Telavancin: A novel lipoglycopeptide antibiotic

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INTRODUCTION

Antibiotic resistance is an emerging crisis as the resistance of some pathogens is reaching epidemic proportions. This increase in resistance coupled with the reducing number of new antibiotics approved projects a major public health concern.[1] The number of new antibiotics approved over 2003–2007 stood only at five compared to 16 in 1983–1987.[1] Only two new antibiotics were approved by FDA in 2009.[2] The diminishing antibiotic pipeline could lead to a preantibiotic era for many infections.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) is of particular importance as it causes increased morbidity and mortality in hospitalized patients. Vancomycin is the first-line drug against MRSA, but strains showing resistance to vancomycin have emerged. Most of these strains have an intermediate sensitivity to vancomycin and are called as vancomycin intermediate *S. aureus* (VISA) and heteroresistant VISA (hVISA), which has subpopulations of an isolate exhibiting resistance to vancomycin.[3] Staphylococci completely resistant to vancomycin (VRSA) are rare.[4] Only few antibiotics like linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin are active against the vancomycin-resistant strains.[5] As resistance to available antibiotics is increasing, there is a need for development of novel antibiotics. The approval of telavancin against this background gains significance. Telavancin is approved for treatment of complicated skin and skin structure infections (cSSSI) caused by Gram positive organisms – *S. aureus, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* group, or *Enterococcus fecalis*.[6]

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MECHANISM OF ACTION

Telavancin is a lipoglycopeptide antibiotic exerting a concentration-dependent bactericidal activity. It is a semisynthetic derivative of vancomycin with a hydrophobic side chain attached to the vancosamine sugar. The activity of telavancin is due to the novel combined action on the cell wall synthesis and disruption of bacterial cell membrane barrier function.

The mechanism of inhibition of cell wall synthesis is similar to that of vancomycin. The glycopeptide core binds to the terminal acyl-D-alanyl- D-alanine chains of the cell wall with high affinity by means of hydrogen bonds and hydrophobic packing interaction.[7] This prevents the polymerization and cross-linking of the cell wall precursors.

Telavancin also binds with high affinity to a specific bacterial target called as lipid II present in the cell membrane. Lipid II is a cell wall precursor and by binding to it, telavancin causes disruption of peptidoglycan synthesis. The binding to lipid II positions the lipophilic side chain of telavancin in the lipid bilayer causing depolarization of the cells and disrupts the membrane barrier function.[7] Fluorescent microscopy studies had demonstrated that telavancin binds avidly to the division septum, the site of active cell wall synthesis, as the site is rich in lipid II.[8] This preferential binding to the lethal target site is responsible for the enhanced antibacterial potency of telavancin when compared to vancomycin. *In vitro* studies have demonstrated that telavancin has a postantibiotic effect at concentrations less than the minimum inhibitory concentration (sub-MIC) lasting for more than 10 h after exposure to a supra inhibitory concentration.[9]

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Pharmacokinetics

The drug has to be administered as intravenous infusion of 10 mg/kg over 60 min every 24 h for 7 to 14 days. It is highly protein-bound as 90% of the administered drug is bound to serum albumin and has a half life of 8 h.[6] The long half-life with significant postantibiotic effect justifies the once daily dosing.[9] The metabolic pathway of telavancin has not been identified yet.[6] *In vitro* studies using human liver microsomal enzymes produced no metabolites of telavancin. So the metabolism of this drug will not be changed by other drugs affecting the microsomal enzymes. It is eliminated primarily by the kidney and 76% of the administered dose is excreted in urine. So dose modification based on creatinine clearance is needed in renal impairment.[6] Compared to vancomycin, telavancin has better penetration into lung tissue. The AUC ratio of the alveolar epithelial lining fluid (ELF) and plasma-free drug levels of telavancin is 0.73 compared to 0.39 of vancomycin.[10] As about 75% of the plasma-free drug enters alveolar space, telavancin is effective in the treatment of pneumonia.

Clinical trials

Phase III trials have been conducted for the evaluation of safety and efficacy of telavancin in complicated skin and skin structure infections and in nosocomial pneumonia.

Atlas trial

The Assessment of Telavancin in Complicated Skin and Skin Structure Infections (ATLAS) was a noninferiority trial conducted to assess the efficacy of telavancin in treating cSSSI when compared to vancomycin. Two identical randomized, double blinded, parallel-group phase III trials were conducted. Totally 1867 patients were enrolled in both the trials. The proportion of patients cured in clinically evaluable population was 88.3% in telavancin group and 87.1% in vancomycin group.[11] Here 579 clinically evaluable patients had MRSA infection at baseline and the cure rates were 90.6% and 86.4% with telavancin and vancomycin, respectively. Eradication rates for patients with MRSA isolates were 89.9% and 85.4% with telavancin and vancomycin respectively.[11] The number of patients discontinuing therapy due to adverse effects is slightly more in telavancin group than with vancomycin group (8% vs. 6%).[11] The differences between the two treatment groups were statistically insignificant. Patients with osteomyelitis, necrotizing fasciitis, diabetic foot ulcers, gangrene and burns involving >20% of body surface were excluded from the study. Inclusion of these patients would have increased the external validity of the study as these infections are difficult to treat.

Attain trial

The Assessment of Telavancin for Treatment of Hospital-acquired Pneumonia (ATTAIN) was a noninferiority trial designed to compare the efficacy and safety of telavancin and vancomycin in treating patients with hospital-acquired pneumonia, including ventilator-associated pneumonia. It consisted of two identical, randomized, double blinded, multicentric, phase III trials. Here 1503 patients were randomized to the two treatment groups. Among the clinically evaluable patients the cure rates were 82.4% and 80.7% with telavancin and vancomycin, respectively.[12] In patients with ventilator-associated pneumonia, telavancin produced a higher but statistically insignificant cure rate compared to vancomycin (80.3% vs. 67.6%).[13] No statistically significant difference was observed between the treatment groups for any of the treatment parameters.

ADVERSE EFFECTS

The most common adverse effects associated with telavancin use are taste disturbance, nausea, vomiting, and foamy urine. Rapid infusion can result in "red-man syndrome" like reaction and so it has to be infused over 60 min. Serum creatinine levels was increased by ≥ 1.5 mg/dl and at least 50% greater than baseline in 6% of patients in the phase III trials.[11] The rise in serum creatinine was reversible and it returned to the baseline values. This increase was higher than the 2% of patients experiencing rise in serum creatinine with vancomycin. It has a propensity to cause QTc prolongation similar to vancomycin and occurs in < 1% of the patients.[11] As with other antibiotics, *Clostridium difficile*-associated diarrhea can occur with this drug. Telavancin is grouped as a class C teratogenic drug. Though no human data are available, animal studies has shown reduced fetal weights and increased rates of digit and limb malformations.[6] So pregnancy tests have to be done in woman of child bearing potential before starting telavancin. In pregnant woman, it has to be used only if potential benefits outweigh the risks.[6] It can interfere with laboratory coagulation tests leading to an increase in INR, PT, and aPTT values.[6]

DRUG INTERACTIONS

No interactions with aztreonam and piperacillin/tazobactum has been observed and they can be safely co-administered.[14] Enzyme inducers/inhibitors do not seem to affect its metabolism.

CURRENT STATUS

Telavancin was approved in September 2009 by USFDA for treatment of complicated skin and skin structure infections. It is available as single use vials containing either 250 or 750 mg telavancin as lyophilized powder. Application for use in nosocomial pneumonia has been filed with FDA in January 2009.[15] In October 2008, Astellas Pharma withdrew its application for marketing authorization in Europe for telavancin in treatment of cSSSI as the Committee for Medicinal Products for Human Use (CHMP) of EMA

expressed concerns over the adverse effects and asked for more data.[16] In October 2009, the company has again filed a application for marketing authorization in Europe for use of telavancin in cSSSI and nosocomial pneumonia with EMA.[15] This drug is not yet available in India.

ADVANTAGES AND LIMITATIONS

The advantages of telavancin are as follows:

- It has a dual mechanism of action, inhibiting both cell wall synthesis, and cell membrane function.
- It can be used in vancomycin intermediate sensitive strains of *S. aureus* (VISA) and heterogenous VISA (hVISA).[8]
- Better penetration into lungs and so effective in Gram positive pneumonia infections.
- The median duration of therapy is shorter than vancomycin. This may reduce the treatment costs with telavancin.[11]
- No known drug interactions.
- The limitations with telavancin are renal dysfunction associated with its use, propensity to cause QTc prolongation, and alteration of laboratory values of PT, aPTT, and INR.

CONCLUSION

Telavancin, a semisynthetic derivative of vancomycin, is a bactericidal, lipoglycopeptide antibiotic approved for use in complicated skin and skin structure infections caused by susceptible Gram positive organisms. It is active against MRSA, VISA, and hVISA strains of *S. aureus*. It has a dual mechanism of action – inhibition of cell wall synthesis and disruption of cell membrane barrier function. It has a more specific action at the division septum, the site of active cell wall synthesis, due to its avid binding to lipid II. The important adverse effects are renal dysfunction and QTc prolongation. The drug is awaiting approval for use in nosocomial pneumonia. All the trials comparing telavancin with vancomycin are noninferiority trials and so there is no proof to say that telavancin is superior to vancomycin. Clinical trials, specifically in patients with VISA and hVISA infections, have to be conducted to determine its efficacy in treating vancomycin-resistant strains. The advantage of this drug over other antibiotics like linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin in treating vancomycin-resistant strains is not known. Clinical trials comparing telavancin with these drugs need to be conducted to determine its role in treating cSSSIs.

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