3%). A temporary rise in serum creatinine was observed in 6% of the telavancin group and 2% of vancomycin group. Prolongation of the QT interval occurred at a similar frequency in both two groups. Serious adverse events leading to cessation of treatment occurred in less than 1% of subjects in both groups.

In the ATTAIN studies, the overall incidence of adverse events was comparable in the two groups. The most common adverse events were diarrhoea (11% versus 12%), renal impairment (10% versus 8%), anaemia (9% versus 11%), constipation (9% in both groups) and hypokalemia (8% versus 11%) in the telavancin and vancomycin groups, respectively. The frequency of serious adverse events and adverse events leading to treatment discontinuation was slightly higher in the telavancin group (31% versus 26% and 8% versus 5%, respectively). Increased serum creatinine levels (>50% from baseline or maximum level >1.5 mg/dl) were more common in the telavancin group than in the vancomycin group (16% versus 10%). The frequency of other laboratory abnormalities (eg, anaemia, thrombocytopaenia, abnormal serum potassium levels, abnormal hepatic enzyme levels) were similar in the two groups. Prolongation of QTcF interval > 60 msec occurred in both groups (8% versus 7%) but no patients experienced arrhythmias attributable to a prolonged QTcF interval.

Telavancin can also interfere with laboratory coagulation tests leading to increases in prothrombin time, international normalised ratio, and activated partial thromboplastin time.[35] It is recommended that these parameters are monitored just prior to giving the next dose of antibiotic. Animal studies have shown reduced fetal weights and increased frequency of digital and limb malformations;[20] for this reason it is considered a class C teratogenic drug. Women of childbearing potential should have a pregnancy test performed prior to commencing telavancin and it should only be used where potential benefits outweigh risks.

Conclusions

In conclusion, as resistance to standard antimicrobial agent increases in Gram-positive organisms there is an urgent need to develop new antimicrobials with novel mechanisms of action and broader spectra of activity. Telavancin is a lipoglycopetide with a dual mode of action which produces a rapid, concentration-dependent bactericidal effect. It is active against a broad range of Gram-positive organisms including methicillin-resistant, linezolid-resistant, daptomycin-resistant, vancomycin-intermediate, and vancomycin-heterogeneous *S. aureus* strains; its limitation is the lack of activity against all vancomycin-resistant enterococci.

Similar to vancomycin, telavancin is predominantly eliminated by the renal route and requires dose adjustment according to creatinine clearance. It has linear kinetics, a half-life of 7 to 9 hours and a post-antibiotic effect of 4 to 6 hours which enables once daily dosing. This property makes it potentially suitable for use as an agent for outpatient parenteral antimicrobial therapy, where once daily administration is preferred although its use in this setting remains to be assessed.[36]

In vitro telavancin has excellent activity against Gram-positive isolates in patients with cSSSI and achieves high concentrations in plasma and blister fluid. It has also been shown to be non-inferior to standard therapy for treatment of cSSSI suspected or proven to be caused by a Gram-positive organism. In vitro telavancin also has activity against and prevents the formation of biofilms.[7] This makes it potentially useful in treating device-related infections caused by Gram-positive organisms although its efficacy remains to be evaluated.

Telavancin also achieves high concentrations in pulmonary epithelial lining fluid and alveolar macrophages and is not inhibited by surfactant. In vitro telavancin has been shown to have equal or more potent activity than comparator agents against Gram-positive isolates from HAP patients. Controlled trials have demonstrated that telavancin was non-inferior to vancomycin in treating HAP caused by Gram-positive organisms but appeared to be inferior in patients with mixed Gram-positive and Gram-negative infections. The role of telavancin in treating nosocomial pneumonia may to be limited to patients with proven Gram-positive infections, in whom other agents are not suitable for reasons of antimicrobial resistance or tolerability.

Overall, the frequency of adverse events in telavancin and standard therapy was comparable and of a

similar nature, apart from temporary unpleasant taste sensation, nausea, vomiting and foamy urine observed more frequently in telavancin-treated patients. In addition it causes reversible rises in serum creatinine and QT interval prolongation. Animal studies have shown evidence of limb defects so telavancin is not recommended for use in pregnant women.

The use of outpatient parenteral antimicrobial therapy (OPAT) is expanding worldwide. Telavancin, with its proven efficacy against cSSSI and convenient once daily dosing regimen, is a potential antimicrobial agent for OPAT although studies comparing it to established agents such as teicoplanin or daptomycin have not been performed. Furthermore its activity against biofilm makes it a possible candidate for the treatment of device-related infections.

All studies performed to date have been non-inferiority trials comparing telavancin with beta-lactams or vancomycin in cSSSI or nosocomial pneumonia. Although these studies have included patients with MRSA infections, there have been no studies in patients with infections caused by more resistant organisms such as hVISA or VISA. Furthermore the advantage of telavancin over other Gram-positive antimicrobial agents, such as teicoplanin, daptomycin and linezolid, has not been established. In terms of other clinical syndromes, telavancin has been shown to be efficacious in treating osteomyelitis, endocarditis and meningitis in animal models.[37–39] There have been case reports of the use of telavancin in treating MRSA endocarditis[40] and osteomyelitis[41] but further research needs to be performed to determine whether telavancin is efficacious and safe these conditions.

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Disclosures

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