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New antimicrobial alternatives in the treatment of pneumonia

Francisco Sanz Herrero

Ceftazidime-avibactam

Servicio de Neumología. Consorci Hospital General Universitari de València, Spain. Spanish Society of Pneumology and Thoracic Surgery (SEPAR)

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ABSTRACT

The increase in nosocomial infections by beta-lactamase-producing Gram-negative bacilli constitutes a therapeutic challenge. The combination of ceftazidime-avibactam offers a very interesting therapeutic option for nosocomial pneumonia caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*, multidrug-resistant *Pseudomonas aeruginosa*, and other enterobacteria. Compared to carbapenems, ceftazidime-avibactam has demonstrated non-inferiority in the treatment of nosocomial pneumonia including better clinical and microbiological cure rates and mortality compared to colistin. The limitation of ceftazidime-avibactam in the treatment of infections caused by metallo-beta-lactamase-producing *Enterobacteriaceae* can be overcome with the addition of aztreonam.

Keywords: Ceftazidime-avibactam. Nosocomial pneumonia. ESBL-producing *Enterobacteriaceae*.

INTRODUCTION

Despite the improvement in health care and the multiple recommendations on the prudent use of antibiotics, nosocomial pneumonia ranks second, after urinary infections of hospital-acquired infections, with an incidence of 5-20 cases for every 1000 admissions [1]. Ventilator-associated pneumonia is also not uncommon and can be found in 2-16 cases per 1000 days/ventilation. These infections lead to a greater use of antibiotics against microorganisms that will frequently present antibiotic resistance, so the challenge is choosing an antimicrobial capable of overcoming these resistances with the most adjusted spectrum. In this context, ceftazidime-avibactam (CAZ-AVI) is positioned as a useful tool for the treatment of these serious infections.

Correspondence:
Francisco Sanz Herrero
Servicio de Neumología. Consorci Hospital General Universitari de València, Spain
E-mail: sanz_fraher@gva.es

MICROBIOLOGICAL PROFILE

CAZ-AVI is composed by a third-generation cephalosporin and a beta-lactamase inhibitor. Ceftazidime is a broad-spectrum third-generation cephalosporin. It has a bactericidal action by binding to penicillin-binding proteins (PBP) and then inhibiting the synthesis of the bacterial wall. It is active against a wide number of Gram-negative bacteria, including penicillinase-producing strains of *N. gonorrhoeae* and a large number of *Enterobacteriaceae* (*E. coli, Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., *Morganella* spp., *Proteus* spp., *Providencia* spp., *and Serratia* spp.) [2]. Ceftazidime is the cephalosporin with the highest activity against *Pseudomonas aeruginosa*.

Resistance to beta-lactams and cephalosporins is configured to a greater extent by the appearance of beta-lactamases. There are different types of beta-lactamases: class A, present in enterobacteria and in extended-spectrum beta-lactamase (ESBL) *Klebsiella* producer, class B, for which there are no inhibitors, class C, which is induced in Gram-negative rods, especially by the transmission of plasmids and those of class D where traditional beta-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam) do not have much effect [3].

Avibactam is a beta-lactamase inhibitor that does not have antibiotic activity "*per se*" and protects the action of ceftazidime. Its action profile is exerted mainly on class A and class C beta-lactams and to a lesser extent on class D. Avibactam has no effect on metallo-beta-lactamases (MBL) present in anaerobes and in some species of *Pseudomonas* spp. [4].

In the INFORM study, samples from lower respiratory track samples of patients with pneumonia hospitalized in 70 hospital centers were analyzed for one year (2017-2018), where the in-vitro activity of CAZ-AVI was studied [5]. The antibiotic susceptibility results for CAZ-AVI were 96% for *P. aeruginosa*, 100% for *E. coli*, and 100% for *Klebsiella pneumoniae*. When comparing the action of CAZ-AVI on carbapenemase-producing *Enterobacteriaceae* isolates, CAZ-AVI showed similar sen-

Table 1 Recommended dose for adults with estimated CrCl ≤ 50 mL/min.

Estimated CrCl (ml/min)	CAZ-AVI dose	Interval	Infusion time
31-50	1 g/0.25 g	q 8 h	2 hours
16-30		q 12 h	
6-15	0.75 g/0.1875 g	q 24 h	
Haemodialysis		q 48 h	

CrCl: estimated creatinine clearance using the Cockcroft-Gault formula

sitivity to colistin and tigecycline (73%, 77%, and 78.1%, respectively). Excluding those MBL-producing isolates, CAZ-AVI showed a sensitivity of 95.9% against carbapenemase-producing *Enterobacteriaceae* [6].

PHARMACOKINETIC-PHARMACODYNAMIC CHARACTERISTICS

The administration and dosage regimen is 2 g of ceftazidime and 0.5 g of avibactam in continuous infusion administered over 2 hours with a dosage of three times a day. CAZ-AVI exhibits linear pharmacokinetics. It is poorly bound to proteins and is not metabolized in the liver. Its excretion is renal, so the doses have to be adjusted in renal failure (Table 1). Like all beta-lactams, the predictive pharmacokinetic/pharmacodynamic (PK/PD) therapeutic efficacy index is the time during which free antimicrobial concentrations remain above the minimum inhibitory concentration (MIC) (%*f*T>MIC), expressed as percentage of the dosage interval [7]. The PK/PD parameter related to the efficacy of avibactam is the time during which blood concentrations are above the critical or threshold concentration (CT), which is the minimum concentration of avibactam below which no inhibition of beta-lactamases *in vivo* occurs (%*f*T > CT). The maximum concentration (Cmax) and area under the curve (AUC) increase proportionally with increasing dose of CAZ-AVI. The penetration of CAZ-AVI into the central nervous system is low.

For *Enterobacteriaceae*, suppression of regrowth within 12-24 h was obtained with ceftazidime 2 g every 8 h and continuous infusions of avibactam providing concentrations of 0.25-0.5 mg/L over 4.5 h so that a CT avibactam 0.5 mg/l is sufficient to achieve the pharmacodynamic target of CAZ/AVI against *Enterobacteriaceae*, while *f*T>CT values of up to 62.5% are required for *Pseudomonas*, with CT of 1 mg/ L, to achieve a bacteriostatic effect [8].

CLINICAL EXPERIENCE

The pivotal study for the comparison of CAZ-AVI versus meropenem in nosocomial pneumonia was the REPROVE study, which is a phase 3, multinational study involving 136 centers, double-blinded, and with a non-inferiority design [9]. Clinical cure, clinical response, and mortality outcomes of CAZ-AVI 2/0.5 g were compared. Similar clinical cure rates (67.2% vs. 69.1%; ITT difference -1.9; 95%CI -8.1,4.3) and mortality (9.6% vs. 8.3%; ITT difference 1.5; 95%CI -2.4,5.3) were observed in the comparison of CAZ-AVI with meropenem, thus demonstrating its non-inferiority in the treatment of nosocomial pneumonia.

Data from clinical experience in an outbreak of 57 patients with nosocomial infection by OXA-48-producing *Enterobacteriaceae* showed that CAZ-AVI used as salvage therapy showed clinical cure rates of 77%, microbiological cure of 65% and microbiological failure of the 10%. All isolates showed complete sensitivity to CAZ-AVI [9].

The use of CAZ-AVI versus colistin in the treatment of *K. pneumoniae* was analyzed in an observational, prospective, multicenter study where data were collected from 137 patients whose isolates came mainly from bacteremia (46%) and respiratory isolates (22%) in which 28% were treated with CAZ-AVI and 72% with colistin. Patients treated with CAZ-AVI had a 64% chance of a better outcome compared to those treated with colistin [10]. When CAZ-AVI has been used as salvage therapy, an improvement in the SOFA score has been observed in patients with bacteremia due to carbapenemase-producing *K. pneumoniae* [11].

One of the potential limitations in the use of CAZ-AVI is infections by metallo-beta-lactamase-producing Enterobacteriaceae, where this antibiotic will not be effective. The combination of aztreonam with CAZ-AVI makes it possible to overcome resistance due to the production of MBLs by enterobacteria. This combination allows simultaneous inhibition of multiple PBPs. Data from in-vitro and observational studies have shown that the addition of aztreonam to CAZ-AVI for bacteremic infections with MBL-producing *Enterobacteriaceae* leads to improved outcomes. The 30-day mortality of the combination versus treatment with other antibiotics was significantly lower for the CAZ-AVI and aztreonam group compared with other antibiotics (hazard ratio [HR], 0.37 [95% confidence interval: 0.13-0.74]; p =0.01) and also clinical failure at 14 days and hospital stay [12,13].

Therefore, CAZ-AVI offers very good antibiotic coverage for patients with pneumonia caused by beta-lactamase-producing Gram-negative bacilli. The limitation of CAZ-AVI for the treatment of MBL-producing *Enterobacteriaceae* can be overcome with the addition of aztreonam.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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