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RETROSPECTIVE ANALYSIS TO CHARACTERIZE THE REAL-WORLD USAGE PATTERNS OF CEFTAZIDIME-AVIBACTAM IN THE MANAGEMENT OF MDR GRAM-NEGATIVE BACTERIAL INFECTIONS IN A TERTIARY CARE CENTER

Praveen B.*[1], Aishwarya B.[2] and Senthur Nambi P.[3]

[1]Associate Consultant, Department of Infectious Disease, Apollo Hospitals, Chennai, Tamil Nadu, India.
[2]Clinical Research Coordinator, Apollo Hospitals, Chennai, Tamil Nadu, India.
[3]Senior Consultant, Department of Infectious Disease, Apollo Hospitals, Chennai, Tamil Nadu, India.

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Corresponding Author: Praveen B.
Associate Consultant, Department of Infectious Disease, Apollo Hospitals, Chennai, Tamil Nadu, India.

ABSTRACT

Carbapenem resistance is a rapidly spreading problem for which only a few antibiotic options exist. Ceftazidime-avibactam (CZA) is one such agent. Real-world data regarding its use is gradually accumulating. We wanted to add to this data our experience. We did a retrospective chart analysis on 100 patients who received the drug for at least 24 hours between 2021 and 2022, for suspected or proven sepsis and looked at their clinical status at days 0, 3, 7, and 21. The cultures grew for 72% of the patients, and the most common pathogen was *Klebsiella pneumoniae* (75%) followed by *E. coli* (22.2%). Carbapenem resistance was noted in 75%. All-cause-outcome of the patients who received the drug as targeted therapy (n=53) was observed as follows: Cured 42 (79.2%), not cured 11 (20.7%). Despite limitations, our study shows CZA can be an effective therapy for MDR gram-negative infections.

KEYWORDS: Ceftazidime-avibactam, real-world, MDR, Gram-negative, Infection.

INTRODUCTION

Carbapenems have served as the antibiotics of choice for infections caused by Gram-negative bacilli for decades. However, the emergence and spread of carbapenemases threaten their utility as our defense against these pathogens.[1,2] The predominant carbapenemase in the United States is Klebsiella pneumoniae carbapenemase (KPC), an Ambler class A enzyme.[3] Bacteria that harbor KPC often carry other genes that encode resistance to a wide array of other antibiotic classes, posing a serious treatment challenge.[2,3] Until recently, polymyxins, one of the few remaining antibiotics with preserved in vitro activity against MDR strains, were limited by unfavorable pharmacokinetic properties and/or toxicity.[4–6] The high burden associated with MDR Gram-negative bacterial infections is in part due to a lack of safe and effective treatment options, warranting novel antibiotic development.[2] Ceftazidime-avibactam (CZA) is one such antibiotic comprising of a cephalosporin and a novel non-beta-lactam beta-lactamase-inhibitor (diazabicyclooctane).[7] Avibactam is incorporated with ceftazidime to withstand the hydrolysis by Ambler class A and some class D

carbapenemase enzymes.[7] In surveillance studies, CZA has demonstrated in vitro activity against carbapenem-resistant Enterobacteriaceae (CRE) and MDR *Pseudomonas aeruginosa*.[8,9] Ceftazidime avibactam has been available in India from 2019 and has been an important drug in management of resistant infections. Real-world experience with CZA for the treatment of CRE infections is gradually accumulating, but data on its use for other MDR Gram-negative pathogens including *P. aeruginosa* remain limited.[10–16] Limited Indian data exists currently on the effectiveness of the molecule in the Indian setting. We intend to describe the clinical characteristics, microbiology, and outcomes of our patients treated with CZA for various MDR Gram-negative bacterial infections.

MATERIALS AND METHODS

Ours is a 600-bedded tertiary care hospital in South India. We analyzed retrospectively, the pattern of usage, and clinical outcomes, of 100 patients who received CZA as an inpatient, for at least 24 hours. Institutional ethics clearance was obtained before the initiation of the study.

All the data was collected from the patient records retrospectively. Patients were categorized as UTI if they were having features suggestive of pyelonephritis; Intra-abdominal infection if they were having features of peritonitis, hepatobiliary infections or abscess; skin and soft tissue infection if they were having features suggestive of abscess or necrotizing fasciitis; sepsis if they were having hypotension, altered mentation along with supporting lab features with or without fever and organ system localization.

For all categories of patients, cultures were drawn before the study antibiotic was started, and based on the cultures and clinical response, the antibiotic was either continued or de-escalated. For antimicrobial susceptibility testing of the study antibiotic CLSI guidelines were followed.[17] If the study antibiotic was initiated without having microbiological information beforehand, it was categorized as empiric usage. If the microbiological information was available beforehand, and the study antibiotic would cover the identified pathogen, it was categorized as targeted usage. The duration of antibiotic use was determined by the clinicians based on clinical scenarios.

CZA was mainly used for treating Gram-negative bacteria, and in combination with other antibiotics; the daily dose, frequency, and duration of infusion observed were according to the approved prescribing information, with the recommended dose adjustments whenever appropriate.

The clinical status of the patients at various time points was assessed by our scoring system. After starting CZA, parameters looked for on days 3, 7 & 21, in comparison with the baseline, are as in table-1.

Table-1: Scoring system to track clinical status after initiating the antibiotic.

Sl.	Parameter	Score
1	Improvement in symptoms	+1
2	Improvement in vital signs	+1
3	Improvement in lab parameters (blood counts / organ function / biomarkers)	+1
4	Shifted to the ward from ICU.	+1
5	Repeat culture (if done) is positive for the same organism	-1
6	Shifted back to ICU from the ward	-1
7	Deterioration in symptoms	-1
8	Deterioration in vital signs	-1
9	Deterioration in lab parameters	-1
10	New sepsis event (may or may not be related to the initial event)	-1

At any assessment day, +1 point was awarded if any one of the parameters 1-4 were met. -1 point was awarded if any one of the parameters 5-7 were met. 0 point was awarded if none of the parameters was met. If the patient was still receiving the drug, cumulative points on days 3, 7 & 21 was taken into account and was registered as improvement, status quo and deterioration if the cumulative point was positive one, zero and negative one respectively. If the patient stopped receiving the drug, their assessment stopped at the next time-point.

Based on the clinical status at the time of discharge, patients were categorised as recovered if they were free of symptoms, and not recovered if they did not meet the criteria/were dead.

RESULTS

The study period spanned from Dec 2021 to Dec 2022. The median age of the study population was 58 years. It comprised of 55% males and 45% females. The number of patients with 0, 1, and 2 or more comorbidities were 16, 29, and 55 respectively. Most of them had systemic hypertension (63%) followed by Type 2 Diabetes mellitus (54%).

The usage patterns observed were as follows: empiric (47%) vs targeted (53%); Intensive care unit (84%) vs ward (16%). The drug was used as part of a combination therapy in 86% and monotherapy in 14%. The suspected or proven clinical syndromes for which the drug was used were as follows: Intra-abdominal infection (17%), Pneumonia (18%), Skin and soft tissue infection (12%), Urinary tract infection (17%), and Sepsis (36%). The cultures grew for 72% of the patients, and the pathogen distribution was as follows: *Klebsiella pneumoniae* (75%), *E. coli* (22.2%), *Pseudomonas aeruginosa* (15.3%), *Acinetobacter baumanii* (9.8%) and others (18%). Polymicrobial growth was observed in 29.2% of the patients. Carbapenem resistance was noted in 75% of all the isolates including Enterobacteriaceae and non-Enterobacteriaceae. 47.4% of the Enterobacteriaceae isolates (n=59) demonstrated in-vitro susceptibility to CZA. Molecular evaluation was done for 11 patients and the results were as given in table-2.

Table-2: Molecular mechanisms looking for Carbapenem resistance whenever evaluated.

Variable	No. of patient's data with genotype analysis	Percentage (%)
OXA-48	6	54.5%
NDM-1	3	27.2%
CTX-M	1	9.1%
NIL	1	9.1%
Total	11	100%

The clinical status of all the patients at various time points was observed as given in the figure-1.

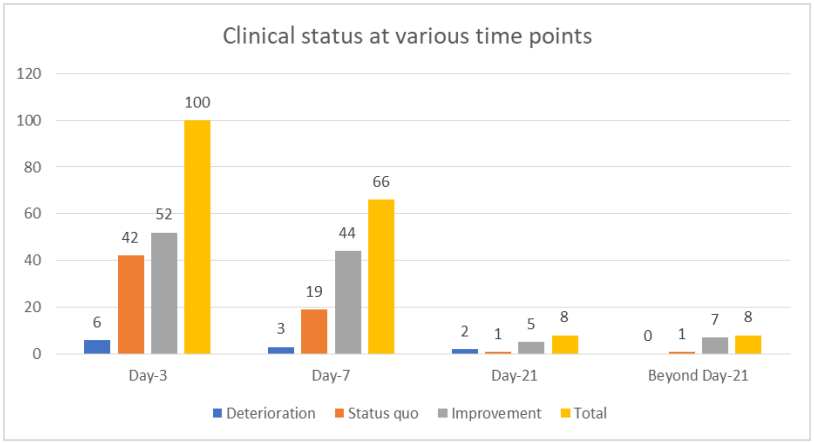

Figure-1: Clinical status at various time-points.

The all-cause-outcome of all the patients in the study: Recovered (66%), Not recovered (34%). All-cause-outcome of the patients who received the drug as targeted therapy (n=53) was observed as follows: Cured 42 (79.2%), not cured 11 (20.7%).

DISCUSSION

This real-world study describes treatment patterns (indications and use), the type of infection treated (indication and microbiology), effectiveness (clinical outcomes), and the safety of CZA in 100 patients enrolled from India who received CZA for at least 24 hours in routine clinical practice. The primary objective of this study was to derive information on the patterns of use of CZA in real-world practice; as such the inclusion criteria were broad to fulfil this purpose.

The comorbidities of the study population were non-homogenous comprising of solid organ transplant, pregnancy, neurogenic bladder, Interstitial lung disease, HIV, and Systemic Lupus Erythematosus with up to 3 patients in each of the above-mentioned categories apart from conditions like Diabetes, Hypertension, CKD, CAD and chronic liver disease. The scenarios for which clinicians used the study antibiotic were also varied, which we broadly classified as UTI, Pneumonia, Skin and soft tissue infection, Intra-abdominal infection, and sepsis. All empiric usage of the study antibiotic was from the ICUs except one patient with suspected graft pyelonephritis received it empirically in the ward awaiting cultures. Targeted usage was from both the ICU and the wards. This reflected a clinicians' tendency to use the antibiotic only when the patients were sicker or the host factors were complicated. Since most of the usage happened in our ICUs where the patients were sicker, the study antibiotic was used as a part of combination therapy. Wherever appropriate source control was achieved e.g.: removal of central venous catheters or devices, surgical debridement, and drainage of abscesses. Of the positive cultures, *Klebsiella pneumoniae* was the most common pathogen and most of them (75%) were resistant to carbapenems. The most common mechanism of Carbapenem resistance identified in our study was OXA-48.

The scoring system we used was indigenous and not adopted from any other source, and it reflected the all-cause attribution to deterioration, remaining status quo, or improvement. Despite being a heterogeneous population and considering the all-cause outcome, 66% had recovered while getting discharged from the hospital, which is remarkable. Of the 34% who did not recover, 2 patients were categorized as not cured as they had a complicated post-operative course but were discharged from the hospital due to various reasons, and could not be followed up. All-cause mortality was 28%.

In a similar study conducted by Sarah et al[18] conducted in the United States, of the 203 patients who received CZA, CRE was isolated from 117 (57.6%) culture specimens. The most common infection sources were respiratory (37.4%), urinary (19.7%), and intra-abdominal (18.7%). The all-cause clinical failure, 30-day mortality, and 30-day recurrence occurred in 59 (29.1%), 35 (17.2%), and 12 (5.9%) patients respectively. In a multicentre study by Madelin King et al[11], also conducted in the United States, out of 60 patients with CRE infection who received CZA, mortality was 32%. Microbiological cure was 53%, and 65% had clinical success. Our study also had similar success and failure rates.

LIMITATIONS

In order to assess the clinical status at various time-points, we adopted an indigenous scoring system, which may or may not be the appropriate tool to do so. The all-cause-outcome approach is a reflection of many factors like host factors, environmental factors and pathogen factors. This may or may not be entirely due to the study antibiotic. The outcome was assessed at the hospital discharge of the patient, which again was due to various factors like non-infectious complications, by-stander preference, financial reasons etc. Extracting the individual contribution of the study antibiotic to all these outcomes was not attempted. Follow-up of the patients after being discharged was also not done, which would have given more information about the recovery patterns.

CONCLUSION

Our study describes the CZA treatment patterns and outcomes for MDR infections. Our study shows that CZA can be an effective therapy for MDR infections. Despite the limitations, our study captures the potential benefits and risks of combination therapy. Our study also highlights the need for continued advances to improve outcomes in vulnerable patient groups including those with MDR Gram-negative bacillary infections.

DISCLOSURES

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