International Journal of Antimicrobial Agents 49 (2017) 770–773

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Treating complicated carbapenem-resistant enterobacteriaceae infections with ceftazidime/avibactam: a retrospective study with molecular strain characterisation

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ARTICLE INFO

Article history:
Received 10 October 2016
Accepted 22 January 2017

Keywords:
Ceftazidime/avibactam
Carbapenem-resistant Enterobacteriaceae
Multidrug resistance
β-Lactamase inhibitor
Klebsiella pneumoniae

ABSTRACT

Ceftazidime/avibactam (CAZ/AVI) is the first antimicrobial agent with activity against carbapenem-resistant Enterobacteriaceae (CRE) approved by the US Food and Drug Administration (FDA). Notably, human clinical outcome data for this indication are limited. Therefore, a retrospective study was performed to evaluate the clinical outcomes and bacterial genomic characteristics of patients hospitalised at a tertiary medical centre with CRE infections treated for the first time with CAZ/AVI. From a total of 44 patients with CRE infections, 6 patients were treated with CAZ/AVI. The duration of CAZ/AVI treatment ranged from 7 days to 28 days. Five patients achieved clinical cure, however two relapsed with the same carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) strain within 3 weeks of completion of CAZ/AVI treatment. In addition, one patient with CR-Kp pneumonia experienced clinical failure despite having a documented CAZ/AVI-susceptible CR-Kp strain [minimum inhibitory concentration (MIC) = 2 mg/L]. Consequently, the overall rate of unsuccessful outcome in this small cohort of patients was 50%. All strains carried KPC-3, OXA-9 and different TEM and SHV β-lactamases, but none carried the intrinsically avibactam-resistant class B metallo-β-lactamases. No obvious differences in antibiotic resistance genes were observed. This study provides an early glimpse of the clinical outcomes of patients with CR-Kp infections treated with CAZ/AVI. Findings of clinical failure and relapse in patients with no prior exposure to CAZ/AVI and with documented susceptibility to CAZ/AVI highlight the urgent need for well-designed clinical studies evaluating the effectiveness of CAZ/AVI in the treatment of CRE infections.

1. Introduction

Treating carbapenem-resistant Enterobacteriaceae (CRE) infections is a major clinical challenge, due in part to limited antibiotic options, often with poor bactericidal activity and/or high toxicities [1–3]. Ceftazidime/avibactam (CAZ/AVI) is a novel antibiotic combination including the new non-β-lactam β-lactamase inhibitor avibactam with broad activity against serine β-lactamases, including class A, class C and some class D carbapenemases, but with no activity against class B carbapenemases [4]. In vitro and animal models have shown that avibactam restores the activity of ceftazidime against extended-spectrum β-lactamase-producing Enterobacteriaceae isolates and most CRE isolates, suggesting that CAZ/AVI could be effective in the treatment of complicated CRE infections [5,6]. However, it is important to highlight that the US Food and Drug Administration (FDA) approval of CAZ/AVI was obtained on the basis of randomised clinical trials that excluded patients with CRE infections [7,8]. Therefore, clinical data to guide and support the use of this novel antibiotic in CRE-infected patients are urgently required.

In August 2015, CAZ/AVI was added to our institution's restricted formulary. Herein we performed a retrospective review of all patients with CRE infections treated with CAZ/AVI at our institution.

2. Materials and methods

Clinical and microbiological data were retrospectively collected through chart review for all hospitalised adult patients who received CAZ/AVI for CRE infection between August 2015 and December 2015 at Northwestern Memorial Hospital (Chicago, IL). Clinical cure was defined as symptom resolution or significant improvement at completion of antibiotic treatment. Microbiological

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http://dx.doi.org/10.1016/j.ijantimicag.2017.01.018
0924-8579/

cure was defined as at least one negative culture obtained from the same source as the index culture. Minimum inhibitory concentrations (MICs) of CAZ/AVI were determined by CAZ/AVI gradient strip Etest (bioMérieux, Hazelwood, MO; for research only). Given the lack of current Clinical and Laboratory Standards Institute (CLSI) breakpoints for CAZ/AVI, the CLSI breakpoints for ceftazidime alone were used as a reference (MIC ≤ 4 mg/L considered susceptible). Whole-genome sequencing (WGS) of each strain was performed using a Nextera XT DNA Library Prep Kit (Illumina Inc., San Diego, CA) following the manufacturer's protocol to identify antibiotic resistance genes, in silico multilocus sequence typing (MLST) and capsule genotype. Whole-genome phylogeny [9] was used to evaluate relatedness between index and relapse strains. This study was approved by the Institutional Review Board of Northwestern University (Chicago, IL).

3. Results

A total of 44 hospitalised patients had a diagnosis of CRE infection during the study period, of which 6 patients (14%), all with carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) infections, were treated with CAZ/AVI. Most of these patients had multiple co-morbidities, including diabetes mellitus in three patients, end-stage renal disease in two patients and immunosuppression [human immunodeficiency virus (HIV), leukaemia and cirrhosis] in three patients, with a mean Charlson comorbidity score of 4. For the six patients receiving CAZ/AVI, the mean sequential organ failure assessment (SOFA) score on the day of culture collection was 6, mainly driven by elevated creatinine (five of six patients had severe renal dysfunction and four patients required dialysis). The time to initiation of CAZ/AVI treatment ranged from 1–14 days, and combination therapy was used in four patients, including tigecycline or inhaled polymyxin B. Although all strains were sensitive to aminoglycosides, these drugs were not used, likely due to the underlying renal dysfunction. Other demographic, clinical and microbiological characteristics are summarised in Table 1.

Overall, five of six patients achieved clinical cure. However, two of these patients relapsed within less than 3 weeks after discontinuation of CAZ/AVI and subsequently died due to persistent sepsis. Using WGS, the two relapses were confirmed to be the same strain as the index strain based on three or less single nucleotide polymorphism differences. No evidence of acquired CAZ/AVI resistance was noted in the two relapse strains, as the CAZ/AVI MIC was similar to the index strain in both cases (MIC = 2 mg/L). Lastly, one patient had clinical failure after 5 days of CAZ/AVI treatment and died from persistent CR-Kp pneumonia and sepsis. No microbiological evaluation was performed to confirm microbiological failure; therefore, acquisition of CAZ/AVI resistance was not assessed.

All strains carried KPC-3, OXA-9 and different TEM and SHV β-lactamases, but none carried the intrinsically avibactam-resistant class B metallo-β-lactamases. No obvious differences in antibiotic resistance genes were observed between the failure or relapse strains and the remaining strains. All strains belonged to ST258 MLST group and had a non-typeable capsule, except for the strain associated with failure, which belonged to ST14 group and had a K2 capsule (Table 1).

4. Discussion

In this study, an unsuccessful outcome was found in 50% of patients with CR-Kp infection treated with CAZ/AVI (one clinical failure and two relapses). Similar findings were reported in a recently published case series of 37 patients with CRE infections treated with CAZ/AVI in which microbiological failure was reported in 27% (10/37) of patients, and recurrence of CRE infection occurred in 23% (5/22) of the patients with initial clinical success [10].

In addition to confirming recently published outcomes by finding similar results in a different setting and a different patient population, this study adds to the recent literature by providing a comprehensive microbiological and molecular characterisation of CR-Kp strains associated with successful and unsuccessful outcomes. Moreover, using whole-genome phylogeny, we confirmed that the recurrences were in fact relapses with the same strain and not re-infections with a different strain.

Whilst relatively higher MICs were found in our strains (all had MIC ≥ 1.5 mg/L) compared with previous surveillance studies performed in the USA (40–60% of CR-Kp strains had an MIC < 1 mg/L) [11,12], no obvious differences in baseline CAZ/AVI MICs were observed between the failure or relapse strains and the remaining strains. Moreover, no obvious differences in resistance genes were found between the strains associated with successful and unsuccessful outcomes.

Interestingly, the strain associated with failure had a K2 capsule genotype. Since K2 has been associated with increased virulence [13], and this strain was susceptible to CAZ/AVI, this finding raises the question whether failure to CAZ/AVI can be driven in some cases by increased virulence rather than CAZ/AVI resistance.

Although the small number of patients in this study limits the analysis of factors associated with failure or relapse, two important observations should be made. First, most of the patients were septic and had multiple co-morbidities, including significant renal impairment (creatinine clearance < 30 mL/min); these factors could have contributed to the poor clinical outcomes observed, not only by increasing their mortality risk but also by potentially affecting the pharmacokinetics/pharmacodynamics of CAZ/AVI. In this sense, little is known regarding the pharmacokinetic/pharmacodynamic (PK/PD) profiles of CAZ/AVI in patients with CRE infections with severe sepsis or renal dysfunction. A larger volume of distribution and/or altered renal clearance may lead to lower CAZ/AVI serum concentrations in this patient type [14]. Only two cases of KPC-producing *K. pneumoniae* infections with renal dysfunction have been published to date, reporting volumes of distribution significantly larger than those listed in the package insert [15]. In addition, the optimal PK/PD target for CAZ/AVI to ensure clinical efficacy against CRE infections has not been established. A target of 50%$fT_{>MIC}$ (time that the free concentration of drug is above the MIC during the dosing interval) is currently used for dosing and is extrapolated from PK/PD data for ceftazidime. However, studies have indicated that for β-lactam antibiotics a 100%$fT_{>MIC}$ is associated with better clinical outcomes [16,17]. Given the retrospective nature of this study, PK/PD parameters were not determined in the patients and it was not possible to evaluate their association with clinical outcome.

Second, both patients with CR-Kp pneumonia had poor outcomes (failure or relapse) and subsequently died. This observation suggests potential limitations in the treatment of CR-Kp pneumonia with CAZ/AVI and highlights the need for additional studies to evaluate the activity and bioavailability of CAZ/AVI in the lungs and other sites of infections. Furthermore, optimal dosing based on the site of infection, renal function and MICs, as well as the role of monotherapy and indications for multiple-drug therapy with CAZ/AVI, should be promptly determined by larger clinical studies in order to maximise the efficacy of this new antibiotic and to avoid rapid development of resistance.

5. Conclusions

The finding of clinical failure and relapse in patients with CAZ/AVI-susceptible CR-Kp infections in this retrospective study highlights the urgent need for well-designed clinical studies to evaluate the effectiveness of CAZ/AVI for the treatment of CRE infections. It is important to identify clinical, microbiological and genetic factors potentially associated with poor outcomes, as well as optimal drug