Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

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Thirty-seven carbapenem-resistant Enterobacteriaceae (CRE)-infected patients were treated with ceftazidime-avibactam. Clinical success and survival rates at 30 days were 59% (22/37) and 76% (28/37), respectively. In 23% (5/22) of clinical successes, CRE infections recurred within 90 days. Microbiologic failure rate was 27% (10/37). Ceftazidime-avibactam resistance was detected in 30% (3/10) of microbiologic failures.

Keywords. ceftazidime-avibactam resistance; carbapenem-resistant Enterobacteriaceae; *Klebsiella pneumoniae* carbapenemase.

Ceftazidime-avibactam is a novel β-lactam/β-lactamase inhibitor combination that was recently approved by the US Food and Drug Administration for the treatment of complicated intraabdominal and complicated urinary tract infections [1]. The agent demonstrates in vitro activity against carbapenem-resistant Enterobacteriaceae (CRE) that produce *Klebsiella pneumoniae* carbapenemase (KPC), but not metallo-β-lactamases such as New Delhi MBL (NDM), Verona integron-encoded MBL (VIM), or imipenemase (IMP) [2]. Ceftazidime-avibactam may offer a significant advance over previously developed antimicrobials with in vitro activity against CRE, such as colistin, gentamicin, and tigecycline, which are limited by concerns over efficacy and/or toxicity. Our objective in this study was to describe our initial clinical experience with ceftazidime-avibactam against CRE infections.

METHODS

We conducted a retrospective study of patients with CRE infection who were treated with ceftazidime-avibactam at the University of Pittsburgh Medical Center between April 2015 and February 2016. CRE was defined by current Centers for Disease Control and Prevention criteria as resistance to any carbapenem [3]. A standard dosage of 2.5 g intravenously (IV) every 8 hours was used, with adjustments for renal impairment made according to manufacturer recommendations [1]. Types of CRE infection were classified according to National Healthcare Safety Network criteria [4]. Clinical success was defined as survival and absence of recurrence at 30 days following the onset of infection, resolution of signs and symptoms of infection, and sterilization of site-specific cultures within 7 days of treatment initiation. Microbiologic failure was defined as isolation of CRE following ≥7 days of ceftazidime-avibactam treatment. Recurrences within 90 days of onset were defined by microbiologic failure and concomitant signs of infection. Minimum inhibitory concentrations (MICs) were determined using reference Clinical and Laboratory Standards Institute broth microdilution methods; avibactam was tested at a fixed concentration of 4 μg/mL [2]. Isolates were tested for the presence of β-lactamases as described previously [5, 6]. Comparisons between groups were made using Fisher exact test (categorical variables) and Mann–Whitney U (continuous variables). Significance was defined as $P \leq .05$ (2-tailed).

RESULTS

Thirty-seven consecutive patients treated for 3 days or longer with ceftazidime-avibactam were evaluated. Median age was 64 years (range, 26–78); 57% (21/37) were men. Median Charlson comorbidity index score was 4 (range, 0–10). Thirty percent (11/37) were transplant recipients (9 solid organ and 2 bone marrow). At the onset of infection, the median simplified acute physiology score II was 34 (range, 8–79) and the mean sequential organ failure assessment (SOFA) score was 5 (range, 0–20). Infections included pneumonia (n = 12; 50% [6/12] ventilator-associated; 50% [6/12] healthcare-associated), primary bacteremia (n = 10), intraabdominal infection (n = 4), skin/soft tissue infection (n = 4), pyelonephritis (n = 4; 50% [2/4] resulted in secondary bacteremia), and mediastinitis, subdural empyema/ventriculitis, and purulent tracheobronchitis (1 each). CR-*K. pneumoniae* (CR-Kp) was the predominant pathogen (84%, 31/37), followed by CR-*Escherichia coli* (8%, 3/37), CR-*Enterobacter cloacae* (5%, 2/37), and CR-*Enterobacter aerogenes* (3%, 1/37).

All initial CRE isolates were resistant to cephalosporins and susceptible to ceftazidime-avibactam (median MIC = 1 µg/mL [range, 0.25–4]). Seventy-eight percent (29/37) of isolates harbored a bla_{KPC} gene, including 90% (28/31) of CR-Kp. Eighty-seven percent (27/31) of CR-Kp were sequence type (ST)-258; 39% (12/31) carried bla_{KPC-2} and 52% (16/31) carried bla_{KPC-3}. No isolates had genes encoding NDM, VIM, IMP, or oxacillinase (OXA)-48-like carbapenemases. The 8 non-KPC producing CRE isolates carried cefotaximase (n = 7), OXA-1-like (n = 4), extended spectrum β lactamase sulhydryl variable (n = 1), and AmpC β-lactamases (n = 1).

Ceftazidime-avibactam was administered as monotherapy or in combination regimens in 70% (26/37) and 30% (11/37) of patients, respectively. All combination agents were started concomitantly with ceftazidime-avibactam and administered for 72 hours or longer. Combinations included intravenous (n = 7) or inhaled (n = 1) gentamicin, intravenous (n = 1) or intrathecal (n = 1) colistin, and tigecycline (n = 1). Median treatment duration was 14 days (range, 4–71).

The 30-day survival rate was 76% (28/37) and the 90-day survival rate was 62% (23/37). Clinical success was achieved in 59% (22/37) and did not differ for patients receiving monotherapy (58% [15/26]) or combination therapy (64% [7/11]). Failures were due to death (n = 9), recurrence (n = 4), or the absence of clinical improvement (n = 2). Success rates were 100% (4/4) for patients with pyelonephritis, 70% (7/10) for primary bacteremia, 50% for pneumonia (6/12), 50% (2/4) for skin/soft tissue infections, 50% (2/4) for intraabdominal infections, and 33% (1/3) for other infections. Success rates were lower for patients who required continuous renal replacement therapy (CRRT; 17% [1/6] vs 68% [21/31], P = .03); dosages ranged from the standard dosage to 0.94 g IV every 12 hours. Among the remaining patients, success rates did not vary by baseline creatinine clearance (<30, 31–50, or >50 mL/min (100% [2/2], 67% [6/9], and 65% [13/20], respectively). At the onset of infection, mean SOFA scores were significantly lower for patients with clinical success (5.2 vs 8.8, P = .047); no other clinical or microbiologic factors were predictive of success.

Microbiologic failures occurred in 27% (10/37) of patients due to recurrent infections within 30 (n = 5) and 90 days (n = 4) and urinary colonization (n = 1) with CRE (Table 1). Twenty-three percent (5/22) of patients with 30-day clinical success had recurrent CRE infections at the same or contiguous sites subsequently; median time to recurrence was 74 days (range, 34–84). Ceftazidime-avibactam resistance (MIC > 8 µg/mL) was detected in 30% (3/10) of microbiologic failures; resistance developed following a median of 15 days (range, 10–19) of ceftazidime-avibactam therapy.

Ten percent (3/31) of patients developed acute kidney injury (AKI) within 7 days of treatment initiation (defined by 1.5× increase in serum creatinine from baseline [7]), including 1 patient

on concomitant colistin. Ceftazidime-avibactam was discontinued after 19 days in 1 patient who developed leukopenia (absolute neutrophil count = 90×10^9/L); the patient was also receiving IV penicillin and quetiapine.

DISCUSSION

In our experience, ceftazidime-avibactam achieved overall survival and clinical success rates that were comparable to previous reports of CRE-infected patients treated with ≥2 in vitro active agents [8]. Moreover, our 10% rate of AKI with ceftazidime-avibactam was considerably lower than the approximately 30% rate we previously reported with carbapenem-colistin or aminoglycoside-based combinations [9, 10]. At the same time, important cautionary notes were sounded by the emergence of ceftazidime-avibactam resistance in 8% (3/37) of cases, including 30% of microbiologic failures. Taken together, our data suggest that ceftazidime-avibactam is an important addition to the limited antimicrobial armamentarium against CRE infections, which is at least as efficacious as alternative regimens and likely to be better tolerated.

Thirty-day mortality among our patients was 24%. Fifty-nine percent of all patients and 75% of patients with primary or secondary bacteremia had positive outcomes at 30 days, as defined using a composite definition of clinical success. Twenty-four percent of our patients with clinical success at 30 days developed recurrent CRE infections within 90 days. In previous reports, mortality rates among CRE-infected patients ranged from 22% to 72% [8], and recurrence rates were similar to those reported here [9]. Creatinine clearance (in the absence of renal failure) was not associated with ceftazidime-avibactam effectiveness. Rather, treatment failures were associated with CRRT and higher SOFA scores. To date, there are no ceftazidime-avibactam dosing recommendations for CRRT, and clinicians at our center used a variety of regimens. Clearly, research on ceftazidime-avibactam pharmacokinetics during CRRT is a priority. The association between SOFA scores and outcomes illustrates that host factors, and not simply antimicrobial activity against CRE, are major determinants of outcomes.

The rapid onset of ceftazidime-avibactam resistance in patients with microbiologic persistence of CRE was the most concerning finding of this study. Resistance was detected following treatment courses of 10, 15, and 19 days. To our knowledge, these are the first 3 cases of ceftazidime-avibactam resistance to be reported following drug exposure. A previous case report described baseline ceftazidime-avibactam resistance in a KPC-3 producing CR-Kp isolate recovered from the bloodstream of a patient with persistent CR-Kp bacteremia [11]; the patient had not been treated previously with ceftazidime-avibactam. In 2 of our patients, resistance was first detected in isolates that were associated with colonization of the respiratory or urinary tract. Therefore, it is essential that clinical microbiology laboratories test CRE, including colonizing isolates, for

Table 1. Clinical Characteristics of Patients in Whom Ceftazidime-Avibactam Treatment Was Associated With Microbiologic Failure

Patient	Age (Sex)	Underlying Disease	CRE Pathogen	Type of Initial Infection	Initial Treatment Regimen (Duration, d)	Clinical Outcome at 30 d	Time to Microbiologic Failure (d)	Cause of Microbiologic Failure and Outcome at 90 d	C/A MIC (μg/mL) of Pretreatment Isolate	C/A MIC (μg/mL) of Recurrent Isolate
1	66 (F)	Double lung transplant	ST258, KPC-3 CR-Kp	Purulent tracheobronchitis	C/A (71)	Failure	10	Progression to empyema	1	2
2	66 (F)	Double lung transplant	ST258, KPC-3 CR-Kp	Pneumonia	C/A (10)	Failure	14	Recurrence: Pneumonia, treated with C/A for an additional 14 d	2	32, 256[a]
							28	Persistent pneumonia, treated with meropenem and gentamicin until death	Not applicable	256
3	68 (M)	Metastatic colon cancer	CTX-M CR *Escherichia coli*	Pneumonia	C/A (11)	Failure	18	Recurrence: Pneumonia, treated with C/A for 14 d and survived	4	Not available for testing
4	61 (M)	Metastatic colon cancer	CTX-M CR *E. coli*	Bacteremia	C/A (7), gentamicin (4)	Failure	19	Recurrence: Bacteremia, treated with C/A for 7 d and survived	1	0.5
5	46 (M)	Kidney transplant	ST258, KPC-2 CR-Kp	Pyelonephritis with secondary bacteremia	C/A (17)	Success	34	Recurrent UTI, treated with C/A for 21 d and survived	1	1, 2[a]
6	73 (M)	Esophageal cancer status post-esophagectomy	ST258, KPC-3 CR-Kp	Pneumonia	C/A (15)	Success	34	Respiratory colonization, not treated	2	2
							58	Respiratory colonization, not treated	Not applicable	64, 128[a]
							76	Recurrent pneumonia, treated with meropenem and colistin for 14 d and survived	Not applicable	2, 64[a]
7	78 (M)	Amyotrophic lateral sclerosis	ST258, KPC-2 CR-Kp	Pneumonia	C/A (15), colistin (7)	Success	36	Recurrent UTI, treated with C/A for 7 d and survived	0.25	0.5
8	58 (F)	Morbid obesity s/p gastric sleeve surgery	ST258, KPC-3 CR-Kp	Intraabdominal infection	C/A (19)	Failure	41	Urine colonization, not treated and survived	4	32, >256[a]
9	75 (F)	Kidney-liver transplant	ST258, KPC-3 CR-Kp	Pyelonephritis	C/A (7)	Success	74	Recurrent UTI, treated with C/A for 21 d and survived	2	4
10	75 (M)	Bickerstaff encephalitis, paraplegia	ST258, KPC-2 CR-Kp	Bacteremia	C/A (14), gentamicin (3)	Success	84	Recurrent bacteremia, treated with meropenem, then ampicillin/ sulbactam for 14 d and survived	0.25	2

Abbreviations: C/A, ceftazidime-avibactam; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; CTX-M, cefotaximase; Kp, *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; s/p, status-post; ST, sequence type; UTI, urinary tract infection.

[a] Two morphologies isolated from the same biologic specimen.

ceftazidime-avibactam MICs if treatment with the agent is contemplated. Selection for ceftazidime-avibactam resistance in vitro previously revealed amino acid substitutions in the Ω-loop and adjacent sites in KPC [12]. Further studies are needed to identify and validate resistance mechanisms among CRE clinical isolates.

This study is limited by its retrospective, single-center design and the small patient population. Due to the study size, we are unable to make definitive conclusions about the role of combination regimens in improving outcomes and suppressing resistance or about the effectiveness of ceftazidime-avibactam in specific types of CRE infection. Nevertheless, we can conclude that ceftazidime-avibactam offers an important advance in the treatment of CRE infections. The development of resistance after as few as 10 days of therapy is troubling, and treatment failures and deaths in a significant minority of patients highlight the need for more agents with activity against CRE. It is incumbent upon healthcare providers to share their clinical experiences with ceftazidime-avibactam and other new β-lactamase inhibitors, so that these agents can be used most effectively for the longest period of time.

Notes

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