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Ceftobiprole for the treatment of pneumonia

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ABSTRACT

Ceftobiprole is a fifth-generation cephalosporin with potent antimicrobial activity against Gram positive and Gram-negative bacteria. It has been approved in major European countries for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP). Ceftobiprole is currently in a phase 3 clinical program for registration in the U.S. In 2015, it was designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA. The efficacy of ceftobiprole in pneumonia has been demonstrated in two-phase III clinical trials conducted in patients with CAP and HAP. The recommended dose in the adult with pneumonia is 500 mg every 8 h infused in 2 h; in case of renal failure, the regimen of administration must be adjusted according to the patient's renal function. It is not necessary to adjust the dose according to gender, age, body weight or liver failure. In case of hyperfiltration, an extension to 4 h infusion of the 500mg TID is required.

INTRODUCTION

Pneumonia is a serious health problem and a significant cause of morbidity and mortality around the world despite advances in clinical treatment and antibiotic therapy [1]. Community-acquired pneumonia (CAP) is associated with elevated health costs and is a common cause of emergency care and hospital admissions, especially in elderly patients and those with multiple comorbidities, whose mortality rate (which is approximately 10%) may reach 40% in cases of severe CAP that requires treatment in the intensive care unit (ICU) [2–5]. Hospital-acquired pneumonia (HAP) represents more than 25% of all infections in the ICU; hospital stays and health costs are very high, with a mortality rate between 27% and 50% [6]. The microbiological diagnosis is generally difficult to establish, including when complex and invasive diagnostic methods are used. In fact, microbiological confirmation is achieved in less than half of the cases and the initial antibiotic regimen must be empirically chosen to prevent delays in establishing an appropriate treatment, which is associated with elevated mortality [7–10].

Streptococcus pneumoniae (pneumococcus) continues to be the most common cause of CAP in all patient treatment settings (outpatient, hospitalized and patients admitted into intensive care units), age groups, and regardless of the patient's comorbidities [11].

However, it is reported that approximately 6% of CAP is caused by antibiotic-resistant pathogens, with *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) being the most common [12].

In cases of pneumonia due to influenza virus, pneumococcus is the most commonly identified pathogen in patients with bacterial co-infection. However, other pathogens such as *S. aureus* (methicillin-susceptible or resistant), *Haemophilus influenzae* and non-fermenting Gram-negative bacilli such as *P. aeruginosa* have also been reported. In patients with severe CAP, *P. aeruginosa* has been identified in 8.3% of patients, with a mortality rate of up to 100% [9, 13]

In HAP, the most common infecting bacteria are members of the *Enterobacteriaceae* family (such as *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp.), *S. aureus*, *P. aeruginosa*, and *Acinetobacter baumannii*, the majority of these microorganisms being multi-drug resistant, highlighting their importance in the current challenge of antibiotic resistance [14].

Ceftobiprole, a fifth-generation (last generation) extended-spectrum cephalosporin, shows potent *in vitro* activity against several Gram-positive pathogens, including methi-

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cillin-susceptible *S. aureus* (MSSA), MRSA with reduced susceptibility to linezolid, daptomycin or vancomycin, methicillin-resistant coagulase-negative staphylococci (MR-CoNS), penicillin- and ceftriaxone-resistant *S. pneumoniae,* along with *in vitro* activity Gram-negative pathogens including *P. aeruginosa* and non-extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae* [15] (table 1). Ceftobiprole has shown to have a time-dependent bactericidal activity, as expected by this class of molecules. It exerts its action by blocking the transpeptidase activity in penicillin-binding proteins (PBP) both in Gram-positive and Gram-negative pathogens. As a result, peptidoglycan synthesis decreases and the bacteria die due to the osmotic effects or by autolytic enzyme digestion [16].

CLINICAL EFFICACY IN PATIENTS WITH PNEUMONIA

The safety and efficacy of ceftobiprole medocaril has been investigated in two phase-III clinical trials in patients with CAP and HAP [17, 18].

Clinical trial on CAP. This was a multi-centre, double-blind, randomised study on 638 patients with CAP who required hospitalization, ceftobiprole (500 mg/8h) was compared to ceftriaxone (2g/day) with or without linezolid (if suspected MRSA infection, 600 mg/12h). Linezolid was administered in patients with suspected MRSA or ceftriaxone-resistant *S. pneumoniae*. Patients were stratified according to severity measured by the Pneumonia Severity Index (PSI) and by need for adding linezolid. Primary endpoint was the clinical cure rate at the TOC visit on the intent-to-treat (ITT) and clinically evaluable (CE) population. The secondary efficacy criteria were microbiological eradication rate at TOC visit, the rate of clinical recovery according to the baseline PSI in ITT and CE populations, and specific mortality due to pneumonia after 30 days in ITT and CE populations. The pre-defined non-inferiority margin of 10% (95% CI) was set for all endpoints.

The study demonstrated that ceftobiprole (500 mg/8 h infused in 2 h) was not inferior to ceftriaxone (2 g/24 h), whether as monotherapy or combined with linezolid (600 mg/12 h). No difference was found in the overall clinical and microbiological analyses, as well as in predefined high-risk subgroups or other subgroups of interest (including those treated with antistaphylococcal agents). For all 469 clinically evaluable patients, the recovery rates were 86.6% versus 87.4%, respectively; in the intent-to-treat (IIT) analysis of 638 patients with CAP, the recovery rate was 76% versus 79%, respectively [17] (figure 1).

For the secondary criterion of microbiological eradication, non-inferiority between ceftobiprole and the comparator was established. Specific mortality due to pneumonia in the first 30 days was very low, both for the ceftobiprole group and the ceftriaxone ± linezolid (1 versus 3 patients in the ITT population and 0 versus 2 patients in the CE population).

Clinical trial on HAP. Similar to the first study, the second was a phase-III , multi-national, randomised, double-blind study that compared ceftobiprole against the combination of ceftazidime plus linezolid in 781 adults with HAP (defined as a pneumonia arising after >72 h of hospitalization or stay in a

Table 1 | **Ceftobiprole's antibiotic activity**

ACTIVE
Gram-positive bacteria
Streptococcus pneumoniae (including the strains resistant to benzylpenicillin and ceftriaxone)
Staphylococcus aureus
Methicillin-resistant *Staphylococcus aureus*
Gram-negative bacteria
Haemophilus influenzae (including clinical isolates resistant to ampicillin)
Pseudomonas aeruginosa
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis Non-extended-spectrum beta-lactamase (ESBL)-producing
INACTIVE
Strains of *Enterobacteriaceae* that express Amber class A beta lactamases, especially TEM, SHV and CTX-M types, as well as KPC-type carbapenemases; it is also inactive against Amber class B, C (high levels of expression) and D, particularly the ESBL variants and OXA-48 carbapenemases.
Strains of beta-lactamase-producing *Pseudomonas aeruginosa* from classes A (PSE-1), B (IMP-1, VIM-1, VIM-2) and D (OXA-10).
Strains of beta-lactamase-producing *Acinetobacter* spp. from classes A (VEB-1), B (IMP-1, IMP-4) and D (OXA-25, OXA-26)

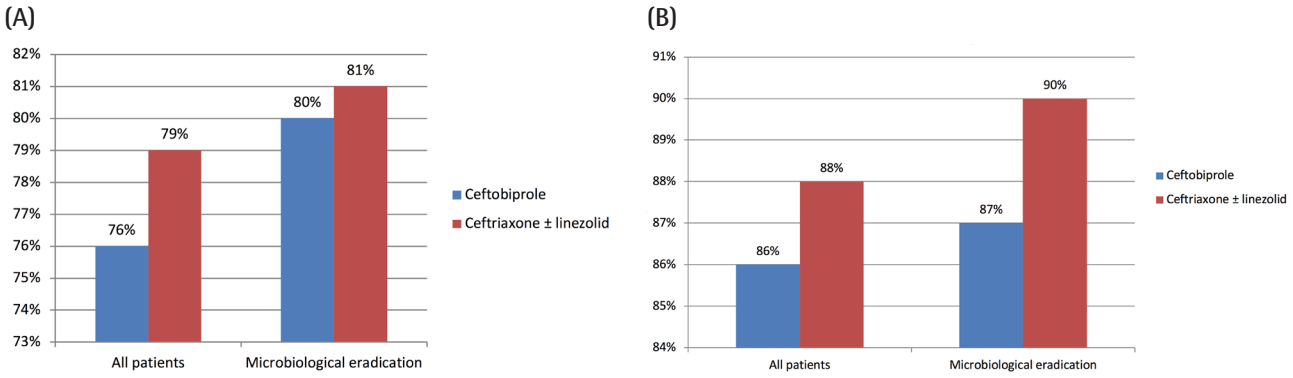
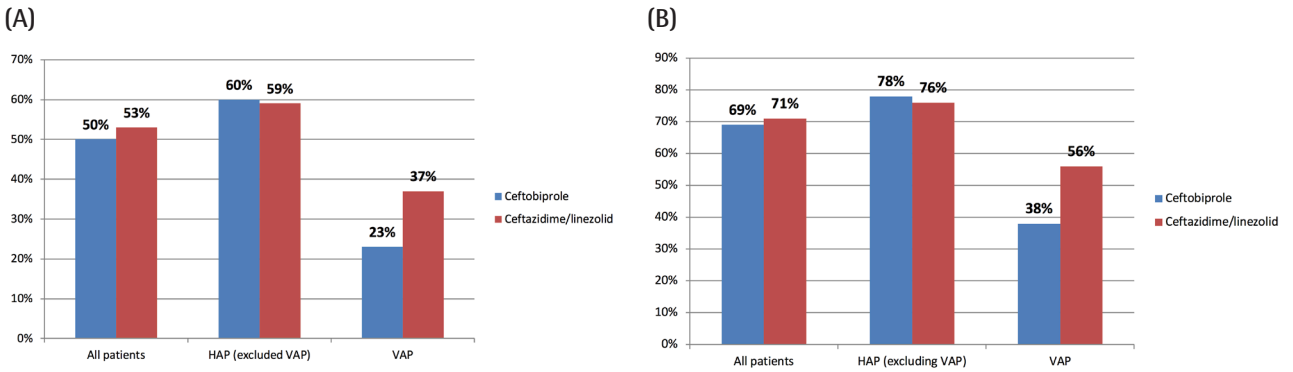


Figure 1 CAP: Percentage of clinical efficacy in the population by intention to treat (A) and in clinically evaluable population (B)



Differences between groups -2.9% (-10.0–4.1) 0.8% (-7.3–8.8) -13.7% (-26.0 to -1.5) IC 95%

Differences between groups -2.0% (-10.0–6.1) 1.6% (-6.9–10.0) -18.2% (-36.4 to -0.0) IC 95%

Figure 2 HAP: Percentage of patients with clinical cure visit of cure test in the population by intention to treat (A) and in clinically evaluable population (B)

long-term care unit). The inclusion criteria were: clinical signs and symptoms of pneumonia (at least two including purulent respiratory secretion, tachypnoea, or hypoxemia); fever or leukocytosis/leukopenia; new or persistent radiographic infiltrates; and an APACHE II score of 8-25. The exclusion criteria were: severe kidney or liver failure; evidence of infection due to ceftobiprole or ceftazidime-resistant pathogens; clinical conditions that could interfere with the efficacy evaluation (for example, sustained shock, active tuberculosis, pulmonary abscess, and post-obstructive pneumonia); and systemic antibiotic treatment for >24 h in the 48 h prior to inclusion. Patients were stratified for treatment according to presence of VAP (pneumonia arising after >48 h after the start of mechanical ventilation) and APACHE II score (8–19/20–25); VAP patients were stratified according to length of mechanical ventilation (</≥5 days).

The primary efficacy endpoint was the clinical cure rate at the TOC visit (7 to 14 days after the last dose of the study drug or early termination) in the ITT and clinically evaluable (CE) populations; non-inferiority was defined using a margin of 15% for the 95% CIs. The secondary criteria were microbiological eradication at the TOC visit in ITT and microbiologically evaluable populations with a valid pathogen at baseline, 30-day all-cause mortality in the ITT population, as well as safety and tolerability.

For the primary efficacy criteria, the study demonstrated that treatment with ceftobiprole monotherapy (500 mg/8 h infused in 2 h) was non-inferior to a combined treatment that included ceftazidime (2 g/8 h) plus linezolid (600 mg/12 h) for patients with HAP, excluding patients with VAP. In the CE population, 86.9% of patients with HAP (excluding patients with VAP) in the ceftobiprole group demonstrated early improvement (4 days after beginning therapy); compared to 78.4% in the ceftazidime plus linezolid group (difference 8.5 [CI of 95%, 0.9–16.1]). A major numerical difference was observed in the subgroup of patients with microbiological evidence of MRSA infection (94.7% in the ceftobiprole group vs. 52.6% in the ceftazidime group plus linezolid (difference, 42.1 [CI 95%, 17.5–66.7]). For the secondary efficacy criteria, the microbio-

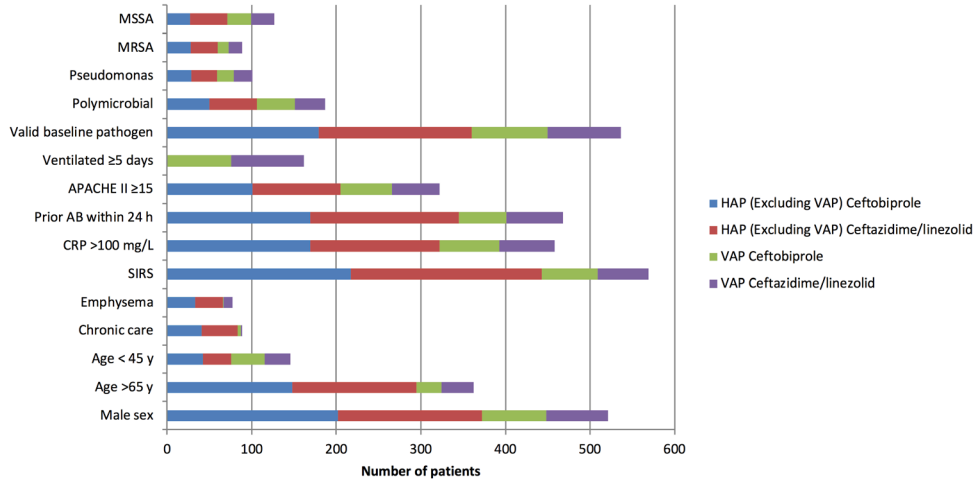


Figure 3 | **Clinical characteristics between groups: HAP (excluding VAP) ceftobiprole, HAP (excluding VAP) ceftazidime/linezolid, VAP ceftobiprole, VAP ceftazidima/linezolid**

logical eradication rates at the completion of treatment (CT) visit in patients with HAP (excluding VAP) were similar in the ceftobiprole and ceftazidime/linezolid groups in the ITT (49% versus 54%; difference 5.0; CI 95%: 15.3–5.3) and microbiologically evaluable groups (63% vs. 68%; difference -4.6; CI 95%: -16.7–7.6) (figure 2A). In addition, clinical recovery and rates of microbiological eradication of pathogens in patients with HAP (excluding VAP) were similar for Gram-positive and the majority of Gram-negative microorganisms.

In the overall population, the recovery rates in clinically evaluable patients for ceftobiprole compared to ceftazidime/linezolid were 69.3% vs. 71.3%, respectively. Ceftobiprole noninferiority was not demonstrated in the subgroup of patients with VAP patients with recovery rates in the clinically evaluable cases of VAP of 37.7% vs. 55.9% [18], respectively (figure 2B).

Interestingly, in patients with HAP requiring mechanical ventilation for less than 48 h, thus not defined as VAP, clinical outcomes favoured ceftobiprole, suggesting that mechanical ventilation itself may not be associated with poor outcomes, whereby ceftobiprole may be administered in patients with HAP requiring mechanical ventilation. There are different explanations for ceftobiprole outcomes observed in the VAP subgroup of patients: the small sample size and considerable heterogeneity of baseline clinical characteristics in the VAP subgroup may have contributed to the difference in outcomes (figure 3) [19].

Furthermore, out of the 16 (62.5%) patients ≤45 years with VAP and cranial trauma who were randomized into the ceftobiprole group, 12 (17.6%) were characterized as treatment failures compared to two out of four assigned to the ceftazidime/linezolid group.

The pharmacokinetics (PK) of ceftobiprole in patients with VAP was different from patients without VAP, which may be attributed to increased cardiac output, augmented glomerular filtration rate, and increased volume of distribution associated with critical illness. For this reason, it is unlikely that ceftobiprole will meet the desired PD objectives when the PK parameters are altered. Indeed, for patients hospitalized in the ICU with creatinine clearance (CrCl) >150 ml/min, extending the ceftobiprole infusion time to 4 h contributes to keep plasma levels above the minimum inhibitory concentration (MIC) (4 mg/L). As such, for patients with increased kidney function (CrCl>150 ml/min), increasing the duration of ceftobiprole infusion is recommended (500 mg for 4 h/8 h), according to linear PK and low protein binding [19].

The inferior outcome of ceftobiprole in VAP may have been the result of suboptimal concentrations of ceftobiprole at the infection site as a result of the change in volume of distribution due to mechanical ventilation capillary filtration.

Ceftobiprole has so far demonstrated a good safety profile in preliminary studies, with a tolerance similar to that of comparators. The most commonly observed adverse events with ceftobiprole include headache and gastrointestinal disorders. Ceftobiprole is the first cephalosporin monotherapy that has been approved in Europe for the treatment of CAP and HAP, excluding VAP. Ceftobiprole is not approved by the Food and Drug Administration (FDA); however in 2015 it was designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA [20]. There is an ongoing phase III study at this time to compare the safety and efficacy of ceftobiprole medocaril versus vancomycin plus aztreonam in the treatment of patients with acute bacterial skin and skin structure infections. BARDA program https://clinicaltrials.gov/ct2/show/NCT03137173?term=Ceftobiprole&draw=3&rank=11

DOSING ROUTES IN PNEUMONIA

Ceftobiprole should be administered at a dose of 500 mg every 8 h, infused over 2 h, in patients with normal kidney function. Ceftobiprole should be reconstituted with 10 ml sterile saline or 5% dextrose. It is further diluted in 250 ml of 0.9% sodium chloride, 5% dextrose, or lactated ringers solution prior to intravenous infusion.

Dosing in Special Patient Populations

• **Patients with Kidney Failure:** it is recommended to adjust the dose of ceftobiprole in patients with moderate to severe kidney failure. For patients with moderate deterioration (CrCl 30 to <50 ml/min), the recommended dose is 500 mg administered as intravenous infusion for 2 h every 12 h, while for those with severe deterioration (CrCl <30 ml/min), the recommended dose is 250 mg administered as intravenous infusion for 2 h every 12 h. For patients with terminal stage kidney disease, the recommended dose is 250 mg once every 24 h, regardless of whether or not they are undergoing haemodialysis.

• **Treatment of Critically Ill Patients:** antibiotics are among the most important and commonly prescribed medicines in the treatment of critically ill patients and β-lactams are the most widely used class of antibiotic. Pathophysiological factors in critically ill patients lead to altered pharmacokinetics and pharmacodynamics of β-lactams. In critically ill patients, capillary leak and oedema, fluid therapy, pleural effusion, ascites, permanent post-surgical drainage and hypo-albuminaemia may all increase the volume of distribution and cause dilution of antibiotics in plasma and extracellular fluids. Some pathophysiological factors may also improve (hyperdynamic condition in early stage sepsis, the use of haemodynamically active drugs) or reduce (kidney failure, bedridden patients) the concentrations of the antibiotic in plasma and extracellular fluid (with implications for MIC over time), prompting high intra and inter-patient variability and promoting the risk of antibiotic overdose. Extra-corporeal support techniques also contribute to the variability of antibiotic concentration [19, 21]. There are very few studies that have investigated β-lactam PK/PD issues in critically ill patients with pneumonia. Rodvolt et al. [22] conducted a prospective, observational, pre-clinical murine model of pneumonia due to MRSA and a clinical study with 24 healthy volunteers who received ceftobiprole 500 mg over 2 h, every 8 h. Its conclusions were that for critically ill patients, particularly in the ICU, higher doses or longer infusion times (to prolong T>MIC), or both, will be required to guarantee adequate achievement of objectives for 90% of critically ill patients with pneumonia due to MRSA.

• **Obese Patients:** the physiological changes that obese patients present may influence the pharmacokinetics of antibiotics. One study compared the pharmacokinetics of a single intravenous infusion of ceftobiprole 500 mg for 2 h in obese adults [body mass index (BMI)] [40 kg/m^2] and those who were not obese (BMI 18-30 kg/m^2)[24]. The average BMI was 45.5 kg/m^2 in the group with severe obesity (n = 12) compared to 24.0 kg/m^2 in the non-obese group (n = 13); other baseline characteristics were similar in both groups. The volume of distribution and total clearance of ceftobiprole were 25.9 and 19.1% higher, respectively, in those who were severely obese compared to non-obese individuals; exposure to ceftobiprole was lower in adults who were severely obese than in those who were not. Plasma concentrations of unbound ceftobiprole remained above the MIC objective of 4 mg/L (fT >MIC) for 76.6 and 79.7% of an 8 h. dose interval in severely obese and non-obese individuals, respectively. Although the volume of distribution and total clearance were higher and exposure was lower in adults with severe obesity compared to non-obese individuals after a ceftobiprole infusion, the % fT >MIC was similar in both groups, which indicates that it's not necessary to adjust the dose of ceftobiprole in patients with severe obesity [24].

TOLERABILITY

With respect to the tolerability of ceftobiprole, one potential benefit of kidney excretion is that it may limit exposure to antibiotics in the intestine, although to date there are no studies that specifically address this topic. Only one study published in 2010 investigated the effect of the administration of ceftobiprole on the normal intestinal microflora of 12 healthy subjects aged 20 to 31 years who received ceftobiprole 500 mg via intravenous infusion every 8 h for 7 days. This study showed that ceftobiprole achieves low levels of intestinal exposure, with only minor effects on the intestinal microbiota. In fact, no measurable concentrations of ceftobiprole were detected in faeces following intravenous administration in healthy volunteers and no *Clostridium difficile* strains or toxins were found. Also, one study on mice showed that ceftobiprole did not promote the growth of *C. difficile* in faecal content and was not associated with toxin production.

Ceftobiprole in CAP and HAP (excluding VAP). Due to its safety profile and good antibiotic activity against an extended spectrum of pathogens in CAP, especially penicillin- and ceftriaxone-resistant *S. pneumoniae,* as well as *S. aureus* especially MRSA, ceftobiprole may be a very good therapeutic option for patients with risk factors for infection caused by these pathogens. Also, ceftobiprole appears to be very promising in patients with CAP due to influenza with suspected or confirmed co-infection with *S. pneumoniae* or *S. aureus* (MSSA or MRSA). Furthermore, a *post hoc* retrospective analysis of the subgroups of high-risk patients with CAP (n= 398) (PORT risk score >III, age >75 years, sepsis, COPD, bacteraemia, need for ICU) and HAP (n=307) (need for mechanical ventilation, APACHE score >15, age >75 years, bacteraemia, treatment in ICU, COPD, >10 comorbidities) from both of the aforementioned phase-III clinical trials has evaluated early clinical response (3rd day in CAP and 4th day in HAP) for ceftobiprole versus the active comparator regimes, yielding overall similar results, with a trend towards better outcomes in the ceftobiprole treated arm (numerical superiority assessed by 10% difference or CI not crossing 0). For this reason, high-risk patients with CAP and HAP (excluding VAP) may show earlier improvement upon ceftobiprole administration [25]. Case series presented at ECCMID 2019 on 57 patients with important

contraindications: 18 months of real-life use of ceftobiprole: clinical experience in an internal medicine ward. Giuseppe Russo et al. https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=68737

Lastly, considering that ceftobiprole shows potent in vitro activity against the pathogens most commonly associated with HAP, above all *S. aureus*, non-ESBL *Enterobacteriaceae*, and *P. aeruginosa*, it has the potential to simplify empirical combination treatment with two antibiotics in a monotherapy regimen for HAP (excluding VAP).

REGISTRATIONS

Ceftobiprole medocaril has been approved in major European countries for the treatment of CAP and HAP, excluding VAP [26, 27]. Ceftobiprole is currently in a phase 3 clinical program for registration in the U.S. In 2015 it was designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA [20]. This year ceftobiprole has been launched in Argentina [28].

CONCLUSIONS

One of the main challenges in the treatment of pneumonia (CAP and HAP) is overcoming the problems of resistance, which have become so important and common in recent years. Ceftobiproles potent activity as a new-generation cephalosporin against broad spectrum of Gram-positive and Gram-negative bacteria has been demonstrated in two clinical trials, one on CAP and the other on HAP (excluding ventilation-associated pneumonia). Ceftobiprole is approved in major European countries as therapy for CAP and HAP (excluding VAP), and is designated as an infectious disease product qualified for the treatment of lung and skin infections by the FDA.

Ceftobiprole may be used in patients with CAP with suspected or confirmed *Staphylococcus aureus* (MSSA or MRSA) as is the case with pneumonia due to the influenza virus in which *S. pneumoniae* may also be involved, and in patients with HAP to cover *S. aureus,* susceptible *Pseudomonas aeruginosa* and non-ESBL *Enterobacteriaceae*.

Extended-spectrum coverage with ceftobiprole monotherapy may simplify empirical treatment in relation to combined therapies against MRSA.

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