

## Update on antimicrobial pharmacotherapy

Mayra Matesanz<sup>1</sup>  
José Mensa<sup>2</sup>

### Ceftazidime-avibactam

<sup>1</sup>Hospital at Home Unit. Department of Internal Medicine. Hospital Clínico San Carlos. Madrid.  
<sup>2</sup>Infectious Diseases Division. Hospital Clinic. Barcelona.

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#### ABSTRACT

Ceftazidime is a 3rd generation cephalosporin active against *Pseudomonas aeruginosa*. Avibactam is an inhibitor of class A, C and some class D  $\beta$ -lactamases. The antibacterial spectrum of ceftazidime-avibactam covers 95% of *P. aeruginosa* isolates and >99% of enterobacteria, including strains carrying extended-spectrum  $\beta$ -lactamases (ESBLs). Selection of resistant mutants in *Klebsiella pneumoniae* and *Enterobacter cloacae* strains producing KPC-3 or KPC-2 after exposure to ceftazidime-avibactam has been described by the appearance of one or more amino acid changes in the  $\Omega$ -loop of the  $\beta$ -lactamase. These strains usually regain susceptibility to meropenem. There is evidence of a shorter multidrug-resistant organisms colonization period in patients treated with this antimicrobial, which could be beneficial in the treatment of infections caused by bacteria carrying ESBLs or carbapenemases.

**Keywords:** Ceftazidime-avibactam, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, KPC-2, KPC-3, decolonization.

Ceftazidime is a 3rd generation cephalosporin active against *Pseudomonas aeruginosa*, which in the 1990s was widely used in monotherapy or associated with an aminoglycoside, in empirical treatment regimens for fever in neutropenic patients [1-3]. With the appearance of extended-spectrum  $\beta$ -lactamases (ESBLs) around the year 2000, its indications were progressively reduced to the targeted treatment of infections caused by *P. aeruginosa*. Avibactam is an inhibitor of class A  $\beta$ -lactamases, including TEM, SHV, CTX-M, KPC, GES, PER, SME; chromosomal class C (AmpC) and plasmid class C such as FOX, MOX, CMY, LAT, ACC, DHA; and some class D such as OXA-48 from *Klebsiella pneumoniae*, and OXA-24, OXA-40

and OXA-69 from *Acinetobacter baumannii*. Activity against OXA-2, OXA-5/10 and OXA-50 is limited; it is not active against class B  $\beta$ -lactamases (metallo- $\beta$ -lactamases). Against most  $\beta$ -lactamases it behaves as a reversible (non-suicidal) inhibitor. Avibactam forms a covalent bond with the serine of the active center of the  $\beta$ -lactamase but, unlike what occurs with clavulanic acid and tazobactam, the molecule is not hydrolyzed, but is slowly separated and recovers its original structure. This mechanism of action, together with the broad spectrum of activity against the different  $\beta$ -lactamases (including carbapenemases KPC, OXA-48) and an elimination half-life of 2.5 hours (longer than that of clavulanic acid, tazobactam and relebactam), justify the greater effectiveness observed in a hollow fiber infection model, in which the effectiveness of the piperacillin association was compared with each of the three  $\beta$ -lactamase inhibitors, tazobactam, avibactam and relebactam. The % fT > MIC of the combination of piperacillin with avibactam (61.4%-73.6%) was significantly higher than that of tazobactam (13.5%-44.5%) in suppressing bacterial growth of 3 clinical isolates, 2 CTX-M-15-producing *K. pneumoniae* and 1 SHV-12-producing *Escherichia coli* isolate [4].

The antibacterial spectrum of ceftazidime-avibactam (CAZ-AVI) covers 95% of *P. aeruginosa* isolates and >99% of enterobacteria [5]. A 2017 study in 51 Spanish hospitals included up to 30 consecutive healthcare-associated *P. aeruginosa* isolates collected from each of the participating hospitals and determined the MICs of 13 potentially active antibiotics. Colistin and ceftolozane-tazobactam were active against 94.6% of isolates (MIC<sub>50/90</sub> = 1/2 mg/L), followed by CAZ-AVI with 94.2% of sensitive isolates (MIC<sub>50/90</sub> = 2/8 mg/L). Four isolates showed mutations in AmpC determinants of resistance to ceftolozane-tazobactam and CAZ-AVI (6). Against enterobacteria, the spectrum of ceftazidime-avibactam is the broadest of the antimicrobials available to date. In a study conducted during 2017-2018 in 70 medical centers in the United States, 3269 enterobacteria were consecutively collected from patients with pneumonia, community or nosocomial origin,

Correspondence:  
Mayra Matesanz  
Hospital at Home Unit.  
Department of Internal Medicine.  
Hospital clinico San Carlos. Madrid.  
E mail: mayra.matesanz@salud.madrid.org

and tested for sensitivity by broth microdilution methods. The most active agents were CAZ-AVI with susceptibility percentages of 99.9%, amikacin 98.7%, meropenem 97.4% and tigecycline 94.6%, but only CAZ-AVI and tigecycline retained good activity ( $\geq 90\%$  susceptible) against carbapenem-resistant isolates (97.5% and 92.4% susceptible, respectively). The most active agents against multidrug-resistant *Enterobacteriaceae* were CAZ-AVI with 99.2% of susceptible isolates and amikacin 90.9%, whereas ceftolozane-tazobactam and meropenem were only active against 53.8% and 78.1% of these organisms, respectively. Among ESBL-producing *Enterobacteriaceae* (excluding carbapenemase-producing *Enterobacteriaceae*), the susceptibility rates to CAZ-AVI, ceftolozane-tazobactam, and meropenem were 100.0%, 84.1%, and 98.9%, respectively [7].

In *K. pneumoniae* and *Enterobacter cloacae* strains producing KPC-3 or KPC-2, exposure to CAZ-AVI can select resistant mutants by the appearance of changes in one or more amino acids of the  $\Omega$ -loop of the  $\beta$ -lactamase. These strains usually regain susceptibility to meropenem [8-10]. The development of resistance in the course of treatment has been observed in patients with pneumonia and renal failure requiring continuous renal replacement techniques [9]. Resistance is probably the consequence of insufficient antibiotic dosage in the presence of a high bacterial load. In vitro, the association of CAZ-AVI with a carbapenem can prevent the selection of these mutants [11]. In *K. pneumoniae*, PBP3 is the main target of ceftazidime, cefepime, and aztreonam, whereas PBP2 is the main target of carbapenems. Complete blockade of both PBPs, obtained with the association of CAZ-AVI with a carbapenem, may have a synergistic effect [12].

Among the non-fermenting gram-negative bacilli, *Burkholderia cepacia* complex, *B. gladioli* and about 50% of *Achromobacter* strains are susceptible to CAZ-AVI. The susceptibility of *Acinetobacter* spp to ceftazidime is not modified by the presence of avibactam, probably due to its low diffusion through the bacterial wall. *Stenotrophomonas maltophilia*, *Elizabethkingia meningoseptica* and *Aeromonas* spp. produce a chromosomal metallo- $\beta$ -lactamase not inhibitable with avibactam. However, up to 30% of *S. maltophilia* isolates are susceptible to CAZ-AVI. Avibactam restores aztreonam activity against *S. maltophilia* and other GNBs when they, in addition to a metallo- $\beta$ -lactamase produce an ESBL.

Intestinal colonization by KPC-producing *K. pneumoniae* (Kp-KPC) is an important risk factor for developing systemic infection by the same strain. Different orally administered non-absorbable antibiotics have been used to decolonize or reduce the bacterial load of the intestinal microbiota. On average, these regimens succeed in decolonizing 60% of patients, but after discontinuation of treatment, within a few days/weeks, patients recolonize. In a retrospective, observational, multicenter, retrospective study, we compared the rate of intestinal decolonization of Kp-KPC under treatment with CAZ-AVI alone or associated with other antibiotics (Group A) versus treatment regimens based on other antimicrobial regimens (Group B) in patients with Kp-KPC infection. Eleven of the 12 patients in Group A (91.7%), achieved intestinal decolonization, compared

to none of the 24 patients in Group B. Group A patients remained decolonized for a mean follow-up of 39.5 days [13,14]. If these results are confirmed, the possibility of decolonization is a serious argument for considering CAZ-AVI as first-choice treatment in infection by ESBL or carbapenemase-producing enterobacteria.

Clinical experience with the use of CAZ-AVI has been reported in several studies. The results of interest from some of the most relevant studies are briefly discussed below. In an observational study conducted in two ICUs, the clinical course of 102 patients with Kp-KPC bacteremia of intra-abdominal (23.5%), urinary tract (20.6%) and skin and soft tissue (17.6%) origin was analyzed. Patients treated with CAZ-AVI-containing regimens had a lower risk of 30-day mortality or nephrotoxicity (HR 0.231 [95% CI 0.071-0.745],  $p = 0.014$ ) compared with those receiving colistin-containing regimens.

Another retrospective, observational study analyzed a cohort of 577 adults with KPC-Kp infection, of whom 391 cases developed bacteremia. All were treated with CAZ-AVI, either as monotherapy ( $n=165$ ) or in association with other active antibiotics ( $n=412$ ). All-cause mortality 30 days after the onset of infection was 25% (146/577). There was no statistically significant difference in mortality between patients treated with CAZ-AVI monotherapy and those treated with combination regimens (26.1% vs. 25.0%,  $p=0.79$ ). In multivariate analysis, 30-day mortality was positively associated with the presence of septic shock ( $P=0.002$ ), neutropenia ( $P<0.001$ ), with an IN-CREMENT score  $>8$  ( $P=0.01$ ), with pneumonia ( $P=0.04$ ), and with dose adjustment of CAZ-AVI for renal function ( $P=0.01$ ). Mortality was negatively associated with CAZ-AVI administration by prolonged infusion ( $P=0.006$ ) [15].

In two intensive care units in Greece, the clinical course of critically ill and mechanically ventilated patients with carbapenem-resistant *Enterobacteriaceae* infection was studied. Forty-one patients were treated with CAZ-AVI and 36 with the best available appropriate antibiotic therapy (other than CAZ-AVI). Significant improvement in SOFA scale score was observed at days 4 and 10 in the CAZ-AVI group compared to the control group ( $P 0.006$  and  $P 0.003$ , respectively). Microbiological eradication was achieved in 33/35 (94.3%) patients in the CAZ-AVI group and in 21/31 (67.7%) patients in the control group ( $P 0.021$ ), and clinical cure was observed in 33/41 (80.5%) vs. 19/36 (52.8%) patients ( $P 0.010$ ), respectively. The results were similar in patients with bacteremia. Survival at 28 days was 85.4% in the CAZ-AVI group and 61.1% in the control group (log-rank test 0.035). There were 2 and 12 relapses in the CAZ-AVI and control groups, respectively ( $P 0.042$ ). The CAZ-AVI-containing regimen was an independent predictor of clinical survival and cure (odds ratio [OR] 5.575 and  $P 0.012$  and OR 5.125 and  $P 0.004$ , respectively), as was disease severity. No significant side effects were recorded [16].

The association of avibactam with aztreonam is active in vitro against class B  $\beta$ -lactamase-producing enterobacteria. Several studies have been published analyzing the potential clinical efficacy of this association. A prospective observational

study conducted in 3 hospitals in Italy and Greece included 102 patients with bacteremia due to metallo- $\beta$ -lactamase-producing enterobacteria treated with ceftazidime-avibactam and aztreonam (CAZ-AVI + ATM) or with associations of other in vitro active antibiotics; in 82 cases the infection was caused by NDM-producing strains (79 *K. pneumoniae* and 3 *Escherichia coli*) and in 20 cases by VIM-producing strains (14 *K. pneumoniae*, 5 *Enterobacter* species, 1 *Morganella morganii*). Mortality at 30 days was 19.2% in the CAZ-AVI + ATM group vs. 44% in the other antibiotics group ( $p = 0.007$ ). In a logistic regression analysis, treatment with CAZ-AVI + ATM was associated with lower 30-day mortality ( $P = 0.01$ ), lower clinical failure at day 14 ( $P = 0.002$ ), and shorter length of hospital stay ( $P = 0.007$ ) [17].

In conclusion, the extensive and favorable experience gained with the use of ceftazidime, the antibacterial spectrum of the association of ceftazidime with avibactam (> 99% of *Enterobacteriaceae* and  $\approx 95\%$  of *P. aeruginosa* susceptible) and the potential decolonizing effect on the fecal microbiota, make CAZ-AVI one of the first options for the empirical treatment of nosocomial infection with possible involvement of gram-negative bacilli, especially if it presents with severity criteria or occurs in the "fragile" patient. The use of CAZ-AVI also reduces the consumption of carbapenems.

## CONFLICTS OF INTEREST

The authors declare no conflict of interests.

## REFERENCES

- Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986; 315: 552-8.
- Lindblad R, Rödger S, Adriansson M, et al. Empiric monotherapy for febrile neutropenia--a randomized study comparing meropenem with ceftazidime. *Scand J Infect Dis* 1998; 30: 237-43.
- Fleischhack G, Hartmann C, Simon A, et al. Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer. *J Antimicrob Chemother* 2001; 47: 841-53.
- Abodakpi H, Chang KT, Zhou J, et al. A novel framework to compare the effectiveness of  $\beta$ -lactamase inhibitors against extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae*. *Clin Microbiol Infect* 2019; 25: 1154.
- Yahav D, Giske CG, Grāmatniece A, et al. New  $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations. *Clin Microbiol Rev* 2020; 34: e00115-20.
- Del Barrio-Tofiño E, Zamorano L, Cortes-Lara S, et al. Spanish nationwide survey on *Pseudomonas aeruginosa* antimicrobial resistance mechanisms and epidemiology. *J Antimicrob Chemother* 2019; 74: 1825-35.
- Sader HS, Flamm RK, Carvalhaes CG, Castanheira M. Comparison of ceftazidime-avibactam and ceftolozane-tazobactam in vitro activities when tested against gram-negative bacteria isolated from patients hospitalized with pneumonia in United States medical centers (2017-2018). *Diagn Microbiol Infect Dis* 2020; 96: 114833.
- Livermore DM, Warner M, Jamroz D, et al. In vitro selection of ceftazidime-avibactam resistance in *Enterobacteriaceae* with KPC-3 carbapenemase. *Antimicrob Agents Chemother* 2015; 59: 5324-30.
- Shields RK, Nguyen MH, Chen L, et al. Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections. *Antimicrob Agents Chemother* 2018; 62: e02497-17.
- Hemarajata P, Humphries RM. Ceftazidime/avibactam resistance associated with L169P mutation in the omega loop of KPC-2. *J Antimicrob Chemother* 2019; 74: 1241-3.
- Compain F, Arthur M. Impaired Inhibition by Avibactam and Resistance to the Ceftazidime-Avibactam Combination Due to the D 179 Y Substitution in the KPC-2  $\beta$ -Lactamase. *Antimicrob Agents Chemother* 2017; 61: e00451-17.
- Sutaria DS, Moya B, Green KB, et al. First Penicillin-Binding Protein Occupancy Patterns of  $\beta$ -Lactams and  $\beta$ -Lactamase Inhibitors in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2018; 62: e00282-18.
- Bassetti M, Carannante N, Pallotto C, et al. KPC-producing *Klebsiella pneumoniae* gut decolonisation following ceftazidime/avibactam-based combination therapy: A retrospective observational study. *J Glob Antimicrob Resist* 2019; 17: 109-11.
- Falcone M, Bassetti M, Tiseo G, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*. *Crit Care* 2020; 24: 29.
- Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study. *Clin Infect Dis* 2021.
- Tsolaki V, Mantzarlis K, Mpakalis A, et al. Ceftazidime-Avibactam To Treat Life-Threatening Infections by Carbapenem-Resistant Pathogens in Critically Ill Mechanically Ventilated Patients. *Antimicrob Agents Chemother* 2020; 64: e02320-19.
- Falcone M, Daikos GL, Tiseo G, et al. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo- $\beta$ -lactamase-Producing *Enterobacteriales*. *Clin Infect Dis* 2021; 72: 1871-8.