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Ceftobiprole review

Pedro Llinares[1]
José Barberán[2]
José Mensa[3]

Introduction

[1]Coordinación de docencia de la Sociedad Española de Quimioterapia. A Coruña, Spain
[2]Servicio de Medicina Interna - Enfermedades infecciosas, Hospital Universitario HM Montepríncipe, Universidad San Pablo CEU. Madrid, Spain
[3]Servicio de Enfermedades Infecciosas, Hospital Clinic, Barcelona, Spain

The increase in resistance to antibiotics has been a concerning matter in recent years. Controlling the spread, the rational use of antibiotics and the search for new agents are among the most effective measures for controlling the progression of resistance. Fortunately, after a long period of time when antibiotic development was very limited, in the last few years new active molecules have appeared against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA) (oxazolidinones, daptomycin, dalbavancin) and multi-resistant Gram-negative bacilli such as ESBL/carbapenemase-producing Enterobacteriaceae and/or *Pseudomonas aeruginosa* (tigecycline, ceftolozane-tazobactam, and ceftazidime-avibactam). However, in the majority of clinical situations, these antibiotics cannot be used as monotherapy in empirical treatment regimens because, despite their elevated intrinsic activity, their antibacterial spectrum is limited.

Recently, two new cephalosporins have been included in the antibiotic treatment armamentarium: ceftobiprole and ceftaroline. These are the first two cephalosporins with activity against both MRSA and non-ESBL-producing *Enterobacteriaceae*. In the case of ceftobiprole, its activity also extends to *P. aeruginosa* and a large number of *Enterococcus faecalis*. A beta-lactam with the antibiotic spectrum of ceftobiprole certainly constitutes an interesting option for empirical treatment as monotherapy as well as in combination with a variety of molecules if is needed to have the widest coverage for many nosocomial infections.

This monograph reviews the most significant characteristics of ceftobiprole, marketed in Spain since the end of 2018 by Correvio under the commercial name Zevtera.

Correspondence:
Pedro Llinares
Coordinación de docencia de la Sociedad Española de Quimioterapia. A Coruña, Spain
E-mail: pedro.llinares.mondejar@gmail.com

From a microbiological point of view, Dr Cantón, Dr Morosini and Dr Aguilar present the mechanisms of action and the antimicrobial activity of ceftobiprole. As outlined above, ceftobiprole is a 5th generation (last generation) cephalosporin with rapid bactericidal activity against a wide range of Gram-positive and Gram-negative bacteria, including methicillin-susceptible and resistant *Staphylococcus aureus* (MSSA, MRSA) and susceptible *Pseudomonas* spp.

Dr Azanza and Dr Sábada review the pharmacokinetic and pharmacodynamic (PK/PD) aspects of the molecule. Ceftobiprole has linear pharmacokinetics with no absorption via the oral route. It is well distributed in the extracellular liquid compartment at its normal dosage of 500 mg iv every 8 hrs. The majority of the administered drug is excreted via the kidneys: for this reason, dose or timing adjustments are required according to renal clearance in patients with moderate to severe kidney failure. However, no dose adjustments are required according to weight or age, even in patients with mild to moderate liver failure. Upon augmented renal clearance or when external clearance techniques are used, an increase in infusion time is required, and increased dosage might also be required for critically ill patients in the Intensive Care Unit (augmented renal clearance). The 2-hour intravenous infusion, along with the excretion half-life greater than 3 hours, allows for an optimal time T>MIC PK/PD parameter to be easily reached when the MIC is ≤4 mg/l. In critically ill patients with hyperdynamic circulation and creatinine clearance >150 ml/min, the infusion may be extended to 4 hours to achieve an adequate therapeutic concentration.

Dr Cillóniz, Dr Dominedo, Dr Garcia-Vidal, and Dr Torres present their experience with ceftobiprole in pneumonia, the antibiotic is approved in major European countries) for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) excluding patients with Ventilator Acquired Pneumonia (VAP). In a phase-3 trial performed on patients with CAP, in which ceftobiprole was compared with ceftriaxone, with the possibility of adding linezolid upon

suspicion or confirmation of MRSA, no significant differences were found in clinical efficacy. Similarly, ceftobiprole was non-inferior in clinical efficacy compared with linezolid associated with ceftazidime in a phase-3 trial in HAP patients (excluding VAP). Patients who received ceftobiprole had an earlier clinical response, including cases with positive MRSA cultures. However, non-inferiority of ceftobiprole has not been demonstrated in the VAP subgroup of patients.

The authors believe that ceftobiprole may be used in patients with CAP and suspected involvement of MSSA or MRSA; such as in the case of post-influenza pneumonia during flu epidemics, and in patients with HAP who do not require mechanical ventilation.

Dr Soriano and Dr Morata will discuss some interesting aspects of the drug, such as the experience with ceftobiprole in staphylococcus bacteraemia. It has powerful activity against both methicillin-sensitive and resistant *S. aureus* as well as coagulase-negative *Staphylococcus,* isolated in episodes of bacteraemia. Its capacity for synergy with other antibiotics, especially daptomycin, suggests that this combination may be an option in the treatment of endovascular staphylococcal infections. On the other hand, ceftobiprole's activity against other clinically relevant pathogens, such as *E. faecalis* and enterobacteria as well as *P. aeruginosa*, positions it as a possibility in the empirical treatment of catheter-related bacteraemia.

Dr Barberán discusses other possible indications for ceftobiprole. Due to its extended-spectrum coverage, which includes MRSA, ceftobiprole may be considered in the treatment of complicated skin and soft tissue infections in special situations. In two comparative studies, one with vancomycin and another with vancomycin and ceftazidime, no significant differences were found. The same applies for diabetic foot infection, where in one clinical study the therapeutic response to ceftobiprole was faster than with the comparator. The author also believes that due to the drug's extended-spectrum antibiotic qualities, ceftobiprole may be an option for the empirical treatment of fever with no apparent focus in hospitalised patients without septic shock or severe immunosuppression, and for infections suspected to originate from vascular catheters.

Lastly, Dr Grau provides us with information concerning the safety and tolerability of ceftobiprole. In phase-3 studies, no significant differences have been observed against its comparators. On the other hand, and in contrast to other cephalosporins, ceftobiprole presents a low risk of infection due to *Clostridium difficile* and, in comparison with ceftaroline, neutropenia has not been reported to present any significant issues.