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Ceftazidime-avibactam as a salvage therapy for infections caused by carbapenem-resistant enterobacteriacee. An experience from real life

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ABSTRACT:

— ***Objective:*** The proportion of Gram-negative infections caused by carbapenem-resistant strains is increasing. Treatment options are limited by high toxicity rates, suboptimal pharmacokinetics and/or known microbiological resistance. Our aim was to assess in-hospital mortality, microbiologic cure and clinical success of an antimicrobial therapy with ceftazidime/avibactam.

— ***Patients and Methods:*** We present a case series of 6 patients with infection caused by CRE who were treated with ceftazidime/avibactam therapy on a compassionate-use basis in a single Center.

— ***Results:*** All isolates were classified as resistant to carbapenems. Ceftazidime/avibactam was used in combination therapy in 3 cases, in all cases as a carbapenem-sparing regimen. All patients experienced clinical and microbiological cure at the end of treatment. No in-hospital mortality occurred in this small cohort of patients. No difference in outcome was observed between monotherapy or combination therapy in terms of microbiological clearance or mortality. No relapses were documented.

— ***Conclusions:*** Taken together, the data from this and other studies support the importance of ceftazidime-avibactam in the treatment of patients with CRE infections, including those who are acutely ill. However, we outline the fact that we must not be too confident on ceftazidime-avibactam as the solution for carbapenem-resistant *Enterobacteriaceae* as report of relapse, resistance, and clinical failure are increasing.

— ***Keywords:*** Klebsiella, KPC, Ceftazidime-Avibactam.

INTRODUCTION

The proportion of Gram-negative infections caused by carbapenem-resistant strains is increasing. According to surveillance of antimicrobial resistance in Europe, the proportion of *Klebsiella spp* isolated from blood that are carbapenem-resistant is now 33.9% in Italy[1].

Treatment options are limited by high toxicity rates (aminoglycosides, colistin), suboptimal pharmacokinetics (colistin, tigecycline), and/or known microbiological resistance (carbapenems). Mortality rates as high as 60% have been reported in numerous studies[2,3]. Ceftazidime/avibactam (CAZ/AVI) is a new beta-lactam-b-lactamase inhibitor combination indicated for treatment of complicated urinary tract infection and complicated intra-abdominal infections in adults with limited therapeutic options. Avibactam is not active against metallo-beta-lactamase enzymes. A promising scenario is the potential to treat infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenem-resistant *Pseudomonas aeruginosa*.

Clinical experience out of clinical trials is limited as ceftazidime/avibactam in Italy is available as a compassionate use only and is limited to case series of salvage use[4] or retrospective studies[5,6].

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PATIENTS AND METHODS

We present a case series of 6 patients with infection caused by CRE who were treated with ceftazidime/avibactam therapy on a compassionate-use basis in a single center.

Primary outcome was in-hospital mortality. Secondary outcomes were microbiologic cure, defined as a negative culture at the end of therapy, and clinical success, defined as improved signs and symptoms from baseline to the end of therapy, with defervescence.

RESULTS

Sample

Ceftazidime/avibactam was required for seven patients in our Center, for CRE infections.

Six patients were treated, while one did not receive the drug because of clinical improvement before ceftazidime/avibactam delivery. The following data are then referred to the six treated patients.

Four patient received ceftazidime/avibactam as a salvage therapy after failure or toxicity of previous treatment. Two patients received ceftazidime/avibactam as first treatment of a pan-resistant complicated IVU infection

Microbiology

All isolates were classified as resistant to carbapenems (carbapenem MIC > 64 in all cases). Genotypic analysis of the resistance mechanism was not available for the majority of patients; in one case a VIM-pattern of carbapenem-resistance was identified.

Five patients out of six had a CRE infection caused by *Klebsiella pneumoniae*. One patient was affected by nosocomial pneumonia by carbapenem-resistant *Pseudomonas aeruginosa*.

Disk diffusion test for ceftazidime-avibactam susceptibility was available for 4 isolates out of six: in 3 cases in the range of susceptibility, in 1 case the test revealed resistance, but the drug was nevertheless used as a component of salvage therapy because of clinical improvement at the moment of receipt of microbiological result. Subsequent molecular analysis outlined a VIM pattern of resistance in this case

Patients' demographic and clinical characteristics

Six patients were included. The median age was 65 years (range 22-85 years). Median Charlson Index was 3 (1-7). Most common comorbidities were: being bedridden (5), cachexia (4), previous ICU admission (3). Primary bacteremia was diagnosed in 2 patients, while the other cases clinical diagnosis were either pneumonia (n=2), or complicated urinary tract infections (n=2). Median Pitt bacteremia score was 1 (0-2). A high degree of acute illness was identified in 3/6 patients (2 bacteremia, one septic shock with disseminated intravascular coagulation, one ventilator pneumonia)

Prior treatment

Five patients received antibiotic therapy before ceftazidime/avibactam (median 2 drugs). The median duration of treatment before ceftazidime/avibactam was 4.5 days (0-10). The treatment needed to be modified because of failure in two cases and or renal toxicity in three cases.

Ceftazidime-avibactam treatment

Ceftazidime/avibactam was used in combination therapy in 3 cases, in all cases as a carbapenem-sparing regimen. The most commonly co-prescribed agents were colistin (2), tigecycline (2), fosfomicin (1), and rifampin (1). In 3 cases ceftazidime/avibactam was used as a monotherapy, in two cases to treat complicated IVU infections without bacteremia, in the other case because no other appropriate treatment was available. The median duration of ceftazidime-avibactam therapy was 14 days (10-28). Two patients needed reduction of standard dose for renal insufficiency.

Outcome

All patients experienced clinical and microbiological cure at the end of treatment. No in-hospital mortality occurred in this small cohort of patients. No difference in outcome was observed between monotherapy or combination therapy in terms of microbiological clearance or mortality. No relapses were documented.

In one case of prolonged bacteremia a *Klebsiella pneumoniae* with a VIM pattern of resistance and disk diffusion test in the range of resistance to ceftazidime/avibactam was documented, but bacteremia resolved with combination therapy (FOSF-TIG- CAZAVI) and device removal. No adverse events were attributed to ceftazidime-avibactam.

DISCUSSION

This is the first report of a clinical experience with ceftazidime-avibactam from real life in Italy. The good news is that no overall mortality was observed, the bad news is that in a two-year period in a single center we needed a compassionate-use drug to treat an otherwise incurable disease. No difference in outcome was recorded between combination and monotherapy; however, the last one was reserved to less severe infections or complicated urinary tract infections in most cases. In one case resistance to ceftazidime-avibactam was sustained by an intrinsically resistant strain harboring a VIM-pattern of resistance. Our experience compares favorably with those reported

in other studies where clinical outcomes have been highly variable. In a single-center retrospective case series ceftazidime/avibactam was administered as the first drug to treat CRE infections, in 70% of cases as a monotherapy. Reported clinical success was 59%. Unfortunately, there was an alarmingly high rate (24%) of relapse from CRE after completion of therapy [6]. Shields et al[7] recently compared outcome of carbapenem-resistant *Klebsiella pneumoniae* bacteremia treated with ceftazidime/avibactam (n=13) *vs.* other treatment regimens (n=96), outlining higher rates of clinical success (p=0-006) and survival (p=0.01) with ceftazidime/avibactam. In a small cohort of patients, ceftazidime/avibactam was used as a monotherapy for salvage therapy: clinical and microbiological cure was achieved for the three-treated patients[8].

King et al[5] report results of a cohort of patients with CRE infections and a high degree of acute illness treated with ceftazidime/avibactam (50% monotherapy). The overall in-hospital mortality rate in this study was 32% (19/60). In-hospital mortality rate was highest for patients with pneumonia. There was no significant difference in the rates of in-hospital mortality for patients receiving combination therapy *vs.* monotherapy (33% *vs.* 30%, p ns) or for patients with or without bacteremia (39% *vs.* 27% p= 0.397)[5].

Temkin et al[4] described a case series of 37 patients treated with ceftazidime/avibactam as a salvage therapy (34.2% in monotherapy). Clinical and/or microbiological cure was obtained for 74% of patients (69.2% for monotherapy, 76% in combination therapy). All cause in-hospital mortality was 39%.

At last, very recently van Duin et al[9] report a superiority of ceftazidime/avibactam *vs.* colistin in the treatment of infections due to CRE selected from the CRACKLE study, a prospective, multicenter, observational study. A significant decrease in all-cause hospital mortality rate was observed (8% *vs.* 33% p=.001); in 37% of cases, ceftazidime/avibactam was used as a monotherapy[9]. In our small case series, a selection bias was certainly due to the enrolment of patients expected to survive long enough to receive the drug after Ethical Committee approval and drug delivery in most cases; however, a high degree of acute illness was identified in 3/6 patients (2 with pneumonia and 1 with sepsis due to DVA infection). Other confounders include administration of additional antibiotics, which differed between patients, dosing regimens, and comorbidities.

Taken together, the data from this study and others support the importance of ceftazidime-avibactam in the treatment of patients with CRE infections, including those who are acutely ill. However, we outline the fact that we must not be too confident on ceftazidime-avibactam as the solution for carbapenem-resistant *Enterobacteriaceae* as report of relapse, resistance and clinical failure are increasing[6,10].

CONCLUSIONS

We sustain the importance of obtaining a genomic study of carbapenemases by polymerase chain reaction for all strains of invasive infections and support combination therapy as the first line for severe infections.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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