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Update on antimicrobial pharmacotherapy

Ceftobiprole: a clinical view

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ABSTRACT

Ceftobiprole is a broad-spectrum, fifth-generation cephalosporin currently approved for community-acquired and non-ventilator-associated hospital-acquired pneumonia. High bactericidal and anti-biofilm activity has been exhibited in *in vitro* and animal models. This, together with its synergism with other antibiotics against gram-positive bacteria, makes it an ideal candidate for treatment of complex infections, such as those associated with devices or infective endocarditis. More clinical data are needed to achieve drug positioning.

Keywords: ceftobiprole, MRSA, synergy, anti-biofilm.

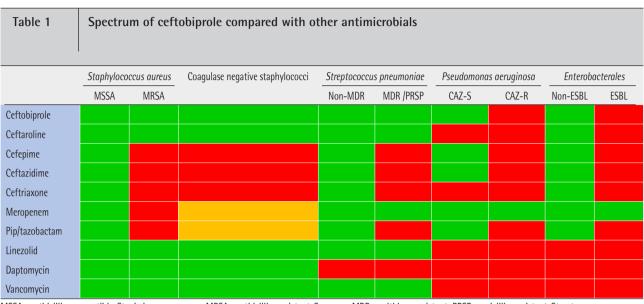
Ceftobiprole is a broad-spectrum, fifth-generation cephalosporin, currently approved for community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) excluding ventilator-associated one [1,2]. This drug exerts potent bactericidal activity against several gram-positive and gram-negative pathogens, as well as Streptococcus spp. (including most Enterococcus faecalis) and Staphylococcus spp. [including methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative Staphylococcus (CNS)], Haemophilus influenzae, Moraxella catarrhalis, most of the Enterobacterales group, and Pseudomonas aeruginosa (Table 1). On the other hand, ceftobiprole shows reduced or no activity against Enterococcus faecium, Proteus vulgaris, most Gram-negative anaerobes, Acinetobacter baumannii, Burkholderia cepacian complex, and Stenotrophomonas maltophilia. With respect to difficult-to-treat bacteria, ceftobiprole has activity against derepressed AmpC producers, but not against extended-spectrum β -lactamases (ESBLs), carbapenemases or metallocarbapenemase-producing Enterobacterales. Epidemiological surveillance studies have shown excellent susceptibility rates (close to 100%) in S. aureus, MRSA, CNS, S. pneumoniae and E. faecalis, although with more discreet results in Enterobacterales and P. aeruginosa. With respect to the latter, ceftobiprole susceptibility rates of about 70% were reported in a recent international cohort that included 1064 isolates [3,4]. To our knowledge, there are no published data concerning the susceptibility of P. aeruginosa to ceftobiprole in Spanish isolates, although in a recent conference communication, only 59% of 95 Spanish isolates tested were susceptible. A limitation is that we do not know which hospitals participated in that study and that may have conditioned these results [5]. Ceftobiprole shows several pharmacokinetic and pharmacodynamic properties that make it a very interesting molecule: high bactericidal activity, proven in experimental models (in vitro and animal studies), low protein binding (16%), a high volume of distribution, and predominantly renal excretion (70-90%). Consequently, concentrations of ceftobiprole found in feces after 7 days of therapy are very low, as was demonstrated in a study in healthy volunteers [6]. This may be associated with a low rate of Clostridioides difficile infection [1,2].

The data sheet recommends 500 mg every 8 hours administered as a 2-hour intravenous infusion, demonstrating linear pharmacokinetics if higher doses than usual are used. It exhibits two very promising features that may help to place it in a wide range of complex infections in the near future. First, it shows in vitro synergy with different antibiotics, highlighting combinations with daptomycin against MRSA, and with piperacillin/tazobactam and amikacin against *P. aeruginosa* [7,8]. Second, it has very good activity against biofilm, once again showing synergy with rifampin and vancomycin [9]. These characteristics could make it an excellent option against MRSA or CNS infective endocarditis, endovascular or prosthesis-related infections, osteomyelitis, among others. While the clinical data about the efficacy of ceftobiprole in these scenarios has increased in recent years, it is not easy to draw solid conclusions because it has been used in most cases as combined or

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MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; MDR: multidrug resistant; PRSP: penicillin-resistant *Streptococcus pneumoniae*; CAZ: ceftazidime; S: susceptible; R: resistant ESBL: extended-spectrum β-lactamases; Pip/tazobactam: Piperacillin/ tazobactam

salvage therapy [10-13]. There are some ongoing clinical trials, such as the one establishing the efficacy and safety of ceftobiprole versus daptomycin in the treatment of *S. aureus* bacteremia, including infective endocarditis [14].

Ceftobiprole is generally well tolerated with a low rate of adverse effects. The most common ones are dysgeusia, nausea, vomiting, and diarrhea, although hyponatremia and myoclonus have also been reported on rare occasions [1,2,11].

In our opinion, the use of ceftobiprole as empirical treatment in nosocomial infections is limited because the number of P. aeruginosa-susceptible strains is not well established in our media and because it has no activity against ESBLs strains. Own susceptibility data are needed for the adequate positioning of the drug in this regard. Nevertheless, ceftobiprole may have a role as targeted therapy to carry out antimicrobial diversification in nosocomial infections, replacing standard combinations such as ceftazidime plus and vancomycin. It could also be useful as salvage therapy in combination with daptomycin in MRSA infections, although comparisons with other combination options, such as daptomycin plus fosfomycin, or daptomycin plus fosfomycin are needed. Preliminary data shows that ceftobiprole is at stable for up to 24 hours at 25°C and protected from light, which also allows for potential administration in outpatient parenteral antimicrobial therapy [15].

In the meantime, we look forward to more observational studies and data from clinical trials that will help us to establish definitively new indications for ceftobiprole.

CONFLICTS OF INTEREST

LELC has served as scientific advisor for Angelini, speaker

for Angelini, ViiV, Gilead and Correvio, and has served as trainer for ViiV. PMMPC declare no clonflic of interest.

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