ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY
Mini Review

The Efficacy of Ceftazidime/Avibactam in CRE Infections with Patients having Cardiovascular Diseases (A Literature Review)

Amjad M AlRashed[1]* and Mohamed Almousa[2]

[1]*Clinical Pharmacist, Saud Albabtin Cardiac Center, Dammam, Saudi Arabia*

[2]*Board of Emergency Medicine, Saudi Arabia*

***Corresponding Author:** Amjad M AlRashed, Clinical Pharmacist, Saud Albabtin Cardiac Center, Dammam, Saudi Arabia.

Received: June 22, 2020; **Published:** July 29, 2020

Abstract

An upsurge in Gram-negative infections such as Carbapenem-resistant *Enterobacteriaceae* (CRE) prompted and motivated the development of this literature review. The objective was to examine and unravel the effectiveness of Ceftazidime-avibactum (CAZ-AVI) as a critical inhibitor combination with the capacity to address the global health threat caused by CRE. The increase in such infections, coupled with a deficiency in antibiotics, makes the situation worse. Previous studies indicate that a 30-day mortality rate is linked to colistin (57%), double-carbapenem (64%) and tigecycline (80%). Ceftazidime-avibactum (CAZ-AVI) is deemed as a last resort or a solution to *Enterobacteriaceae*. Previously, polymyxins were used for treating CRE infections. However, issues such as low-efficiency level, toxicity and increased resistance rendered them unviable. CAZ-AVI is formed after combining the β lactam/β lactamase inhibitor. The efficacy of CAZ-AVI, coupled with its capacity to provide microbiology cure and improve therapy experiences, illustrates that CAZ-AVI is an effective alternative towards dealing with Gram-negative infections such as CRE.

Keywords: *Carbapenem-resistant Enterobacteriaceae (CRE); Ceftazidime-avibactum (CAZ-AVI)*

Literature Review

There has been an increase in Gram-negative infections that emanates from the emergence of the carbapenem-resistant bacterium. According to a U.S. survey, carbapenem resistance and the resulting diseases rose from 2% in 2001 to 10% in 2011 and the increase varies depending on the regional differences [1]. Despite the sharp increase, there are limited antibiotics that effectively deals with the onset of carbapenem resistance and include colistin, tigecycline and double-carbapenem treatment for CRE infections. As a result, the 30 days mortality rates have been increasing depending on the type of treatment regimen selected to treat a patient. The 30-day mortality rate associated with colistin is 57%, tigecycline is 80% and the mortality rate for double-carbapenem is 64%. For a long time, colistin has been the primary intervention method for patients with CRE infections, but the colistin resistance has increased among the CRE isolates. The previous treatment methods were inefficient as they registered high mortality rates, high relapse rates, and lengthy stays at the hospital due to the long-time taken to clear the bacterium. The adverse effects and the deficiencies of the existing treatment options necessitated the introduction of ceftazidime-avibactam (CAZ-AVI) to address the issue of carbapenem resistance. The introduction of CAZ-AVI was delayed until 2015 to minimize the chances of resistance to the antibiotic and examine the side effects of the antibiotic. Since its introduction, patients with CRE infections show sharp clinical improvements when using CAZ-AVI compared to other CRE antibiotics and clinics registers lower CRE-related mortality when using the antibiotic. The antibiotic is especially effective in treating KPCs and OXA 48 pathogens and other carbapenem-resistant infections [1]. It registers high clinical success due to the presence of avibactam in the ceftazidime that enhances its activity against multiple carbapenem-resistant pathogens.

Ceftazidime-avibactum (CAZ-AVI) is an approved inhibitor combination that has the potential to minimize the global health threat posed by the advent of carbapenem-resistant *Enterobacteriaceae* (CRE). The inhibitor is considered as a major breakthrough against the *Enterobacteriaceae* because of its substantial burden on patients that include a more extended stay in the hospital, high mortality rate especially for patients with cardiovascular diseases, and higher clinical care costs compared to carbapenem-susceptible *Enterobacteriaceae* (CSE) [2]. In the past, clinicians used polymyxins to treat CRE infections. Still, the option was not viable due to the increased resistance, low-efficiency levels, and the toxicity of this mode of treatment. However, the emergence of CAZ-AVI, a combination of β lactam/β lactamase inhibitor, has provided a viable treatment option and clinical outcomes for patients with CRE infections [3]. CAZ-AVI has proved to be successful in the treatment of *Enterobacteriaceae* that produces *Klebsiella pneumoniae* carbapenemase (KPCs) and OXA 48 due to its mechanism of action and low resistance levels.

The efficacy of CAZ-AVI emanates from its capability to bind to several types of Penicillin-binding proteins (PBPs) that makes the primary inhibitor of cell wall synthesis [4]. Further, clinical trials have established that humans well tolerate the cephalosporin, and this increases the safety levels that make it an adequate intervention for the treatment of cardiovascular diseases. Unless a patient suffers from an undisclosed infection, the most common side effects of CAZ-AVI include vomiting, increased liver enzymes, nausea, and minor abdominal pains that make it ideal for human consumption. In addition, there is low evidence of resistance against this mode of treatment unless there is an occurrence of a mutant or the cardiovascular cells have a decreased permeability in their outer membrane. It has emerged as the most promising inhibitor that helps in controlling and the treatment of CRE.

According to Tempkin., *et al*. [1], 74% of patients suffering from infections related to CRE who receive CAZ-AVI salvage therapy experiences clinical and microbiological cure and all-cause hospital mortality rates reduce to 39%. A patient who receives microbiological cure has a 79% chance of survival and the mortality rate for the other 21% arises from non-infection related or other underlying medical conditions. However, the patients with OXA 48 pathogen have a higher mortality rate compared to patients with KPCs OXA 48 pathogen does not effectively hydrolyze ceftazidime, but it does not cause ceftazidime resistance. Similarly, Tempkins., *et al*. study established that CAZ-AVI works well in conditions where other CRE-related antibiotics such as dual-carbapenem and colistin have failed to work. The antibiotic also works well with other antibiotics to control and treat severe cases of carbapenem resistance. CAZ-AVI is an efficient treatment intervention in patients with life-threatening conditions due to carbapenem-resistant infections, especially when such cases have not responded to previous treatments [5]. Over three-quarters of patients experience clinical cure after the administration of CAZ-AVI treatment, and the results are promising given that there exist limited options of treating CRE-related infections.

Further, the efficacy of CAZ-AVI is proved by the *P* value of the outcomes of the patients who have contracted CRE infections and used ceftazidime-avibactam and the outcomes of a comparative group comprising of patients who used other CRE infection antibiotics as shown in the table below.

Outcome	CAZ- AVI Group (n = 10%)	Comparative Group (n = 28%)	P Value
Clinical remission	8 (81)	15 (54)	0.14
Total clinical cure without any relapse or mortality within 30 days	4 (45)	11 (40)	> 0.1
30 days mortality due to all causes	5 (55)	16 (57)	0.6
Mortality due to CRE	2 (22)	11 (40)	0.28
The median of length of stay in days	70 (48 - 97)	41 (22 - 80)	0.08
Relapse of the isolate in 30 days	2 (21)	1 (4)	0.1
The time taken to clear the bacteremia	4 (3 - 5)	5 (3 - 8)	0.7

Table: *Source: Efficacy of ceftazidime-avibactam in the treatment of infections due to Carbapenem-resistant Enterobacteriaceae.*

From the P values indicated in the table, it is evident that CAZ-AVI is more efficient in the treatment of CRE infections compared to other CRE-related antibiotics on offer due to the positive impact of the antibiotic on the clinical outcomes of the patients. The antibiotic leads to clinical remission, more patients recover fully from the bacterium without a relapse and it reduces mortality rates among the patients under clinical care. In addition, it reduces hospital stay, relapse, time taken to clear the bacterium, and reduces mortality rate associated with CRE infections. The P value table proves that CAZ-AVI antibiotic is more effective in combating CRE infections than other CRE-related antibiotics. Since its introduction, the drug has played a major in combating the effects of carbapenem-resistant infections, and it has proved to be a clinical success with fewer side-effects on humans.

Carbapenem resistance is a serious health problem that reduces the efficacy of antibiotics, especially when treating cardiovascular diseases [3]. There has been an increase in the resistance, and this has caused multiple problems on the patients due to high mortality rates, lengthy hospital stays, high mortality rates, and high costs of treating CRE-related infections. Therefore, the emergence of CAZ-AVI is a welcome relief to clinicians and patients as it has proved to be the last line of defense against CRE. CAZ-AVI has proved to be a promising intervention against CRE infections according to various clinical studies, especially for cases involving OXA 48 and KPCs. The clinical success of the antibiotic is evident from the clinical outcomes for the many patients who show dramatic improvements after the administration of CAZ-AVI compared to other CRE-related antibiotics such as colistin and tigecycline. Further, the antibiotic has helped in reducing mortality rates that emanate from CRE-related infections and recuperation of severe cases of such infections that had previously not responded to other treatment options [5]. The antibiotic helps in achieving a microbiological cure for severely ill patients where most of the population has clinical success and walk out of the clinic alive after the end of the hospital stay. Such stays are also short compared to other antibiotics, and relapse levels are low.

Conclusion

Further, the antibiotic is safe for humans as it does not have a lot of side effects. CAZ-AVI is a potential treatment option for patients CRE-related infections and those admitted in the intensive care unit because other CRE-related treatment antibiotics did not respond.

Bibliography

1. Temkin E., *et al*. "Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms". *Antimicrobial Agents and Chemotherapy* 61.2 (2017): e01964-16.

2. King M., *et al*. "Outcomes with ceftazidime/avibactam in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections: a multi-center study". *Open Forum Infectious Diseases* 3.1 (2016): 2047.

3. Alraddadi BM., *et al*. "Efficacy of ceftazidime-avibactam in the treatment of infections due to Carbapenem-resistant *Enterobacteriaceae*". *BMC Infectious Diseases* 19.1 (2019): 772.

4. Lagacé-Wiens P., *et al*. "Ceftazidime-avibactam: an evidence-based review of its pharmacology and potential use in the treatment of Gram-negative bacterial infections". *Core Evidence* 9 (2014): 13-25.

5. Camargo JF., *et al*. "Successful treatment of carbapenemase-producing pandrug-resistant *Klebsiella pneumoniae* bacteremia". *Antimicrobial Agents and Chemotherapy* 59.10 (2015): 5903-5908.

Volume 8 Issue 8 August 2020