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BRIEF REPORT

Early Experience With Eravacycline for Complicated Infections

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Eravacycline (ERV) was used in 35 patients for various infections. The most common pathogen was *Klebsiella pneumoniae,* and 30-day survival was 74%. Absence of 30-day recurrence and resolution of signs and symptoms of infection were 91% and 57%, respectively. ERV was well-tolerated, with adverse events leading to drug discontinuation in one patient.

Keywords. eravacycline; multidrug-resistant Enterobacteriaceae; tetracyclines.

The Centers for Disease Control and Prevention (CDC) released their 2019 report maintaining carbapenem-resistant Enterobacteriaceae (CRE) and *Acinetobacter baumannii* as urgent threats, requiring aggressive action to improve treatment [1]. Eravacycline (ERV) is a novel fluorocycline of the tetracycline (TET) class approved by the Food and Drug Administration (FDA) in August 2018 for treatment of complicated intra-abdominal infections (cIAIs) following the IGNITE1 and IGNITE4 trials [2–4]. ERV has demonstrated potent in vitro activity against most gram-positive and gram-negative pathogens, including CRE and *A. baumannii*. Eravacycline was generally well tolerated in phase 3 trials, with gastrointestinal (GI) disturbances being the most common adverse events (AEs) [4]. Because of its potential role in patients with multidrug-resistant (MDR) organisms, allergies to ß-lactams, and/or if *Clostridioides difficile* infection (CDI) is present or of concern, we aimed to explore the clinical and safety outcomes among patients treated with ERV in the real-world setting [5].

METHODS

Our study was a multicenter, retrospective observational study conducted at 5 geographically distinct medical centers in the United States between December 2018 and October 2019. Inclusion criteria were age ≥18 years and ≥72 hours of treatment with ERV for any infection. Primary outcome was 30-day survival. Secondary outcomes included absence of 30-day recurrence and resolution of signs and symptoms while on ERV. Outcomes were measured from the first dose of ERV. Nosocomial infections were defined as those with positive index cultures ≥48 hours after hospital admission [6]. Combination therapy was defined as receiving any concomitant antimicrobial for ERV-targeted infection for ≥48 hours. CRE was defined by CDC criteria [7]. The FDA or Clinical and Laboratory Standards Institute breakpoints were applied for minimum inhibitory concentration (MIC) interpretation, whereas severity of illness was estimated using the Charlson Comorbidity Index (CCI) and Acute Physiology and Chronic Health Evaluation Score (APACHE II) [8]. The Fisher exact test and Mann-Whitney *U* test were used to compare nominal and continuous variables, respectively. IBM SPSS software, version 25.0 (SPSS, Inc., Chicago, IL, USA), was used for all statistical analyses.

RESULTS

Overall, 35 patients were included in our analysis. The median (interquartile range [IQR]) age was 56 (48–67) years, and 63% (22/35) were male. The median (IQR) APACHE II score and CCI were 16 (11–21) and 3 (2–7), respectively. Common comorbidities were diabetes (31%,11/35), followed by moderate to severe chronic kidney disease (29%, 10/35) and having any immunocompromised condition (29%, 10/35). Nosocomial infections comprised (26%, 9/35) of all infections. All patients were admitted to the intensive care unit at least once during their admission. Median (IQR) length of hospital stay was 44 (25–65) days. The majority (89%, 31/35) of patients had ≥1 risk factor for MDR organisms (n = 31; 68% [21/31] received antimicrobials for ≥24 hours, 61% [19/31] were hospitalized for ≥48 hours, 26% [8/31] underwent surgery in the past 30 days, and 26% [8/31] had a prior infection with a resistant organism). Common sources of infection were intra-abdominal (34%, 12/35), followed by respiratory tract (29%, 10/35), bone/joint (14%, 5/35), and skin/soft tissue (9%, 3/35). Positive blood cultures comprised 34% (12/35) of all index cultures, with the

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main source being intra-abdominal (42%, 5/12). Ultimately, all patients with positive blood cultures achieved clearance (100%, 12/12); however, 58% (7/12) cleared before ERV initiation.

The total number of isolated pathogens was 49, and in 26% (9/35) of patients, ERV was used for more than 1 pathogen. The most common pathogens were *Klebisella pneumoniae* (8/49), *Enterococcus faecium* (7/49), *Acinetobacter baumannii* (7/49), *Escherichia coli* (6/49), *Enterococcus faecalis* (4/49), *Enterobacter cloacae* (4/49), *Mycobacterium* spp. (3/49), *Klebsiella oxytoca* (2/49), *Proteus mirabilis* (2/49), *Stenotrophomonas maltophilia* (2/49), *Enterobacter aerogenes* (1/49), *Bacteroides fragilis* (1/49), *Clostridioides difficile* (1/49), and other non–*Clostridium perfingens* clostridia (1/49). Eight patients had CRE, with the most common pathogens being *K. pneumoniae* (4/8), *E. cloacae* (2/8), *E. coli* (1/8), and *K. oxytoca* (1/8). Among the tested *K. pneumoniae* (n = 2), the MIC for meropenem was ≥8 mg/L. Similarly, the ertapenem MIC was ≥2 mg/L for *E. cloacae* (n = 2). Carbapenem MICs for the remaining isolates were not reported.

Antibiotics with in vitro activity to index culture were administered to 66% (23/35) of subjects before ERV initiation, with some consuming >1 agent. The most common agents were meropenem (17%), ceftazidime/avibactam (12%), and piperacillin-tazobactam (10%). The FDA-approved dose of 1 mg/kg Q12 was administered to all patients except 1, who was on primidone, a CYP inducer, who therefore received a dose of 1.5 mg/kg Q12. Combination therapy was administered in 51% (18/35) of patients, with some consuming >1 agent. The most common agents were cefepime (13%), meropenem (13%), and polymyxin B (13%). Two patients received inhaled antibiotics; 1 received tobramycin and colistin, and the other received amikacin.

Among patients with previous positive cultures, ERV was initiated within a median (IQR) of 166 (99–412) hours of index cultures. Only 11% (4/35) of ERV initiation was within 72 hours of positive cultures, respectively. Overall, the median ERV duration was 9 (4–18) days. Notably, 97% (34/35) of patients had an infectious diseases consult. Fifty-four percent (19/35) of patients had a surgery consult; of these, 68% (13/19) underwent source control.

The most common reasons to select ERV were consolidation of the regimen (43%, 15/35), double coverage for suspected CRE infection (17%, 6/35), MDR *A. baumannii* (6%, 2/35), and lack of orally access (6%, 2/35). Other noteworthy reasons include ceftazidime-avibactam-related rash (3%, 1/35), tigecycline-related AE (3%, 1/35), recurrent infection with tigecycline (3%, 1/35), and a history of CDI (3%, 1/35).

Seventy-four percent (26/35) of patients had 30-day survival. Absence of 30-day recurrence occurred in 91% (32/35) of cases, and 57% (20/35) had resolved their signs and symptoms of infection. Eighty-eight percent (7/8) of subjects who were infected with CRE achieved 30-day survival. Details for patients who did not achieve 30-day survival are in Table 1. Notably, median APACHE II scores were significantly higher in patients with 30-day mortality compared with those who experienced 30-day survival: 21 vs 15, respectively ($P < .024$). There were no other remarkable differences in any of the patients' baseline criteria, such as age, infection type, and combination therapy.

Most cases continued on ERV until completion of their parenteral therapy (74%, 26/35). If therapy was switched, common agents included cefepime (2/9) and meropenem (2/9). Among those who switched, only 3/9 switched due to worsening signs/symptoms. Ultimately, 7/35 switched to an oral regimen, primarily a fluoroquinolone agent (2/7).

There were 7 probable ERV-AEs in 14% (5/35) of patients. The AEs observed were GI-related (57%), nephrotoxicity, altered mental status, and rash (14%). Overall, only 1 case of ERV GI AE led to drug discontinuation.

DISCUSSION

The results of our cohort demonstrate that the majority of ERV-treated patients achieved 30-day survival and absence of 30-day recurrence. Although the majority of patients had risk factors for clinical failure (ie, high index illness severity, immunocompromised states, and high bacterial burden infection sources), ERV had favorable outcomes in survival and protection from recurrence and resolution of signs and symptoms. In our study, 67% (8/12) of patients with positive blood cultures survived. Recent data show that ERV demonstrates similar eradication rates in bacteremic patients as comparators [9]. Survival benefit in this population is of high interest, particularly in comparison to tigecycline (TIG) [10]. Because TIG demonstrates lower serum drug concentrations due to higher volume of distribution when compared with ERV, it would be of interest to demonstrate if this translates to ERV being better suited for bacteremia [11]. Over half of subjects in our cohort had a surgery consult, and 37% (13/35) achieved adequate source control. Notwithstanding the benefit of ERV on patients' outcomes, these results cannot yet be corroborated independent of source control.

Tetracycline antibiotics are associated with frequent GI-AEs. The proportion of patients experiencing a probable ERV GI-AE in our cohort (14%) was comparable to that observed in the IGNITE1 and IGNITE4 trials [2, 3]. This is remarkably lower than the rates observed with its historical comparator TIG, which were as high as 24% for nausea alone [12]. Interestingly, failure/intolerance to TIG was the primary reason for ERV selection in 2 study subjects. With only 1 AE case leading to drug discontinuation, it appears that ERV is at least better tolerated than TIG.

In our study, ERV was used primarily for regimen consolidation. This was somewhat anticipated due to its wide spectrum of activity, which covers most gram-negatives including CRE

Table 1. Clinical Characteristics of Patients With 30-Day Mortality

Case	Age, Sex	Pathogen	Culture Specimen	Infection Source	ERV Start, h	ERV Duration, d	APACHE II	SOFA Score	ICU Stay, d	Prior Active Antimicrobial Therapy	Combination Antimicrobial Therapy With ERV	Days to Mortality	30-Day Recurrence	Reason for ERV Selection
1	48 F	*Proteus mirabilis* *Enterococcus faecium*	Blood[a]	Urinary	8	3	21	4	20	AMK, CZA, IPM, MEM, C/T	CZA	5	No	Consolidation of therapy regimen
2	53 M	*Escherichia coli*	Fluid	Intra-abdominal	NA[b]	26.5	11	4	26	None	None	26	No	Double coverage for suspected CRE[e]
3	54 M	*Stenotrophomonas maltophilia*	Blood[a]	Respiratory	2.5	13.5	23	8	45	None	None	16	No	Pathogen resistant to LVX and SXT
4	61 M	*Enterococcus faecium* *Klebsiella pneumoniae*	Fluid	Intra-abdominal	NA[b]	9.5	24	14	63	MEM, TZP	None	22	No	Concern for polymicrobial infection
5	77 F	*Acinetobacter baumannii* *Enterobacter cloacae* *Escherichia coli*	Tissue	Skin/soft tissue	19	15.5	15	1	1	TGC	None	15	No	Preference to TGC due to adverse event profile
6	65 M	*Acinetobacter baumannii*	BAL	Respiratory	20	12	26	4	20	AMK, CZA, IPM, MEM, C/T, CZA	CZA	13	No	Recurrent infection with previous regimens of TGC and TOB
7	69 M	*Enterococcus faecium* Bacteroides fragilis	Blood[a] Fluid[c]	Intra-abdominal	7	28	15	2	22	None	DAP LZD	28	Yes[d]	Persistent VRE bloodstream infection
8	59 F	None: empiric coverage per patient history	None [f]	Respiratory	NA[g]	3	21	3	4	None	MEM, VAN	26	No	Drug rash to CZA and double coverage for suspected CRE
9	62 M	*Escherichia coli* *Klebsiella aerogenes* *Enterococcus faecalis*	Blood[a]	Intra-abdominal	1.5	3	28	4	5	MEM, TZP, VAN	MEM, MTZ	20	No	Consolidation of therapy regimen

Abbreviations: AMK, amikacin; BAL, bronchoalveolar lavage; CRE, carbapenem-resistant Enterobacteriaceae; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; DAP, daptomycin; ERV, eravacycline; F, female; FEP, cefepime; IPM, imipenem; LVX, levofloxacin; LZD, linezolid; M, male; MEM, meropenem; MTZ, metronidazole; NA, not applicable; PMB, polymyxin B; SXT, trimethoprim-sulfamethoxazole; TOB, tobramycin; TGC, tigecycline; TZP, piperacillin-tazobactam; VAN, vancomycin; VRE, vancomycin-resistant enterococci.

[a]All cases have cleared their blood cultures. Cases 1 and 7 used ERV after blood culture clearance, whereas cases 3 and 9 used ERV before blood culture clearance.

[b]Time to ERV administration from positive culture was not possible to calculate because patient was a transfer with no documentation of timing of first culture in cases 2 and 3, while in case 8 no culture was isolated from the patient (empiric therapy).

[c]*Enterococcus faecium* growing from blood and *Bacteroides fragilis* from fluid.

[d]The subject's symptoms resolved initially, but the subject had a 30-day recurrence, followed by 30-day mortality.

[e]Patient was administered eravacycline for the purpose of double coverage at another institution before referral to the current institution. In the current study institution, no double coverage or combination agent was administered.

[f]No organisms were isolated because the regimen was empiric.

[g]Time to ERV administration from positive culture was not possible to calculate because therapy was empiric with no culture.

and *A. baumannii* and gram-positives including vancomycin-resistant enterococci and anaerobes. If the drug continues to perform efficiently in the real-world setting, it may be a valuable tool for antimicrobial stewardship, particularly as a fluoroquinolone- and carbapenem-sparing agent. Notably, ERV was selected due to ß-lactam allergies, CDI history, and tigecycline failure or intolerance. These circumstances are certainly evidence of the potential place in therapy that ERV has among its historical competitors.

Our study has several limitations. First, the small sample size challenges the external validity of the study. Second, therapy success, particularly in cIAIs, is complex and highly dependent on achieving timely, proper source control, appropriate in vitro active antibiotics, and effective standardized preoperative care practices. Therefore, it is challenging to attribute clinical success to the antibiotic selected alone. Finally, survival is a multifactorial outcome that was challenging to assess given the diversity observed in our patients' baseline pathogens, patient characteristics, and numerous ERV infection sources.

We present the largest early real-world multicenter experience evaluating ERV use in various infections across geographically distinct medical centers in the United States. Additionally, the majority of infectious sources in our cohort were beyond the FDA-approved indication of cIAIs. Larger real-world studies are essential to further confirm our early clinical findings.

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References

1. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2019*. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; **2019**.
2. Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) trial: a randomized clinical trial. JAMA Surg **2017**; 152:224–32.
3. Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs. meropenem in the treatment of complicated intra-abdominal infections. Clin Infect Dis **2019**; 69(6):921–9.
4. XERAVA (eravacycline) [package insert]. Tetraphase Pharmaceuticals, MA: Tetraphase Pharmaceuticals, Inc.; **2018**.
5. Alosaimy S, Abdul-Mutakabbir JC, Kebriaei R, et al. Evaluation of eravacycline: a novel fluorocycline. Pharmacotherapy **2020**; 40:221–38.
6. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, et al. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. Clin Infect Dis **2002**; 34:1431–9.
7. Center for Disease Control and Prevention. Healthcare-associated infections (HAIs): CRE definition. Available at: https://www.cdc.gov/hai/organisms/cre/definition.html. Accessed July 2019.
8. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med **1985**; 13:818–29.
9. Lawrence K, Olesky M, Izmailyan S, Tsai L. Efficiacy of eravacycline in secondary bacteremia: a post hoc analysis of two phase 3 studies of complicated intra-abdominal infections [poster 1978]. Presented at: 2018 Infectious Diseases Society of America (IDSA) Meeting; October 6, 2018; San Francisco, CA.
10. Wang J, Pan Y, Shen J, Xu Y. The efficacy and safety of tigecycline for the treatment of bloodstream infections: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob **2017**; 16:24.
11. Zhanel GG, Cheung D, Adam H, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. Drugs **2016**; 76:567–88.
12. Babinchak T, Ellis-Grosse E, Dartois N, et al; Tigecycline 301 Study Group; Tigecycline 306 Study Group. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clin Infect Dis **2005**; 41(Suppl 5):S354–67.