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Review

The clinical positioning of telavancin in Europe

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ABSTRACT

Telavancin was the first marketed lipoglycopeptide. Although licensed in Europe in 2011 for the treatment of nosocomial pneumonia caused by meticillin-resistant *Staphylococcus aureus* (MRSA), it did not become clinically available until March 2014. Given the limited clinical experience with telavancin in Europe, this review provides an overview of its antimicrobial and clinical activity as well as its position among today's antimicrobials, with particular focus on the implications of its licensing requirements. Telavancin has potent in vitro activity against isolates of Gram-positive pathogens, including MRSA and glycopeptide-intermediate *S. aureus* strains. In addition, at clinically attainable doses telavancin inhibits Gram-positive isolates of antibiotic-resistant strains from biofilm models. The in vitro potency of telavancin has been corroborated in the clinical setting. Comparative clinical studies of telavancin demonstrate non-inferiority compared with vancomycin in the treatment of hospital-acquired Gram-positive pneumonia, with high cure rates for telavancin-treated patients with monomicrobial *S. aureus* infection, including isolates with reduced vancomycin susceptibility. These studies also demonstrate an overall similar safety profile for telavancin and vancomycin, although importantly, patients with moderate-to-severe renal impairment at baseline are at greater risk for mortality with telavancin and this feature must be taken into account when selecting patients for its usage. In Europe, telavancin is a useful alternative for patients with difficult-to-treat, hospital-acquired MRSA pneumonia when there are very few alternatives. For example, it should be considered in such patients when vancomycin and linezolid are not suitable and where renal function permits.

1. Introduction

On 18 March 2014, the lipoglycopeptide antimicrobial telavancin (VIBATIV®) became available once again in Europe. This followed the original 2011 approval of telavancin for proven or suspected meticillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia, including ventilator-associated pneumonia [1]. However – and uniquely in this field – the positive opinion of the European Medicines Agency (EMA) was qualified by the statement that telavancin should be used only in situations where it is known or suspected that other alternatives are not suitable. Given that clinical experience with telavancin in Europe is limited and that the compound comes into clinical use with this significant caveat about its utilisation, this review is intended to provide an overview of telavancin's clinical positioning in today's anti-MRSA hospital antimicrobial armamentarium.

2. History of telavancin in Europe

Telavancin was the first marketed lipoglycopeptide. It is a semisynthetic derivative of vancomycin with structural alterations instigating potent activity against multiple Gram-positive organisms. Discovered in 2004, telavancin was designed to share the favourable distribution properties of its parent compound while

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maintaining potent activity against antimicrobial-resistant organisms, as evaluated in animal models [2].

Telavancin was jointly developed by Theravance, Inc. (South San Francisco, CA) and Astellas Pharma US, Inc. (Deerfield, IL), with the majority of the early studies performed in the USA [3–7]. Data from phase 1 and pharmacokinetic studies in healthy volunteers and selected patients with renal or hepatic impairment indicated that the recommended therapeutic dose of telavancin was 10 mg/kg daily in those with a creatinine clearance (CL_{Cr}) of >50 mL/min [8,9]. An observed half-life of 7–9 h was reported for the 10 mg/kg daily dose of telavancin, whilst plasma concentrations increased linearly in proportion to dose, with no evidence of clinically significant drug accumulation [7].

Randomised, double-blind, active-controlled, phase 2 studies of telavancin for complicated skin and skin-structure infections (SSSIs) suspected or confirmed to be caused by Gram-positive pathogens were conducted in 2004 and 2005 [10,11].

These were followed in 2005 and 2006 by two randomised, double-blind, active-controlled, parallel-group phase 3 studies in patients with suspected or confirmed Gram-positive complicated SSSIs [12]. Two identical randomised, double-blind, comparator-controlled, parallel-group phase 3 studies of telavancin in patients with confirmed nosocomial pneumonia caused by Gram-positive pathogens were also started in 2005 [13]. The phase 2 and 3 studies are described in more detail below.

European marketing approval for telavancin was first granted in September 2011 for the treatment of adults with nosocomial pneumonia, including ventilator-associated pneumonia, known or suspected to be caused by MRSA, for whom alternative treatments are not suitable [1]. However, the drug was not launched into the European market because in early 2012 the EMA suspended the marketing authorisation for telavancin owing to shortcomings in quality assurance at the manufacturing facility producing telavancin [14]. Despite being approved for marketing, telavancin was unavailable in Europe until the suspension of its marketing authorisation was lifted on 18 March 2014 when an alternative manufacturing facility, approved by the EMA, resumed its production [15,16]. In July 2014, the National Institute for Health and Care Excellence (NICE) in the UK published advice on the appropriate use of telavancin based on evidence of its efficacy and safety [17].

3. Licensing of telavancin

Telavancin was approved and launched in the USA in 2009 for the treatment of adult patients with complicated SSSIs caused by susceptible Gram-positive bacteria, including both MRSA and meticillin-susceptible *S. aureus* (MSSA) [18]. Although approved in Canada in 2009 for the same indication as in the USA (complicated SSSI), telavancin has not been launched in this country [19]. In June 2013, licensing of telavancin in the USA was expanded to include the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *S. aureus* when alternative treatments are not suitable [20].

In Europe, telavancin was licensed in 2011 for the treatment of adults with nosocomial pneumonia, including ventilator-associated pneumonia, known or suspected to be caused by MRSA, in situations where it is known or suspected that other alternatives are not suitable [21]. Although application was also made for a SSSI indication, this was not successful since an assessment of telavancin's toxicity did not regard the agent as being a useful addition in this therapeutic area [17,22].

Owing to renal toxicity reported in the clinical development of telavancin, both European and US labels for the antimicrobial contain boxed precautions for its use. In the European label, telavancin is contraindicated in patients with pre-existing (baseline) acute renal failure and those with severe renal impairment (CL_{Cr} < 30 mL/min and patients undergoing haemodialysis). In addition, renal function (serum creatinine and urinary output for oliguria/anuria) should be monitored daily for at least the first 3–5 days of therapy and every 48–72 h thereafter in all patients receiving telavancin. Initial dose and dosage adjustments during treatment should be made based on calculated or measured CL_{Cr} according to the dosing regimen: a dose of 10 mg/kg every 24 h (q24h) for CL_{Cr} > 50 mL/min and a dose of 7.5 mg/kg q24h for CL_{Cr} of 30–50 mL/min. If renal function markedly decreases during treatment, the benefit of continuing telavancin should be assessed. In addition, caution should be exercised when prescribing telavancin to patients receiving concomitant nephrotoxic medicines, those with pre-existing renal disease or those with a co-morbidity known to predispose the patient to kidney dysfunction, such as diabetes mellitus and hypertension [21]. In the telavancin label in the USA, the boxed precaution advises that telavancin use in patients with pre-existing moderate-to-severe renal impairment ($CL_{Cr} \leq 50$ mL/min) should be considered only when the anticipated benefit outweighs the potential risk to the patient and that renal function should be monitored in all patients. Women of childbearing potential should have a pregnancy test before administration of telavancin and the antimicrobial should be avoided during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus [23].

4. Antimicrobial properties of telavancin

Telavancin displays activity against a broad spectrum of Gram-positive organisms, including those with reduced susceptibility to vancomycin [2,3,24–30]; however, as with other glycopeptides, it does not have activity against Gram-negative organisms. Telavancin has a dual mechanism of action, targeting the bacterial cell wall and membrane. As with vancomycin, and oritavancin and dalbavancin (the other semisynthetic lipoglycopeptides), telavancin inhibits the late stages of bacterial cell wall synthesis by interfering with the polymerisation and cross-linking of peptidoglycan [2,4,31]. Telavancin is 14-fold more potent than vancomycin at inhibiting peptidoglycan synthesis [4]. Unlike vancomycin, telavancin and oritavancin also disrupt bacterial membrane integrity and increase membrane permeability, leading to efflux of intracellular ATP and potassium [4,24,31,32]. Telavancin's multiple mechanisms of action account for its faster bactericidal action against Gram-positive pathogens, including MRSA and glycopeptide-intermediate *S. aureus* (GISA), compared with vancomycin [5,33–36]. In contrast, vancomycin is slowly bactericidal against *S. aureus* [34,35]. Furthermore, unlike the glycopeptides, human albumin and serum appear to have little effect on the bactericidal properties of telavancin [37]. Also, in vitro studies show that telavancin has a low propensity to select for resistant strains compared with the glycopeptide antimicrobials and linezolid [38,39].

4.1. Revision of susceptibility breakpoints

Antibiotic susceptibility surveillance revealed that minimum inhibitory concentration (MIC) data for telavancin vary widely, suggesting that the tests used may not give reproducible results. Telavancin is water insoluble and adsorbs onto the plastic or glass in the assay equipment, a similar phenomenon to that of oritavancin [40], which reduces the availability of the antimicrobial to the bacteria being tested [41].

Hope et al. evaluated the agreement between telavancin MICs determined by Etest and by the British Society for Antimicrobial