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Short Communication

Evaluation of ceftazidime/avibactam for serious infections due to multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa*

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ABSTRACT

Objectives: The steady progress in resistance of *Pseudomonas aeruginosa* (PA) has led to difficulties in treating infections due to multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Ceftazidime/avibactam (CAZ/AVI) has in vitro activity against many of these strains, however clinical experience with CAZ/AVI is limited. This study aimed to evaluate the characteristics and outcomes of eight patients with infections due to MDR- or XDR-PA treated with CAZ/AVI, including four strains resistant to ceftolozane/tazobactam.
Methods: This was a retrospective descriptive study of patients admitted to a teaching hospital between January 2016 and May 2017 who received CAZ/AVI as initial or continuation therapy for infection due to MDR- and XDR-PA.
Results: The sources of infection were hospital-acquired lower respiratory tract infection in five patients (62.5%) and osteomyelitis, meningitis and catheter-related bacteraemia in one patient each. Clinical cure was achieved in 4 patients (50.0%). The 30-day and 90-day mortality rates were 12.5% and 37.5%, respectively. One patient (12.5%) developed encephalopathy that improved with discontinuation of the drug.
Conclusions: CAZ/AVI may be a valuable option for serious infections due to resistant PA.

1. Introduction

The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* (PA) has become a serious problem since both are frequently related to healthcare-associated infections with significant morbidity and mortality. Nevertheless, the introduction of a new generation of antimicrobial agents, such as ceftolozane/tazobactam (C/T) and ceftazidime/avibactam (CAZ/AVI), has marked a milestone in the era of MDR Gram-negative bacilli. The clinical role of C/T in infections due to PA, including MDR and XDR strains, is being increasingly acknowledged [1–4]. However, the number of studies supporting the use of CAZ/AVI in PA infections is limited [5,6]. The novel non-β-lactam β-lactamase inhibitor avibactam has in vitro activity against Ambler class A, class C and some class D serine β-lactamases. As long as resistance to antipseudomonal cephalosporins in PA is mediated by the overproduction of an AmpC enzyme or, less often, by the acquisition of a class A β-lactamase, it is expected that avibactam will restore the activity of ceftazidime against these resistant strains [7].

Based on this, here we described our experience with the use of CAZ/AVI in eight patients with MDR- or XDR-PA infections and evaluated their characteristics and outcomes.

2. Materials and methods

This was a retrospective study performed between January 2016 and May 2017 in a 750-bed tertiary-care teaching hospital

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and represents an expansion of a previous work [6]. Patient data were collected from the hospital electronic records. Isolate identification and antimicrobial susceptibility testing were performed by matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) and by disk diffusion or Etest, respectively. Minimum inhibitory concentrations (MICs) were classified according to current European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. Antimicrobial-resistant PA was classified according to the definition of Magiorakos et al. [8]. The standard dosage of CAZ/AVI consisted of 2 g of ceftazidime with 0.5 g of avibactam intravenously as a 2-h infusion every 8 h and the dosage was adjusted in case of kidney failure according to the manufacturer's recommendations. When data for this study were collected, the antibiotic had not been approved in the European Union so it was prescribed based on the compassionate-use programme. Appropriate empirical treatment was defined as receiving at least one active drug within the first 48 h after sample collection and before antimicrobial susceptibility was reported. Clinical cure was considered as survival, resolution of symptoms and signs of infection, and absence of relapse at 30 days following the end of treatment with CAZ/AVI. Overall mortality at 30 days and 90 days after sample collection was recorded. The study was approved by the ethics committee of Hospital Clínic de Barcelona (Barcelona, Spain).

3. Results

Eight patients received CAZ/AVI for $\geq$72 h as treatment for infection due to MDR- or XDR-PA. A brief description of the cases follows.

3.1. Patient 1

A 69-year-old male with cerebral abscess caused by *Escherichia coli* developed fever without any clinical source 1 month after hospital admission. XDR-PA was isolated from blood and catheter cultures (meropenem MIC = 8 mg/L), hence 2 g of meropenem every 8 h and intravenous (i.v.) colistimethate were initiated. After 1 week of treatment the patient remained febrile and respiratory symptoms appeared. A computed tomography (CT) scan revealed the presence of multiple cavitary nodules suggestive of embolic lung infection. XDR-PA was isolated from a bronchoalveolar lavage sample (meropenem MIC = 16 mg/L). Susceptibility testing to C/T and CAZ/AVI was not performed. Owing to the high risk of developing acute kidney injury (AKI), treatment with CAZ/AVI and nebulised colistimethate was administered. CT performed 3 weeks later showed complete resolution of the abscess and antimicrobials were discontinued after 29 days of therapy. The patient was alive at 90 days.

3.2. Patient 2

A 58-year-old female with a history of renal transplantation due to diabetic nephropathy had an episode of acute transplant rejection 1 month before admission and received immunosuppressive treatment with methylprednisolone pulses. She presented a 2-week history of malar pain and neurological impairment. A CT scan revealed extensive left rhinosinusitis with bone erosion of the ethmoidal cells. Cerebrospinal fluid (CSF) analysis showed purulent meningitis and the patient was transferred to the intensive care unit (ICU) under empirical treatment with meropenem and ciprofloxacin. An urgent maxillofacial operation was performed and XDR-PA was isolated from intraoperative cultures. Intravenous colistimethate was initiated. CSF cultures were negative but 16S rRNA gene PCR confirmed PA. Susceptibility testing to C/T and CAZ/AVI could not be performed. A regimen consisting of CAZ/AVI plus i.v. colistimethate was considered the best option. One week later the patient developed AKI (attributed to the colistimethate), hence monotherapy with CAZ/AVI was continued for 31 days. The patient was alive at 90 days.

3.3. Patient 3

A 64-year-old male receiving chronic haemodialysis due to vascular disease and diabetes presented a chronic diabetic foot ulcer and calcaneus osteomyelitis. In a smear obtained from the ulcer, a carbapenem-resistant MDR-PA was isolated and initial empirical treatment with meropenem was switched to gentamicin plus ciprofloxacin. One day later this regimen was optimised to CAZ/AVI, tobramycin and ciprofloxacin and was administered for 34 days as hospital-at-home care with clinical improvement. For orthopaedic reasons, a calcaneus osteotomy was performed 1 month later. Culture of the bone yielded *Corynebacterium striatum* but there was no evidence of PA. The patient was alive after 90 days.

3.4. Patient 4

A 64-year-old male diabetic patient had a pneumectomy for lung cancer complicated by a bronchopleural fistula of the right main bronchus stump. After 1 month of hospitalisation he was diagnosed with bacteraemic ventilator-associated pneumonia (VAP) caused by XDR-PA. The strain was resistant to C/T (MIC > 256 mg/L) but was susceptible to CAZ/AVI (by disk diffusion). CAZ/AVI plus nebulised colistimethate were initiated after the microbiological report, but on the seventh day of therapy the patient died of refractory septic shock.

3.5. Patient 5

A 51-year-old male with cirrhosis (Child–Pugh class C) and cardiovascular disease was admitted to the ICU owing to ascites and pleural effusion with AKI. During his hospital stay he developed pneumonia with empyema. A pleural drainage was placed and empirical therapy with i.v. meropenem and amikacin was started. An XDR-PA susceptible both to C/T (MIC = 1 mg/L) and CAZ/AVI (by disk diffusion) was isolated from sputum and pleural fluid, and monotherapy with amikacin was continued. Following initial improvement, on Day 13 of therapy the patient presented respiratory worsening and AKI, hence C/T plus nebulised amikacin were prescribed. During the following week the patient presented an unfavourable clinical course and C/T was replaced by CAZ/AVI in monotherapy. After 9 days the patient died due to multiorgan failure.

3.6. Patient 6

A 65-year-old male with a history of diabetes, a permanent tracheotomy after excision of tracheal squamous cancer and bronchiectasis was admitted with respiratory failure due to an acute exacerbation caused by XDR-PA. Since the strain was resistant to C/T (MIC = 64 mg/L), CAZ/AVI (MIC = 6 mg/L) plus nebulised colistimethate were administered for 10 days. The patient had a favourable clinical course. However, microbiological success was not achieved at the end of therapy and tracheobronchitis recurred 30 days later. He was alive at 90 days.

3.7. Patient 7

A 71-year-old male renal transplant patient was admitted to the ICU with *Pneumocystis jirovecii* pneumonia and invasive