

Treating hospital-acquired pneumonia

8 August, 2014 01:54 PM

This article reviews telavancin's pharmacological characteristics as evidenced by clinical trials and studies, to provide a detailed picture of its use in the management of hospital-acquired pneumonia

Adamantia Liapikou MD PhD
6th Respiratory Department of Sotiria Hospital, Athens, Greece
Antoni Torres MD PhD
Director of ICU, Department of Pneumology, Institut Clinic del To´rax, Institut d'investigacions Biomediques August Pi i Sunyer IDIBAPS, University of Barcelona UB – Ciber de Enfermedades Respiratorias – CIBERES, Hospital Clinic, Barcelona, Spain
E-mail: atorres@clinic.ub.es

Hospital-acquired pneumonia (HAP) is a frequent and lethal infection, reaching a mortality rate of 60% in intensive care unit (ICU) cases. Methicillin-resistant Staphylococcus aureus (MRSA) is a frequent pathogen of nosocomial pneumonia. The increased frequency of MRSA and vancomycin-resistant strains, has led to inappropriate antibiotic treatment and to an urgent need for new antibiotics. Telavancin (TLV) is a novel lipoglycopeptide with a dual mode of action and proven efficacy against Gram-positive bacteria, and especially MRSA. Its efficacy is not reduced by the presence of MRSA strains with reduced susceptibility to vancomycin. Because of its nephrotoxicity, TLV is contraindicated in patients with severe renal insufficiency. TLV is a useful alternative for patients with difficult-to-treat, hospital-acquired MRSA pneumonia.

HAP is the second most common nosocomial infection, which accounts for up to 25% of all ICU infections with mortality rates as high as 76% reported under some circumstances in ventilated patients.(1,2)

Antimicrobial agents for nosocomial pneumonia differ according to the population of ICU patients, duration of hospital stay and prior antimicrobial therapy. Gram-negative pathogens are the most frequent cause of HAP, while *Staphylococcus aureus* (*S. aureus*) is the predominant pathogen commonly isolated in HAP from Gram-positive pathogens.

A public health priority
MRSA remains a public health priority in Europe and despite a decrease in the incidence of MRSA infections in recent years, the proportion of S. aureus isolates reported as MRSA in 2012 was ≥25% in seven of 30 European countries that provided surveillance reports.(3) Rello et al(4) reported that MRSA was isolated in 16% of patients with nosocomial pneumonia (21.4% in HAP and 14.6% in ventilator-associated pneumonia (VAP)). A study of HAP/VAP in ten Asian countries conducted in 2008/2009 showed that multidrug resistance among *S. aureus* isolates was 60.7%, and 82% of isolates were MRSA.(5)

Bacteraemia, shock and mortality are significantly higher in MRSA pneumonia. A large, prospective study reporting 474 patients with VAP in Spain found that patients with MRSA VAP had significantly higher in-hospital mortality than patients with VAP caused by other microorganisms (59.5% versus 46.8%; p =0.02).(6)

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines for the management of HAP1 recommend the addition of antibiotics with activity against MRSA depending on the local prevalence of MRSA, the presence of risk factors for MRSA and the severity of infection. Currently, for hospital-acquired MRSA, vancomycin, linezolid, daptomycin, ceftaroline, tigecycline or rifampin (not used as monotherapy) are suitable.

Related articles

EAHP China tour develops important relationship
Management of facial flushing in rosacea
Advanced therapy medicinal products
Treating hospital-acquired pneumonia
Improving medicines reconciliation on admission

The 'gold standard'

For decades, vancomycin was viewed by many as the 'gold standard' for the treatment of MRSA infections. Because of increased vancomycin usage, strains of *S. aureus* are becoming less susceptible. Unfortunately, treatment failure and poor outcomes have been described with MRSA infections caused by isolates with high-vancomycin minimum inhibitory concentration (MIC) ≥2mg/ml, so-called vancomycin-intermediate *S. aureus* (VISA) or glycopeptide-intermediate *S. aureus* (GISA) and heteroresistant isolates (heteroresistant VISA; hVISA).(7)

Recently, an outbreak of linezolid and methicillin-resistant *S. aureus* (LRSA) was reported in an ICU in Madrid and was associated with nosocomial transmission and extensive usage of linezolid. In that report, 12 patients with LRSA were identified and a mortality of 50% was reported. cfr-Mediated linezolid resistance was demonstrated in all isolates.(8)

As antimicrobial resistance continues to increase, more active antibacterial agents are still required, especially with activity against MRSA.

TLV

Chemistry–antimicrobial activity

TLV (Vibativ®) is a first-in-class lipoglycopeptide that deploys a dual mechanism of action, which involves the inhibition of cell-wall synthesis and disruption of bacterial cell-membrane barrier functions. It has a rapid bactericidal effect against clinically important Gram-positive bacteria, such as Streptococcus pneumoniae independent of penicillin susceptibility and staphylococci including the MRSA, VISA and hVISA strains.(9)

Additionally, penetration of TLV into possible sites of infection has been examined in healthy subjects and in animal models.(7,9) TLV penetrates well into epithelial lining fluids and into alveolar macrophages.(10) It has also the potential to kill non-growing bacteria.

Furthermore, *in vitro* studies show that TLV has a low propensity to select for resistant strains compared with other glycopeptide antimicrobials and linezolid.(11) Evaluation of TLV against biofilm-producing *S. aureus, S. epidermidis* and *Enterococcus faecalis* revealed that MICs for TLV were 8–16-times lower than for vancomycin, and TLV concentrations lower than respective MICs of the isolates inhibited the development of biofilm.(12)

TLV is extensively protein bound (>90%) and its elimination half-life ranges at doses above 5mg/kg, supporting once-daily dosing. Over typical intravenous (IV) dose ranges and treatment times, TLV pharmacokinetics are linear and steady-state concentrations are achieved by the third daily dose. TLV, similar to members of the glycopeptide class, are large compounds with poor oral bioavailability, and therefore is administered in a dose of 10mg/kg over 60 minutes via IV infusion. TLV is excreted mainly via the kidneys.

The post-antibiotic effect (PAE) of TLV against most Gram-positive organisms has been reported to range from 0.9 to 6 hours.(13)

Antimicrobial activity

The efficacy of TLV against MRSA isolates from Europe studied in a report of Mendes et al14 and all isolates were inhibited at a concentration of ≤0.5µg/ml with a MIC90 of 0.25µg/ml.

Results from a European surveillance study showed that TLV MICs range between 0.06 and 0.5µg/ml for both methicillin-sensitive *S. aureus* (MSSA) and MRSA, which was two- to fourfold lower than that for vancomycin,

4–80-fold lower than that for linezolid and twofold lower than that for daptomycin.(15)

In agreement with the results of studies performed to find any potential synergy or antagonism resulting from combinations of TLV with other antimicrobial agents, the highest synergy rates were observed at 24 hours when sub-inhibitory concentrations of TLV were combined with clinically relevant, sub-inhibitory concentrations of gentamicin, ceftriaxone, meropenem and rifampin.(16)

Safety/warnings

In clinical trials, TLV was well-tolerated, with a low incidence of drug discontinuation due to adverse effects.(7,9,13) The most common adverse reactions occurring in >10% of TLV-treated patients in trials to date included taste disturbance, nausea, vomiting and foamy urine.(17)

TLV is excreted mainly via the kidneys, so the dose of the drug needs adjustment for patients with moderate renal insufficiency. Nephrotoxicity was most likely to occur in patients with baseline comorbidities that predisposed them to kidney dysfunction (for example, pre-existing renal disease, diabetes mellitus, congestive heart failure or hypertension).(18) The nephrotoxic effect of TLV is greater than that associated with vancomycin. In addition, renal function (serum creatinine and urinary output for oliguria/anuria) should be monitored daily for at least the first three to five days of therapy and every 48–72 hours thereafter in all patients receiving TLV.(19) So, a pharmacist is vital to help manage dose adjustments.

The mortality rate among patients from the ATTAIN studies with moderate-to-severe renal impairment at baseline (creatinine clearance (CrCl) ≤50ml/minute) was 39% in the TLV group and 30% in the vancomycin group, while in patients without such pre-existing renal impairment (CrCl >50ml/ minute), the corresponding mortality rates were 17% and 18%, respectively.(18)

Although the findings of the trials suggest otherwise, TLV should not be used in patients with congenital long QTc syndrome, prolongation of the QTc interval, uncompensated heart failure or severe left ventricular hypertrophy.

Women of childbearing potential should have a pregnancy test before administration of TLV and the antimicrobial should be avoided during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.(19)

Clinical efficacy in hospital pneumonia
The clinical efficacy of TLV for the treatment of HAP was assesed from two prospective randomised studies (ATTAIN) published by Rubinstein et al(17) indicating that TLV is non-inferior to vancomycin on the basis of clinical response in the treatment of HAP due to Gram-positive pathogens, mainly MRSA. A total of 1503 patients, from 38 countries, were enrolled to receive either vancomycin 1g every 12 hours or TLV 10mg/kg every 24 hours in combination with aztreonam or piperacillin–tazobactam if a polymicrobial infection was identified.

Among patients with HAP due to monomicrobial infection with MRSA, the cure rate (regardless of vancomycin MIC) was 82% for TLV and 74% for vancomycin (95% confidence interval (CI) –3.5 to 19.3). Corey et al(20) reported the clinical cure rate among patients with MRSA with reduced susceptibility to vancomycin (MIC ≥1mg/dl) as 87% in those who received TLV versus 74% in those who received vancomycin (95% CI 0.5–23.0).

A study of Pfaller et al(21) examined the antimicrocrobial activity of TLV against 2279 clinical Gram-positive cocci obtained from patients with nosocomial pneumonia worldwide. TLV inhibited all staphylococci at <0.5mg/l and demonstrated equal or greater potency than the comparators (vancomycin, teicoplanin, daptomycin, linezolid and quinupristin/dalfopristin) against Gram-positive pathogens implicated in HAP.

Responding to the matter of nephrotoxicity of the drug, in a post-hoc analysis of data from the two Phase III ATTAIN trials(22) excluding patients with severe renal impairment (CrCl <30ml/min, including patients on haemodialysis) and pre-existing acute renal failure, the clinical and safety outcomes were similar in the TLV and vancomycin treatment groups. Cure rates with TLV were higher than those with vancomycin in the microbiologically evaluable patients with only Gram-positive pathogens isolated at baseline (85.0% versus 75.2%, respectively). Also a statistically significant higher number of patients receiving Vibativ than vancomycin achieved the combined endpoint of clinical cure rate plus 28-day survival (84% versus 72%; 11.8% difference; 95% CI: 2.4–21.3%).(22) Renal adverse events (acute renal failure, chronic renal failure, renal insufficiency, renal impairment and blood creatinine increase) were reported in 8.8% of patients in the TLV group and 6.7% of patients in the vancomycin group, respectively, and the majority of these events (63.6% and 53.5% in the TLV and vancomycin groups, respectively).

Regulatory affairs
On September 2011, the European Medicines agency (EMA) approved TLV for proven or suspected MRSA nosocomial pneumonia, including VAP known or suspected to be caused by MRSA, only when alternative treatments are not suitable. Despite being approved for marketing, TLV was unavailable in Europe due to a halt in production at its contract manufacturing site, causing the EMA to suspend the marketing authorisation (MA). Following the acquisition of European commercial rights by Clinigen, the suspension of its MA was lifted on 18 March 2014 following the approval of a new manufacturer. In 2009, the US Food and Drug Administration (FDA) approved TLV for the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria, including MRSA. In June 2013, the licensing of TLV in the US was expanded to include the treatment of adult patients with HAP and VAP caused by susceptible isolates of *S. aureus* when alternative treatments are not suitable.(23)

The FDA has included a warning for TLV in patients with pre-existing moderate or severe renal impairment (CrCl ≤50ml/minute) who were treated with TLV for HAP or VAP had increased mortality compared with vancomycin.(23,24)

Conclusions
Based on current evidence, greater microbiological and clinical cure rates against MRSA are achieved with alternative agents, such as TLV.
TLV is a rapidly bactericidal drug with a dual mechanism of action against Gram-positive cocci, including organisms with reduced susceptibility to vancomycin (for example, VISA, vancomycin-

resistant *S. aureus*). The lack of serum concentration monitoring and once-daily dosing are advantages of this agent over vancomycin. Overall, TLV may benefit critically ill patients with MRSA pneumonia who require a rapidly bactericidal agent, because linezolid and tigecycline are bacteriostatic and daptomycin cannot be used for pneumonia. The only limitation is the nephrotoxicity of the drug, so the use of TLV in patients with pre-existing moderate or severe renal impairment (CrCl ≤50ml/minute) should therefore be considered only when the potential benefit to the patient outweighs the potential risk. In these difficult to treat infections, the collaboration of a multi-disciplinary team including clinical pharmacists and infectious disease specialists, will facilitate the treatment of MRSA HAP/VAP with telavancin.

Key points

- Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection- accounts for up to 25% of all intensive care unit (ICU) infections, with mortality rates as high as 76% in some ventilated patients.
- *Staphylococcus aureus* (*S. aureus*) and especially methicillin-resistant *S. aureus* (MRSA) is the predominant Gram-positive pathogen in HAP and ventilator-associated pneumonia (VAP), resulting in higher mortaliy (>50%) compared with other pathogens.
- Telavancin (Vibativ) is a vancomycin-derived lipoglycopeptide, deploys dual mechanism of action that involves the inhibition of cell-wall synthesis and disruption of bacterial cell-membrane barrier functions and is effective against MRSA and Gram-positive bacteria resistant to vancomycin.
- Two prospective randomised studies of patients with HAP (ATTAIN) by Rubinstein et al, indicating that telavancin is noninferior to vancomycin on the basis of clinical response in the treatment of HAP due to gram-positive pathogens, mainly MRSA.
- The FDA and the European Medicines Agency have accepted telavancin for the treatment for adults with nosocomial pneumonia, including VAP known or suspected to be caused by MRSA, only when alternative treatments are not suitable.

References

1. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.

2. Vallés J, et al. Excess ICU mortality attributable to ventilator-associated pneumonia: the role of early vs late onset. Intensive Care Med 2007;33:1363–8.

3. www.ecdc.europa.eu/en/Pages/home.aspx (accessed 16 July 2014).

4. Rello J et al; EU-VAP/CAP Study Group.Determinants of prescription and choice of empirical therapy for hospital-acquired and ventilator-associated pneumonia. Eur Respir J 2011;37:1332–9.

5. Chung DR et al. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Resp Crit Care Med 2011;184:1409–17.

6. Vincent JL et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323–9.

7. Liapikou A, Fernandez L, Torres A. Telavancin in the treatment of nosocomial pneumonia: review of the clinical evidence. Clin Invest 2012:2:939–48.

8. Sánchez García M et al. Clinical outbreak of linezolid-resistant Staphylococcus aureus in an intensive care unit. JAMA 2010;303:2260–4.

9. Nannini EC, Stryjewski ME. A new lipoglycopeptide: telavancin. Expert Opin Pharmacother 2008;9:2197–207.

10. Lodise TP Jr et al. Telavancin penetration into human epithelial lining fluid determined by population pharmacokinetic modeling and Monte Carlo simulation. Antimicrob Agents Chemother 2008;52:2300–4.

11. Kosowska-Shick K et al. Activity of telavancin against staphylococci and enterococci determined by MIC and resistance selection studies. Antimicrob Agents Chemother 2009;53:4217–2.

12. Smith K, Gemmell CG, Lang S. Telavancin shows superior activity to vancomycin with multidrug-resistant Staphylococcus aureus in a range of in vitro biofilm models. Eur J Clin Microbiol Infect Dis 2013;32:1327–32.

13. Theravance Inc. VIBATIV (Telavancin) For Injection, U.S. Prescribing Information. 2012. www.vibativ.com/docs/VIBATIV_PI_Final.pdf (accessed 16 July 2014).

14. Mendes RE et al. Update on the telavancin activity tested against European staphylococcal clinical isolates (2009–2010). Diagn Microbiol Infect Dis 2011;71:93–7.

15. Bassetti M et al. The role of telavancin in the treatment of MRSA infections in hospital. Expert Opin Investig Drugs

2009;18:521–9.

16. Lin G et al. Antistaphylococcal activity of telavancin tested alone and in combination by time-kill assay. Antimicrob Agents Chemother 2010;54:2201–5.

17. Rubinstein E et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clin Infect Dis 2011;52:31–40.

18. Barriere SL. The ATTAIN trials: efficacy and safety of telavancin compared with vancomycin for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia. Future Microbiol 2014;9:281–9.

19. Vibativ (telavancin) - Highlights of prescribing information. www.vibativ.com/docs/VIBATIV_PI_Final.pdf (accessed 15 July 2014).

20. Corey GR et al. Telavancin for hospital acquired pneumonia caused by S. aureus: efficacy analysis according to the in vitro susceptibility to vancomycin [abstract K-528]. In: Program and abstracts of the 48th Annual ICAAC/IDSA 46th Annual Meeting. Washington, DC: American Society for Microbiology/Infectious Diseases Society of America, 25–28 October 2008.

21. Pfaller MA et al. Telavancin activity against Gram-positive bacteria isolated from respiratory tract specimens of patients with nosocomial pneumonia. J Antimicrob Chemother 2010;65:2396–404.

22. Torres A et al. Analysis of Phase 3 telavancin nosocomial pneumonia data excluding patients with severe renal impairment and acute renal failure. J Antimicrob Chemother 2014;69:1119–26.

23. www.fda.gov/newsevents/newsroom/pressannouncements/ucm358209.htm (accessed 15 July 2014).

24. US Food and Drug Administration. Highlights of prescribing information, revised February 2014. www.accessdata.fda.gov/drugsatfda_docs/label/2014/022110s007lbl.pdf (accessed 15 July 2014).

FEATURED IN ISSUE:
Hospital Pharmacy Europe issue 74 Summer 2014