International Journal of Antimicrobial Agents 000 (2018) 1–8

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Review

Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 21 February 2018
Accepted 7 July 2018
Available online xxx

Editor: Dr Jim Gray

Keywords:
Avibactam
Gram-negative bacteria
Carbapenem-resistant Enterobacteriaceae
Clinical response
Microbiological response
Safety

ABSTRACT

Data on the efficacy and safety of ceftazidime/avibactam (CAZ-AVI) are limited. A systematic review and meta-analysis was conducted to clarify the role of CAZ-AVI for patients with serious Gram-negative bacterial infections. The PubMed, EMBASE and Cochrane Library databases were searched for randomised controlled trials (RCTs) and cohort studies involving CAZ-AVI. Summary risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a fixed- or random-effects model. Twelve articles (4951 patients) were included, consisting of nine RCTs and three observational studies comparing CAZ-AVI with other regimens, e.g. carbapenems or colistin. CAZ-AVI showed a comparable clinical response (RR = 0.99, 95% CI 0.96–1.02; $I^2 = 0\%$) and non-inferior bacterial eradication (RR = 1.04, 95% CI 0.93–1.17; $I^2 = 79.1\%$) to carbapenems. No significant difference was detected between groups regarding mortality and adverse events. Moreover, subgroup analyses demonstrated that CAZ-AVI improved the clinical response (RR = 1.61, 95% CI 1.13–2.29) with reduced mortality (RR = 0.29, 95% CI 0.13–0.63) in patients infected by carbapenem-resistant Enterobacteriaceae versus comparators. Likewise, CAZ-AVI improved the clinical cure rate of bloodstream infections (RR = 2.11, 95% CI 1.54–2.88). An improved ability of CAZ-AVI in microbiological eradication was also detected in patients with complicated urinary tract infections (RR = 1.13, 95% CI 1.05–1.21). CAZ-AVI exhibited comparable efficacy and safety with carbapenems. Therefore, this agent might be a potential powerful agent for patients with serious Gram-negative bacterial infections.

1. Introduction

The increasing prevalence of resistance to currently available antimicrobial agents for bacterial infections, especially for complicated infections caused by Gram-negative bacteria (GNB), is still a challenge [1]. Currently, carbapenems are the first-line recommended therapy for patients with severe infections [2]. However, there is concern that the extensive utilisation of carbapenems may result in an increasing incidence of resistant strains, in particular carbapenem-resistant Enterobacteriaceae (CRE) [3,4]. Hence, it is important to use carbapenems selectively and to develop more effective agents [5].

Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor with potent ability in inhibiting most of the Ambler classes A, C and some D serine β-lactamases, including extended-spectrum β-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs), which may address the demand for a weapon against resistant GNB [6,7]. Nowadays, numerous studies are investigating the combination of AVI with ceftaroline fosamil [8], aztreonam (ATM) [9,10] and ceftazidime (CAZ) [11]. The combination CAZ-AVI was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for infections without additional therapeutic options in adults, including complicated intra-abdominal infections (cIAIs), complicated urinary tract infection (cUTIs) and hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) (Europe only). However, the most important characteristic of this combination is its potential activity against carbapenemase-producing bacteria [5,12].

Previous systematic reviews have demonstrated that CAZ-AVI has a favourable pharmacological profile and may be an option for empirical therapy of severe GNB infections. However, neither statistical analysis nor quality validation was performed in those reviews [2,13]. Recently, a meta-analysis reported the potential

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https://doi.org/10.1016/j.ijantimicag.2018.07.004
0924-8579/

benefit of novel β-lactam/β-lactamase inhibitor combinations, including CAZ-AVI, in cUTI and cIAI, whilst no other indication is referred to [14]. Likewise, another meta-analysis including six randomised controlled trials (RCTs) documented the efficacy of CAZ-AVI in cUTI and cIAI [15]. Considering that a number of studies have demonstrated the impact of CAZ-AVI in infectious diseases, especially those caused by CRE [16–18], here we conducted a systematic review and meta-analysis to better understand the activity and safety profile of this newly approved drug combination.

2. Methods

2.1. Literature search

The PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases were searched by two authors (HZ and X-YZ) independently from inception to 9 February 2018 without language restriction.

The PubMed search strategy was 'avibactam' or 'AVE1330A' or 'NXL104' searched both in Medical Subject Headings (MeSH) and free text. The search strategy was then adapted for EMBASE and CENTRAL.

The two authors also conducted complementary searches by screening all of the reference lists of included articles to identify any other potentially relevant articles. The ClinicalTrials.gov website of the US National Library of Medicine (http://clinicaltrials.gov/) was also searched for completed and ongoing trials.

2.2. Selection of studies

The titles, abstracts and full-text of articles from the retrieved literature were screened by two authors (HZ and X-YZ) independently to identify their eligibility (Fig. 1). Studies that (i) evaluated the impact of AVI or AVE1330A or NXL104 and (ii) were conducted among patients with infectious diseases compared with other treatments were considered eligible for inclusion. In addition, the following studies were excluded: (i) case reports or case series without a control group; and (ii) studies lacking quantitative or qualitative target outcome results. Any disagreements were resolved by discussion.

Target outcomes of interest in these studies were clinical response, microbiological response, mortality, adverse events (AEs) and serious adverse events (SAEs).

2.3. Data extraction and management

Data extraction was performed independently by two authors (HZ and X-YZ). The following information was extracted from each study: (i) study author and year of publication as well as the region(s) where the study was conducted; (ii) study characteristics (including study design and sample size); (iii) characteristics of the patients (including age, sex, infection type and causative pathogen); (iv) characteristics of the treatment (including dosage of avibactam, concomitant therapy and antimicrobial duration); (v) characteristics of the control group; and (vi) types of outcome measures.

2.4. Assessment of risk of bias in the included studies

The risk of bias of the included RCTs in the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting was assessed by two authors (HZ and X-YZ) using the Cochrane Risk of Bias Tool (Supplementary Table S1) [19]. For each item, the quality characteristics of each study were rated as (i) low risk of bias, (ii) unclear or (iii) high risk of bias. When observational studies were considered, the Newcastle–Ottawa Scale (NOS) was used to assess the risk of bias in patient selection, comparability between groups, and outcome and exposure factors assessment. NOS scores range from 0–9, with scores $\geq$7 indicating good quality (Supplementary Table S2) [20]. Disagreements between the reviewers were resolved by an open discussion to develop a consensus.

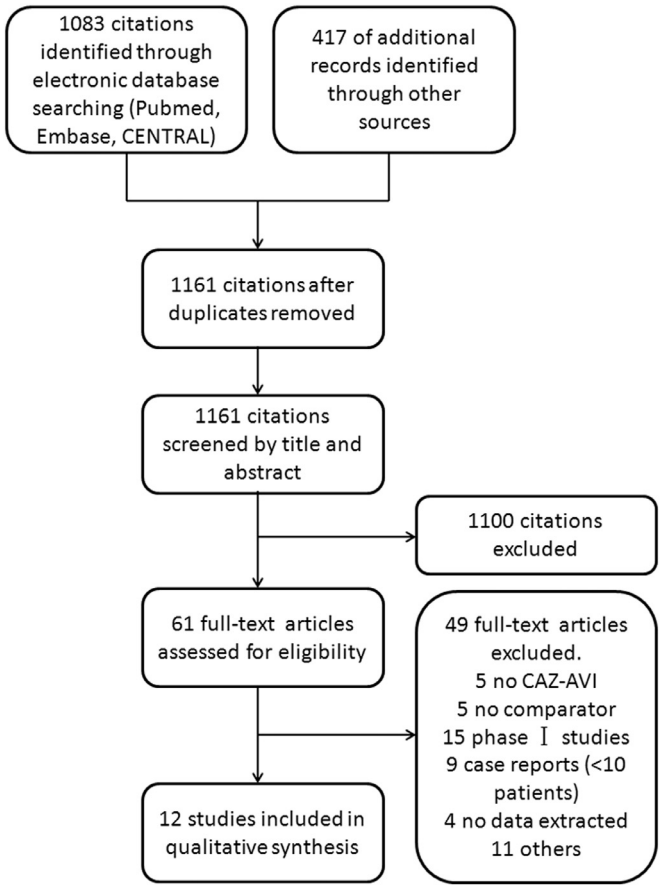

Fig. 1. Flow diagram of assessed and included studies. CENTRAL, Cochrane Central Register of Controlled Trials; CAZ-AVI, ceftazidime/avibactam.

2.5. Statistical analysis

Statistical analyses were performed according to the *Cochrane handbook for systematic reviews of interventions* [21]. Data were analysed using Stata 13.1 (StataCorp LP, College Station, TX). Treatment effects were calculated as risk ratio (RR) with 95% confidence interval (CI) for dichotomous data using a fixed- or random-effects model according to heterogeneity among studies. Heterogeneity was identified using the Cochrane I^2 statistic. An I^2 statistic of >50% was considered to indicate statistically significant heterogeneity. Subgroup analysis for clinical response, microbiological response and mortality were performed for different causative pathogens, infection types, renal status and illness severity levels. Sensitivity analyses were also conducted by excluding each study to investigate the confidence of the outcomes.

3. Results

Electronic and manual searches identified 1500 potential studies, from which 339 duplicates were removed. After the initial screening of titles and abstracts, 1100 studies were excluded. Thus, 61 full-text articles were assessed for eligibility. Finally, 12 studies

Please cite this article as: H. Zhong et al., Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis, International Journal of Antimicrobial Agents (2018), https://doi.org/10.1016/j.ijantimicag.2018.07.004