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Efficacy and safety of eravacycline: A meta-analysis

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ABSTRACT

Objectives: This study was conducted to evaluate the efficacy and safety of eravacycline, a recently approved fluorocycline for treatment of complicated intra-abdominal infections (cIAIs).
Methods: PubMed, EMBASE and three trial registries were searched for randomised controlled trials (RCTs) comparing the efficacy and safety of eravacycline versus comparators. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using random-effects models. The study outcomes included clinical response, all-cause mortality and adverse events (AEs).
Results: Three RCTs (1128 patients) with cIAIs were included. There were no significant differences in clinical response in the modified intention-to-treat (ITT) (OR, 0.91, 95% CI 0.62–1.35; I^2 = 0%), microbiological ITT (OR, 0.93, 95% CI 0.61–1.41; I^2 = 0%) and clinically evaluable (OR, 0.98, 95% CI 0.55–1.75; I^2 = 0%) populations or in all-cause mortality (OR, 1.18, 95% CI 0.16–8.94; I^2 = 0%). Eravacycline was associated with significantly greater odds of total AEs (OR, 1.55, 95% CI 1.20–1.99; I^2 = 0%) and nausea (OR, 5.29, 95% CI 1.77–15.78; I^2 = 1.70%) but the increase in vomiting was non-significant (OR, 1.44, 95% CI 0.73–2.86; I^2 = 1.70%). There were no significant differences in serious AEs or discontinuation due to AEs.
Conclusion: This meta-analysis of RCTs found similar clinical efficacy and mortality for eravacycline compared with carbapenems for treatment of cIAIs. However, the odds of total AEs and specifically nausea was higher with eravacycline, while no significant differences were observed in vomiting (although numerically higher), serious AEs or discontinuation due to AEs.

1. Introduction

Complicated intra-abdominal infections (cIAIs) most typically manifest as peritonitis, abscess or phlegmon and often require a source control procedure for definitive management [1]. The microbiology of these infections is variable depending on the type of infection and previous healthcare and antibiotic exposure. It is not uncommon for these infections to be polymicrobial, with *Escherichia coli*, streptococci and enteric anaerobes predominating in community-acquired infections. Non-fermenting Gram-negative bacteria (e.g. *Pseudomonas aeruginosa* and *Acinetobacter* spp.) and enterococci may also be isolated, but these pathogens tend to be significantly more prevalent in healthcare-associated and hospital-acquired infections. The worldwide increase in the prevalence of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and the decrease in fluoroquinolone susceptibility rates, along with decreasing rates of carbapenem susceptibility in certain parts of the world, have led to a need for new agents with reliable activity against these intra-abdominal pathogens [2,3].

Eravacycline is a novel fluorocycline antibiotic that was approved in 2018 by the US Food and Drug Administration (FDA) for the treatment of cIAIs [4]. As the first fully synthetic tetracycline compound, eravacycline maintains stability against the efflux pumps and ribosomal protection proteins that typically confer resistance to other members of this antibiotic class [5]. Eravacycline displays reliable activity against most multidrug-

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resistant (MDR) *E. coli*, including ESBL-producing and carbapenem-resistant isolates, as well as against many streptococcus species. Its activity against other Enterobacteriaceae, *Acinetobacter* spp., enterococci and anaerobes is more variable, with MIC_{50} values (minimum inhibitory concentration at which 50% of isolates are inhibited) typically at or below the FDA breakpoints, but MIC_{90} values (minimum inhibitory concentration at which 90% of isolates are inhibited) above the susceptibility cut-offs [6]. In addition, it has been suggested that eravacycline might be less likely than tigecycline to cause nausea (an often treatment-limiting adverse event), although head-to-head comparative trials are lacking [7]. To date, three separate trials of eravacycline for the treatment of cIAIs have been completed, with no upcoming randomised controlled trials (RCTs) anticipated (http://www.clinicaltrials.gov). Therefore, we conducted this systematic review and meta-analysis of the available RCTs to evaluate the efficacy and safety of eravacycline for the treatment of cIAIs.

2. Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Search strategy and selection criteria

We searched the PubMed and EMBASE bibliographic databases using the search terms 'Eravacycline', 'TP434' and 'Xerava', without language restriction. As an example, the PubMed search was as follows: ((((eravacycline) OR (TP434)) OR (xerava))) OR 'eravacycline' [Supplementary Concept]. The searches and data extractions were completed independently by two authors up to 22 June 2020. We also searched the references of included studies in addition to unpublished studies on ClinicalTrails.gov, the EU Clinical Trials Register and the WHO International Clinical Trials Registry Platform. Any disagreement in the literature screening or data extraction was resolved through discussion. We included comparative RCTs evaluating the efficacy and safety of intravenous eravacycline versus comparators for adults with any infection. RCTs that used oral eravacycline and patients who received non-recommended doses were excluded.

2.2. Outcomes, data analysis and risk of bias

All study outcomes were assessed at the test-of-cure visit, which included clinical response in the modified intention-to-treat (MITT), microbiological ITT (mITT), clinically evaluable (CE) and ESBL-producing Enterobacteriaceae populations, all-cause mortality in the ITT population, total adverse events (AEs), nausea, vomiting, serious AEs and discontinuation due to AEs. Odds ratios (ORs) with 95% confidence intervals (CIs) were assessed using random-effects models, and heterogeneity (I^2) was evaluated using Cochran's Q test. We assessed study quality using the Cochrane risk-of-bias tool for RCTs (low, unclear or high) [8]. We performed all analyses using Comprehensive Meta-Analysis v.3 software (Biostat, Englewood, NJ, USA).

3. Results

3.1. Search results and study characteristics

The search process identified 420 articles, of which 3 RCTs [9–11] with a total of 1128 randomised patients were included in this meta-analysis (Fig. 1). One arm of the phase 2 study [9] was not included in the analyses based on our exclusion criteria owing to the use of a non-recommended dose. Characteristics of the included studies are summarised in Table 1, and the quality

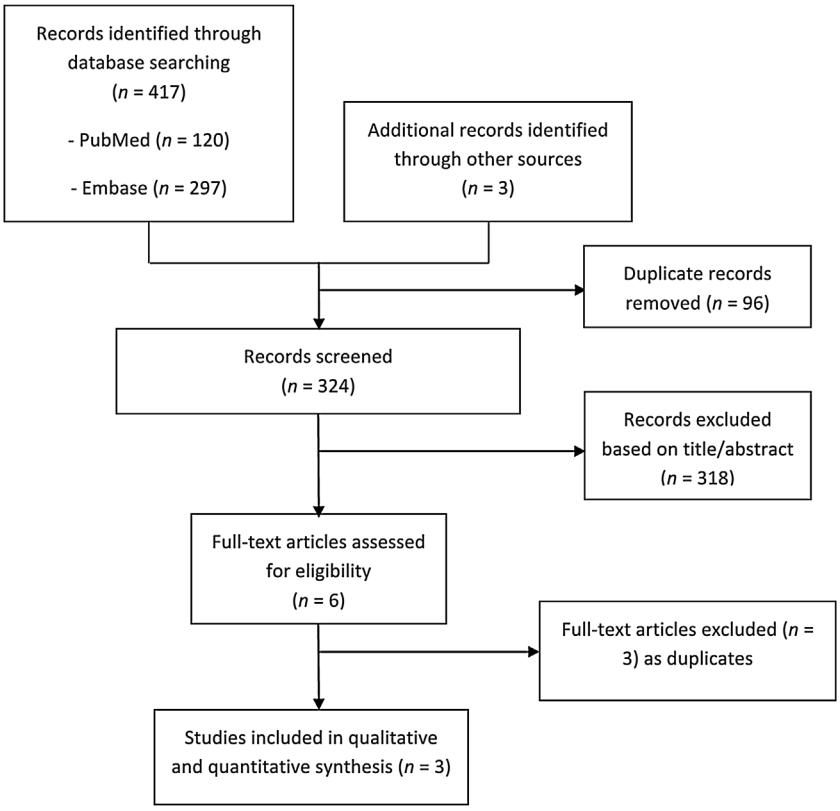

Fig. 1. Flowchart of the literature search and data extraction process from studies meeting the inclusion criteria.

Table 1
Characteristics of the included studies.

Study	Design	Location	No. of patients randomised	Patient characteristics	Eravacycline vs. comparator therapy	Duration of therapy (days)
Solomkin et al. [9]	Superiority, double-blind RCT	19 sites in USA, Europe and India	87	42 years; cIAIs; APACHE II score, 6; most common diagnosis, appendicitis (53%)	Eravacycline 1 mg/kg i.v. q12 h vs. ertapenem 1 g i.v. q24h	4–14
Solomkin et al. [10]	Non-inferiority, double-blind RCT	66 sites in USA, Argentina and South Africa	541	55 years; cIAIs; APACHE II score, 6.7; most common diagnosis, appendicitis (30%)	Eravacycline 1 mg/kg i.v. q12 h vs. ertapenem 1 g i.v. q24h	4–14
Solomkin et al. [11]	Non-inferiority, double-blind RCT	65 sites in USA and Europe	500	51 years; cIAIs; APACHE II score, 6.5; most common diagnosis, appendicitis (46%)	Eravacycline 1 mg/kg i.v. q12 h vs. meropenem 1 g i.v. q8h	4–14

RCT, randomised controlled trial; cIAI, complicated intra-abdominal infection; APACHE, Acute Physiology and Chronic Health Evaluation; i.v., intravenous; q12 h, every 12 h; q24 h, every 24 h; q8h, every 8 h.

assessment of these studies is provided in Table 2. All RCTs were double-blind and funded by Tetraphase Pharmaceuticals, the drug company manufacturing eravacycline. Most patients were from Europe followed by the USA, and a few were from South Africa, Argentina and India. The mean age of patients ranged from 41–51 years and the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was ~6. The duration of therapy was 4–14 days in all studies. All RCTs included patients with cIAIs, with complicated appendicitis being the most common diagnosis (30–55%). Other types of infection included peritonitis (24–50%), intra-abdominal abscess (3–63%), complicated cholecystitis (7–23%) and gastrointestinal perforation. Between 59–62% of patients in the phase 3 studies underwent open surgery and 31–34% underwent laparoscopic surgery [10,11]. Polymicrobial infections were predominant, and *Bacteroides* spp. isolates were found in 12–44% of patients. Gram-negative aerobes were isolated from 68–80% of patients and ESBL-producing Enterobacteriaceae were encountered in 7–19% of patients.

3.2. Study outcomes

There was no significant difference in clinical response between eravacycline and comparators in the MITT population (OR = 0.91, 95% CI 0.62–1.35; $P = 0.643$; $I^2 = 0\%$), mITT population (OR = 0.93, 95% CI 0.61–1.41; $P = 0.733$; $I^2 = 0\%$) or CE population (OR = 0.98, 95% CI 0.55–1.75; $P = 0.944$; $I^2 = 0\%$) (Fig. 2). Among patients with ESBL-producing Enterobacteriaceae, no significant difference was found in clinical response (OR = 1.59, 95% CI 0.38–6.55; $P = 0.524$; $I^2 = 0\%$). In addition, all-cause mortality also did not differ between the two groups (OR = 1.18, 95% CI 0.16–8.94; $P = 0.871$; $I^2 = 0\%$).

Eravacycline was associated with a significantly higher rate of total AEs (OR = 1.55, 95% CI 1.20–1.99; $P \leq 0.001$; $I^2 = 0\%$) and specifically with nausea (OR = 5.29, 95% CI 1.77–15.78; $P = 0.003$; $I^2 = 1.70\%$) (Fig. 3). An increase in vomiting was observed but this was not significant (OR = 1.44, 95% CI 0.73–2.86; $P = 0.291$; $I^2 = 1.70\%$). There were no significant differences in serious AEs (OR = 0.97, 95% CI 0.59–1.60; $P = 0.918$; $I^2 = 0\%$) or rates of drug discontinuation due to AEs (OR = 0.83, 95% CI 0.35–1.98; $P = 0.669$; $I^2 = 3.88\%$).

4. Discussion

This systematic review and meta-analysis of RCTs supports similar efficacy of eravacycline to carbapenems, specifically ertapenem and meropenem, in the treatment of cIAIs. We found no significant difference in all-cause mortality or clinical response rates, which were evaluated among three different populations within each study (MITT, mITT and CE). However, eravacycline was associated with a significant increase in total AEs, although no difference was found in the rate of serious AEs or discontinuation of therapy due to these AEs. The most common AEs that led to discontinuation of eravacycline were related to gastrointestinal disorders [4]. The odds of experiencing nausea among patients treated with eravacycline was more than 5-fold higher than among patients who received carbapenem therapy. The studies did not detail the severity of nausea or whether it was well controlled with anti-nausea medications; regardless, the significantly higher rates did not result in a significantly higher incidence of vomiting. However, there was a numerical increase in vomiting rate, for which this meta-analysis could be underpowered.

The data presented in our meta-analysis are from only three RCTs but with a total of 1128 randomised patients. One strength of this meta-analysis is that all studies were of high quality, double-blind and multi-continent. Importantly, however, the included trials in this meta-analysis excluded patients who were severely ill or who had renal or hepatic impairment, which may have reduced the chances of clinical failure and mortality. In fact, mortality did not exceed 2% in any of the three studies. Therefore, these results are likely ungeneralisable to critically ill patients until more data are available on the efficacy of eravacycline among sicker patients. Another limitation is that all included studies were of patients with

Table 2
Quality assessment of the included studies

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Solomkin et al. [9]	+	+	+	+	+	+	?
Solomkin et al. [10]	+	+	+	+	–	+	?
Solomkin et al. [11]	+	+	+	+	–	+	?

+, low risk of bias; ?, unclear risk of bias; –, high risk of bias.

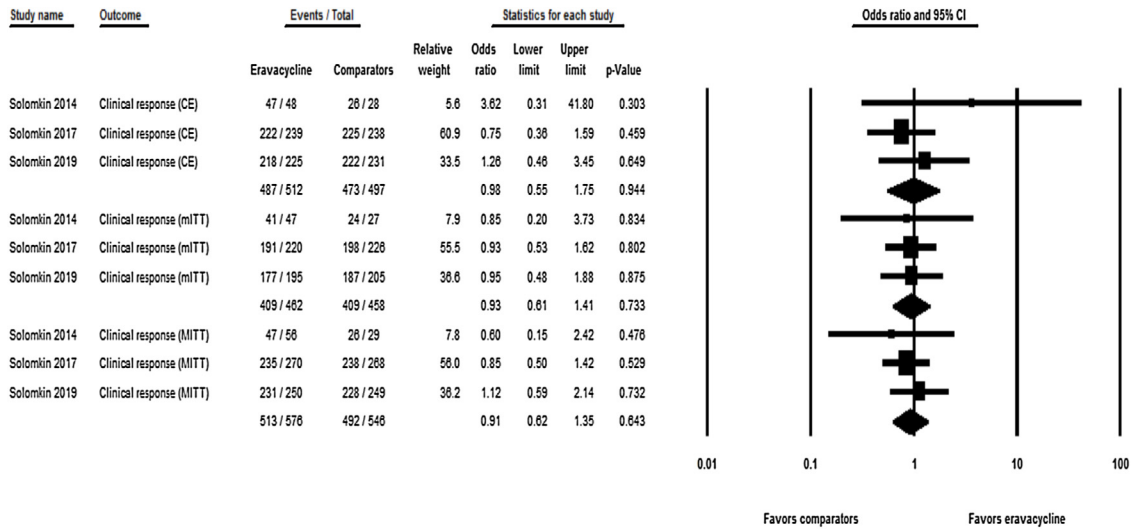

Fig. 2. Forest plot showing the odds ratios of clinical response in the clinically evaluable (CE), microbiological intention-to-treat (mITT) and modified intention-to-treat (MITT) populations receiving eravacycline versus comparators. Central vertical line indicates the 'no difference' point between the two groups. Squares, odds ratios; diamonds, pooled odds ratios.

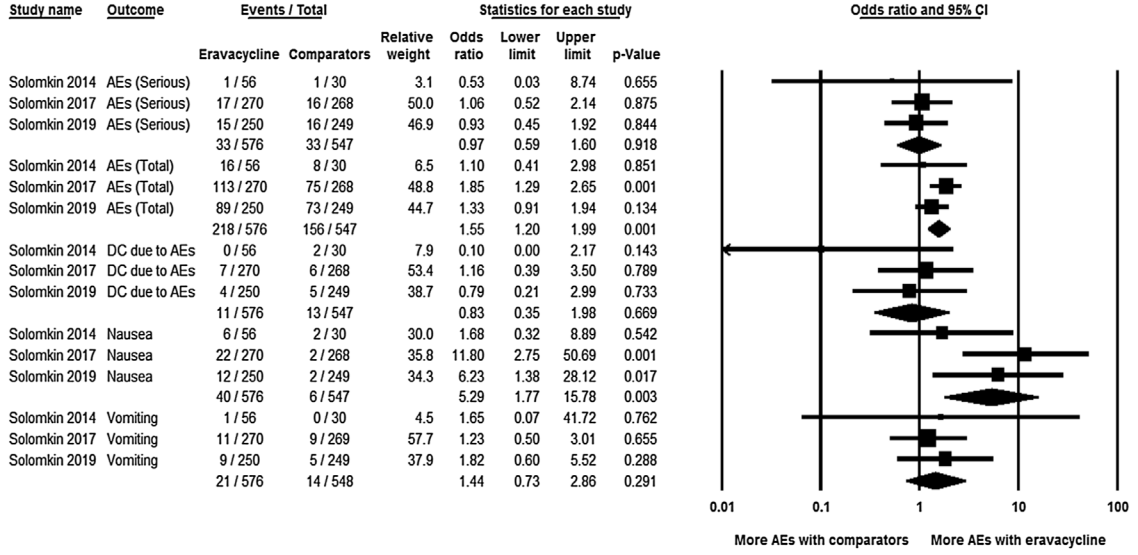

Fig. 3. Forest plot showing the odds ratios of total adverse events (AEs), serious AEs, discontinuation (DC) due to AEs, nausea and vomiting in patients receiving eravacycline versus comparators. Central vertical line indicates the 'no difference' point between the two groups. Squares, odds ratios; diamonds, pooled odds ratios.

cIAIs, and future RCTs should be conducted in other types of infections.

Carbapenems represent the current drug of choice for ESBL-producing bacteria, an increasingly common cause of cIAI [2]. However, the selective pressure caused by the use of carbapenems is likely responsible, to some degree, for the increase in carbapenem-resistant infections, which carry mortality rates of 30–50% [12]. In addition, previous meta-analyses reported higher risks of *Clostridioides difficile* and superinfection with carbapenems compared with other β-lactams [13,14]. Our meta-analysis did not identify a significant difference between eravacycline and carbapenems in clinical cure of cases caused by ESBL-producing Enterobacteriaceae. New options such as eravacycline provide potential alternatives to carbapenems for the treatment of MDR Gram-negative infections, including those caused by ESBL-producing organisms, which in turn may help to limit the spread of carbapenem resistance. Of the few antibiotic options that exist, most are limited in their utility owing to concerns for nephrotoxicity (aminoglycosides and polymyxins) or high rates of resistance (fluoroquinolones) [2,15,16]. In these cases, safer agents such as newer tetracyclines and plazomicin can be valuable options [17]. Although the new β-lactam/β-lactamase inhibitors can be used in some carbapenem-resistant Enterobacteriaceae (CRE) infections, β-lactam allergy and resistance impose a challenge. Tigecycline may remain a susceptible antibiotic option in MDR Gram-negative cases; however, the boxed warning for higher mortality and the high rates of nausea and vomiting that often lead to treatment discontinuation also hinder its clinical utility [18,19]. No head-to-head data exist at this time comparing tolerability rates between tigecycline and eravacycline. It is reassuring, however, that while all three of the eravacycline RCTs did document numerically higher rates of nausea and vomiting compared with carbapenem therapy, very few patients discontinued eravacycline therapy due to an AE. Antibiotic stewardship programmes have an important role in

reducing unnecessary use of broad-spectrum agents and selecting the appropriate option [20].

More pertinent to the current labelled indication is the benefit observed in the MIC ranges for certain pathogens. In general, eravacycline MICs have been noted to be 2–4 times lower than tigecycline MICs against most Gram-positive, Gram-negative and anaerobic organisms [21]. Importantly, Livermore et al. documented greater activity against CRE due to various resistance genes, including bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{NDM} and bla_{OXA-48}, as well porin loss + ESBL/AmpC production. MIC_{50} and MIC_{90} ranges for eravacycline against these resistance types were 0.25–0.5 mg/L and 0.5–2 mg/L, respectively, compared with 0.5–1 mg/L and 1–4 mg/L, respectively, for tigecycline [22]. The MIC_{50} and MIC_{90} ranges were also reported for both tetracycline agents against *Acinetobacter* spp. harbouring OXA-23/-40/-51/-58 carbapenemases, with eravacycline displaying values of 0.5–1 mg/L compared with 2–4 mg/L for tigecycline [22]. Unfortunately, none of the trials included in this meta-analysis included data on the efficacy of eravacycline in treating CRE and/or MDR *Acinetobacter* spp. Future clinical studies should evaluate the efficacy of eravacycline for these MDR bacteria.

In conclusion, eravacycline is clinically as effective as carbapenems for the treatment of cIAIs. As carbapenem utilisation may be linked with increased rates of carbapenem resistance and an increased risk of *C. difficile*, alternate therapeutic options are desirable. Rates of total AEs, and nausea specifically, were higher with eravacycline, but no difference between treatment options was found for serious AEs or drug discontinuation due to AEs.

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None.

Competing interests

None declared.

Ethical approval

Not required.

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