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Possible clinical indications of ceftobiprole

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ABSTRACT

Ceftobiprole is a fifth-generation cephalosporin approved for the treatment of adult community-acquired pneumonia and non-ventilator associated hospital-acquired pneumonia. However, its microbiological and pharmacokinetic profile is very attractive as armamentarium for empirical monotherapy treatment in other infections too. Among these, the following scenarios could be considered complicated skin and soft tissue infections, moderate-severe diabetic foot infections without bone involvement, vascular-catheter-associated-bloodstream infections, and fever without apparent focus in the hospitalized patient without septic shock or profound immunosuppression.

Key words: ceftobiprole, skin soft tissue infections, diabetic foot infections, vascular-catheter-associated-bloodstream infections and fever without apparent focus.

INTRODUCTION

Ceftobiprole is a fifth-generation cephalosporin currently approved in major European countries for the treatment of adult community-acquired (CAP) and Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP) [1]. However, the safety profile of this molecule as demonstrated in clinical trials, along with its antimicrobial and pharmacokinetic profile [2, 3], makes it a very attractive treatment option as monotherapy for empirical treatment of infections in which many patients could benefit from this potential alternative, despite the lack of data from clinical trials and observational studies.

Ceftobiprole is an extended-spectrum cephalosporin with demonstrated *in vitro* activity on the majority of Gram-positive cocci and aerobic Gram-negative bacilli of clinical relevance. On the former, it has heightened bactericidal action and includes: 1) *Staphylococcus* spp., both methicillin- and vancomycin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, 2) *Streptococcus* spp., including *Streptococcus pneumoniae* resistant to penicillins and third-generation cephalosporins, and 3) *Enterococcus faecalis*, as it is the first and only cephalosporin here with demonstrated activity. With regard to Gram-negative bacilli, its spectrum includes the majority of non-extended spectrum beta-lactamase (ESBL)-producing enterobacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, *Proteus mirabilis*), with activity similar to that of cefotaxime and ceftriaxone, and *Pseudomonas aeruginosa*, with similar activities to ceftazidime and cefepime [2].

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OTHER POSSIBLE MONOTHERAPY INDICATIONS

The unique antibiotic spectrum of ceftobiprole, which for the first time combines activity against methicillin-resistant *Staphylococcus* spp. and *P. aeruginosa*, along with non-ESBL-producing enterobacteria, *Streptococcus* spp and *E. faecalis*, makes it a very attractive and advantageous monotherapy alternative compared to antibiotic combinations commonly used for empirical treatment of infections (table 1), which may be caused by one or several of the aforementioned microorganisms.

1. Complicated skin and soft tissue infections (cSSTIs)

According to data from a pharmacovigilance study conducted in Europe over the course of 7 years, *S. aureus* was the primary agent in SSTIs (37.5%), of which 22.8% were MRSA. This was followed by *P. aeruginosa* (12%), *E. coli* (10.8%), and *Enterococcus* spp. (6.1%). Considering the polymicrobial aetiology and mechanisms of resistance that these microorganisms

Table 1 Possible indications of ceftobiprole

1. Community-acquired pneumonia, non-ventilator-associated hospital-acquired pneumonia
2. Complicated skin and soft tissue infections
   a) Infections in areas with high prevalence of methicillin-resistant *S. aureus*
      - Severe and extensive, which may be life-threatening
      - Elderly patient with significant comorbidity (Child B or C cirrhosis of the liver or haemodialysis)
      - Immunosuppressed patient
   b) Manipulated or previously treated chronic ulcers with signs of infection
   c) Surgical or traumatic wound infections
3. Moderate or severe diabetic foot infections without bone involvement
4. Infection originating from a vascular catheter
5. Fever with no apparent focus in hospitalised patient without septic shock or severe immunosuppression

can express, an initial extended-spectrum empirical treatment appears as an obvious choice, where ceftobiprole may have great potential [4].

In this regard, within the vast group of SSTIs, the use of ceftobiprole should be considered in a) infections in areas with large prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), which are severe and extensive and may be life-threatening, b) elderly patients with significant comorbidities (Child B or C cirrhosis of the liver, haemodialysis) or immunosuppression c) manipulated or previously treated chronic ulcers with signs of infection, and d) surgical or trauma wound infections [5].

The factors to bear in mind when selecting empirical treatment for these infections are the following: severity, history of infection/colonisation by resistant microorganisms, previous antibiotic treatment and local sensitivity patterns [6]. Recently, a prospective, observational Spanish study analysed bacteraemia's associated with pressure ulcers. The microorganisms most commonly isolated from blood were the following: *S. aureus* 17 (30%), *Proteus* spp. 16 (28%), *Bacteroides* spp. 13 (23%), *E. coli* 8 (14%) and *P. aeruginosa* 4 (7%). In 25% of cases, the infection was polymicrobial. Bacteraemia-related mortality was 21% and was independently associated with nosocomial origin and polymicrobial aetiology [7].

Published data on experiences with ceftobiprole in this context is already available. In an experimental murine model of MRSA and *P. aeruginosa* infections, ceftobiprole achieved a significantly greater reduction in lesion volume and bacterial load than linezolid and vancomycin (in MRSA) and cefepime (in *P. aeruginosa*) [8].

The concentration of ceftobiprole (free drug) in subcutaneous cellular and musculoskeletal tissue, following a dose of 500 mg IV and determined *in vivo* by microdialysis, remains above 2 mg/L for at least 40% of the 8-hour interval between consecutive doses [9]. The cut-off points established by EUCAST, which determine the sensitivity of ceftobiprole, are as follows: *S. aureus* ≤2 mg/L, *S. pneumoniae* ≤0.5 mg/L, and *Enterobacteriacea* ≤0.25 mg/L [10].

The efficacy and safety of ceftobiprole in cSSTI was also assessed in two multi-centre, non-inferiority, phase-III, double-blind, and randomised clinical studies with over 1600 patients [11, 12]. In one study, ceftobiprole (500 mg/12 h. IV) (n= 397) was compared to vancomycin (1000 mg/12 h IV) (n= 387) (1:1 ratio) for the duration of 7-14 days in infections due to Gram-positive microorganisms. Approximately 50% of the infections were abscesses, 30% wounds (surgical, traumatic and burns), and 20% cellulitis. Around 80% of infections were caused by *S. aureus* (1/3 MRSA). The clinical recovery rate was similar in clinically evaluable patients (>90%) and in the intent-to-treat analysis (77%). The same was observed in the rate of microbiological eradication (>90%). There were no differences in tolerability. The most common side effects of ceftobiprole were nausea (14%) and changes in taste (8%) [11].

The second study included Gram-positive and Gram-negative infections. Ceftobiprole (500 mg/8 h IV administered over a two-hour infusion) (n= 547) was compared with the combination of vancomycin (1000 mg/12 h. IV) and ceftazidime 1000 mg/8 h IV) (n=281) (2:1 ratio). The most common infections were: diabetic foot abscesses and infections (30%), wounds (surgical, traumatic, and burns), and cellulitis 20%. *S. aureus* was the most common causative microorganism (64%, 1/3 MRSA), followed by *E. coli* (10.7%) and *P. aeruginosa* (6.6%). The clinical recovery rate in clinically evaluable patients and in the intent-to-treat was similar (90.5% vs. 90.2% and 81.9% vs. 80.8%, respectively). There were neither differences observed in patients who experienced bacteraemia in infections with severity criteria (CRP >50 mg/L, fascia or muscle involvement, with systemic inflammatory response syndrome or Panton-Valentine toxin-producing MRSA infection), nor by type of microorganism (Gram-positive 91.8% vs. 90.3%,

Gram-negative 87.9% vs. 89.7%, respectively). In the ceftobiprole group, it is noteworthy that in cases with isolation of *P. aeruginosa* only, failure occurred when the MIC_{90} was >8 mg/L. Tolerability was equivalent, and nausea was the most common adverse effect of ceftobiprole [12]. Despite the favourable results of these studies, the FDA (*Food and Drug Administration*) and the EMA (*European Medicines Agency*) have not approved the use of ceftobiprole in cSSTIs due to a lack of inspections and audits in one-third of patients [13, 14]. For this reason it is being carried out a new phase 3 clinical trial in the treatment of patients with acute bacterial skin and skin structure infections, to establish the efficacy and safety of ceftobiprole compared with vancomycin plus aztreonam [15].

2. Moderate or severe diabetic foot infections without bone involvement

In Spain, the aetiology of diabetic foot infections has been well documented in recent studies. *S. aureus* (>30% MRSA) remains the most common agent, followed by Gram-negative bacilli (enterobacteria and *P. aeruginosa*) [16, 17].

The experience with ceftobiprole in diabetic foot infections has been analysed in detail. One three-year study examined the *in vitro* activity of ceftobiprole against 443 isolates (251 aerobic and 192 anaerobic) of complicated diabetic foot infections, in which it was demonstrated to be active against a wide range of aerobic and anaerobic Gram-positive and Gram-negative microorganisms. Ceftobiprole's activity was also compared with other antibiotics. In the case of aerobic Gram-positive cocci (*S. aureus*, including MRSA, *Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae* and other streptococci) ceftobiprole was more active than cefepime, ceftazidime, cefotaxime, cefoxitin, levofloxacin, linezolid, daptomycin and vancomycin [18]. Furthermore, in a multi-centre, double-blind, randomised clinical study on cSSTIs, in which ceftobiprole (500 mg/8 h) was compared to vancomycin (100 mg/12 h) plus ceftazidime (1000 mg/8 h), approximately one-third of the cases included were diabetic foot infections (n=257, 72% of these considered to be moderate or severe). The most frequently isolated microorganisms were: Methicillin-sensitive *S. aureus* (MSSA) 38%, MRSA 18%, *Enterobacter cloacae* 9%, *Streptococcus agalactiae* 9%, *P. aeruginosa* 8%, and *Proteus mirabilis* 7%. In this sub-population, the clinical recovery rates were as follows: 125/145, 86.2% for ceftobiprole and 63/77, 81.8% for vancomycin plus ceftazidime (mild infection 97.6% vs. 100% and severe infection 70.6% vs. 53.8%, respectively). However, the average duration of treatment was significantly shorter with ceftobiprole (8.7 vs. 9.5 days, respectively, $p < 0.05$), suggesting a faster response to treatment when ceftobiprole is used [19].

3. Infections originating from vascular catheters

S. aureus (MRSA: 9.5-26.6%) and coagulase-negative staphylococci (methicillin-resistant: 53.4%) are the most common causative organisms of infections associated with venous catheters (central and peripheral) in our country [18-20]. However, in recent years a significant increase in Gram-negative bacilli has been reported, most notably *P. aeruginosa*, *E. coli* and *Klebsiella* spp., which have been associated to a significant degree with solid organ transplant, post-surgery, prior use of beta-lactams, prolonged hospital stay (>7-11 days), and more than 3 days post-catheter insertion [21, 22].

In this context, choosing ceftobiprole as monotherapy may replace the usual combinations of a glycopeptide with a beta-lactam, preferentially active against *P. aeruginosa*. Experience with ceftobiprole in the treatment of bacteraemia, although favourable, is still limited. In the first cSSTI study due to Gram-positive cocci, three episodes of staphylococcal bacteraemia (2 due to MRSA) treated with ceftobiprole resolved without complication [11]. In the other cSSTI study, 13 cases of bacteraemia were reported in the ceftobiprole group, 11 of which (84.6%) resolved. In the control group, 8 cases of bacteraemia were observed with favourable outcome in 62.5% (5/8) [12]. In the hospital-acquired pneumonia study, 41 cases of bacteraemia were identified in the ceftobiprole arm and 45 in the comparator group. The authors do not comment on the aetiology or clinical and microbiological outcomes in this sub-group [23]. In the community-acquired pneumonia clinical trial, several cases of bacteraemia are described with no mention of causal agents. The recovery rate in this subpopulation does not differ between treatment groups or in comparison to treated cases without bacteraemia (ceftobiprole 6/7, 85.7%, comparator 12/14, 85.7%) [24]. Also at this time there is a phase III ongoing study in *S. aureus* bacteremia. The purpose of this study is to compare the efficacy and safety of ceftobiprole medocaril versus daptomicyn in the treatment of patients with complicated *S. aureus* bacteremia [25].

4. Fever with no apparent focus in hospitalised patients

The first point to consider in this patient type is to determine whether the origin of the fever is infectious, thus evaluating the clinical, biological and imaging data that may suggest infection. The second aspect is taking culture samples prior to starting treatment. The third decision involves choosing the empirical antibiotic treatment, clouded by a lack of focality [26]. In a large number of patients, the origin may be the venous catheter. In any case, one must always consider the most prevalent microorganisms as a cause of infection in hospitalised patients (*S.* aureus, coagulase-negative staphylococci, *Enterococcus* spp., and Gram-negative bacteria (enterobacteria and *P. aeruginosa*) which depend on the comorbidity, the invasive diagnostic or therapeutic procedures performed, and local epidemiology [27]. Furthermore, one must consider the risk of resistance, which is closely related to prior use of antibiotics, loss of colonisation immunity and colonisation pressure [28]. In patients without significant immunosuppression or septic shock, ceftobiprole may be used empirically as monotherapy with the goal of addressing the possible role of methicillin-resistant *Staphylococcus* spp., *E. faecalis*, *P. aeruginosa* and non-ESBL-producing enterobacteria.

CONCLUSIONS

Ceftobiprole may be a good therapeutic alternative for the empirical treatment of cSSTIs, including those involving diabetic foot, vascular catheter, and fever with no apparent infectious origin, which require hospitalisation and have risk factors for MRSA and *P. aeruginosa*. Always within the treatment protocols established at each hospital.

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