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BRIEF REPORT

Real-world Multicenter Analysis of Clinical Outcomes and Safety of Meropenem-Vaborbactam in Patients Treated for Serious Gram-Negative Bacterial Infections

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Fourty patients were treated with meropenem-vaborbactam (MEV) for serious Gram-negative bacterial (GNB) infections. Carbapenem-resistant *Enterobacteriaceae* (CRE) comprised 80.0% of all GNB infections. Clinical success occurred in 70.0% of patients. Mortality and recurrence at 30 days were 7.5% and 12.5%, respectively. One patient experienced a probable rash due to MEV.

Keywords. carbapenem-resistant *Enterobacteriaceae*; Gram-negative infections; meropenem-vaborbactam; multidrug-resistant.

Antimicrobial resistance in Gram-negative bacterial (GNB) infections, particularly carbapenem-resistant *Enterobacteriaceae* (CRE), is a key area of unmet clinical need [1]. CRE infections are independently associated with high mortality rates, have few effective therapeutic options, and may spread without adequate infection control strategies [2]. Meropenem-vaborbactam (MEV) combines meropenem, a carbapenem used in the clinical setting for decades, with vaborbactam, a novel boronic acid β-lactamase inhibitor with high potency against Ambler class A and C β-lactamases, including *Klebsiella pneumoniae* carbapenemases (KPC) [3]. In the TANGO I trial, the combination was associated with improved microbiological eradication and clinical cure compared to piperacillin/tazobactam. In the TANGO II trial, this combination was associated with improved clinical cure, decreased mortality, and less adverse events (AE) compared to best available therapy in resistant pathogens [4, 5]. In the current study, we describe early clinical experience with MEV for treatment of GNB infections in a real-world setting.

METHODS

This was a multicenter, retrospective observational study at 7 medical centers in the United States between October 2017 and June 2019. We included adult patients treated with MEV for any GNB infection, regardless of in vitro activity, for ≥72 hours. CRE was defined by the Centers for Disease Control and Prevention criteria [6]. Patients with concomitant infections were not excluded. Clinical success was defined as (1) 30-day survival following the first MEV dose; (2) absence of recurrence at 30 days following the last MEV dose; and (3) resolution of signs and symptoms of infection while on MEV. Thirty-day recurrence was defined as culture positive for the same organism isolated from index culture, counted 30 days from the end of treatment. Clinical failure was defined as lack of clinical success. Combination therapy was defined as receiving MEV plus any concomitant antibiotic with GNB activity for ≥48 hours. Infections were considered nosocomial if the positive index culture was obtained ≥48 hours after hospital admission. Active antibiotic therapy was defined according to in vitro activity. Risk factors for multidrug-resistant (MDR) organisms were defined as antimicrobials for >24 hours or hospitalization for >48 hours in the 90 days before index culture, admitted from nursing home or extended nursing facility, home infusion, chronic dialysis or surgery in the previous 30 days of index culture, home wound care, colonization or resistant with prior infection. The Clinical and Laboratory Standards Institute (CLSI) breakpoints were applied for minimum inhibitory concentration (MIC) interpretation. MEV testing was done using E-test or Liofilchem based on availability. At onset of infection, the severity of illness was estimated using the Acute Physiology and Chronic Health Evaluation Score (APACHE) II and the INCREMENT-CPE score in patients with CRE infections [7, 8]. Patient and treatment characteristics associated with clinical success were compared using the Fisher exact test for nominal

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data and the Mann-Whitney *U* test for continuous data, as appropriate. Statistical significance was determined at a *P* value of <.05. All analyses were performed using SPSS Statistics, version 25.0 (IBM corp., Armonk, NY, USA).

RESULTS

Study Population

Overall, 40 patients were included in our analysis. The median (interquartile range [IQR]) age was 58 (34–69) years, 65.0% (26/40) were male and 47.5% (19/40) were African American. The median APACHE II and INCREMENT-CPE scores (IQR) were 17 (10–24) and 8 (6–12), respectively. The median Charlson Comorbidity Index (CCI) score (IQR) was 6 (2–7). Common comorbidities included diabetes 60.0% (24/40), chronic kidney disease 37.5% (15/40), and heart failure 27.5% (11/40). Median creatinine clearance (IQR) was 55 (31–95) mL/min, and 22.5% (9/40) of patients were on dialysis within 30 days of index culture. Ninety percent (36/40) of patients had at least 1 risk factor for developing MDR organisms. Seventy percent (28/40) of patients were admitted to the intensive care unit (ICU) during their admission, with a median ICU stay (IQR) of 55 (9–96) days. Nosocomial infections comprised 45.0% (18/40) of all infections.

The most common sources of infection were pneumonia (32.5%, 13/40), urinary tract (20.0%, 8/40), intra-abdominal (12.5%, 5/40), and skin and soft tissue (SST; 12.5%, 5/40). Blood cultures were positive in 27.5% (11/40) of patients (n = 11; 2/11 primary bacteremia, 9/11 secondary bacteremia).

There was a total of 45 pathogens isolated among the 40 patients, with 10.0% (4/40) having polymicrobial infections. *Enterobactericeae* comprised 86.7% (39/45; n = 39 [33/39] CRE). The most common pathogens were *Klebsiella pneumoniae* (46.7%, 21/45), *Enterobacter cloacae* (20.0%, 9/45), *Escherichia coli* (13.3%, 6/45), *Burkholderia cepacia* (6.6%, 3/45), *Pseduomonas aeruginosa* (4.4%, 2/45), *Acinetobacter baumannii* (2.2%, 1/45), *Morganella morganii* (2.2%, 1/45), *Proteus mirabilis* (2.2%, 1/45), and *Serratia marcescens* (2.2%, 1/45).

Among tested *K. pneumoniae* (n = 16), *E. cloacae* (n = 8), and *E. coli* isolates (n = 4), MEV had an MIC_{50} (range) of 0.29/8 (0.032/8–4/8) mg/L, 0.38/8 (0.05/8–6.00/8) mg/L, and 0.77/8 (0.05/8–2.0/8) mg/L, respectively. For *A. baumannii*, *M. morganii*, and *P. mirabilis*, the MICs were 256/8, 0.38/8, and 0.094/8 mg/L, respectively. *P. aeruginosa* and *S. marcescens* MICs were not reported. Among strains that were tested for ceftazidime/avibactam (CZA) susceptibility, the MIC_{50} (range) was 2.0/4 (0.25/4–8/4) mg/L for *K. pneumoniae* (n = 15), 1.75/4 (8/4–256/4) mg/L for *E. cloacae* (n = 6), and 0.625/4 (0.25/4–1/4) mg/L for *E. coli* (n = 4) isolates. The *A. baumannii* and *S. marcescens* isolates had a CZA MIC of 256/4 and ≤8/4 mg/L, respectively. One isolate of *P. aeruginosa* exhibited a CZA MIC of 256; the other isolate's CZA MIC was not reported. *M. morganii* and *P. mirabilis* CZA MICs were not reported.

MEV was initiated within a median (IQR) of 71 (25–104) hours of index culture. Only 37.5% (15/40) were initiated within 48 hours, and 65% (26/40) within 96 hours. The median MEV duration (IQR) was 12 (7–15) days. All patients had an infectious disease consult, while 27.5% (11/40) had a surgical consult (n = 11; 9/11 underwent source control).

Active antibiotic therapy before MEV was administered to 27.5% (n = 11; 5/11 CZA, 2/11 amikacin, and 2/11 cefepime). Median time to active antibiotic therapy (IQR) was 38 (12–105) hours. Combination therapy was administered to 37.5% (n = 15; 4/15 minocycline, 4/15 levofloxacin, and 3/15 amikacin) with a median duration (IQR) of 12 (3–24) days. Twenty percent (8/40) of patients received inhaled antibiotics (n = 8; 6/8 colistin, 2/8 tobramycin). Ten percent of patients (4/40) switched to an alternative agent after at least 72 hours of MEV (n = 4; 3/4 CZA, 1/4 minocycline). Oral step-down therapy was given to 3 patients following MEV (n = 3; 2/3 minocycline, 1/3 ciprofloxacin). Only 5 patients were re-tested for MEV resistance; none developed MEV resistance.

Clinical success was achieved in 70.0% (28/40) of patients. Failure was primarily due to persistence of signs and symptoms in 22.5% (9/40), followed by recurrence in 12.5% (5/40) and mortality in 7.5% (3/40). Clinical criteria for patients who have experienced mortality or recurrence are displayed in Table 1. The most common infection type was pneumonia among subjects with clinical success (8/28) and clinical failure (4/12). Similarly, among those with clinical success, the most common infection type was pneumonia (9/28). Among 30-day survivors, 46.9% (17/37) were readmitted within 60 days. Sixty-day morality and 90-day mortality were 15.0% (6/40) and 22.5% (9/40), respectively.

Clinical success was lower in patients who had a nosocomial vs a community infection (50.0% vs 86.4%; *P* = .01), who were initiated on MEV late (>72 hours post–index culture) vs early (55% vs 85%; *P* = .038), and who received MEV combination therapy vs monotherapy (64% vs 80%; *P* = .29). There were no statistically significant differences in any of the disease severity markers between patients who had clinical success and those who did not. Among patients who died within 30 days, 100% (n = 3) received monotherapy, 66.6% (2/3) had APACHE II scores >20, and 66.6% (2/3) received inactive initial antibiotics.

One patient experienced a severe dermatological reaction consistent with Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) spectrum of disease 3 days after MEV initiation. MEV was discontinued, and the patient was managed with intravenous immunoglobulins, without improvement. The patient ultimately died upon withdrawal of care, and pathology report was consistent with the diagnosis. Notably, the patient had received meropenem within 90 days before infection.

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

Patient	Age Sex	Pathogen[a,b]	Culture Specimen	Infection Source	MEV Start From Index Culture, h	APACHE II	ICU Stay, d	Empiric Antimicrobial Therapy	Active Concomitant Antimicrobial Therapy	30-d Mortality	30-d Recurrence	Persistence of Signs and Symptoms	MBV MIC, mg/mL	CBP MIC, mg/L	CZA MIC, mg/L
1	59 M	*Enterobacter cloacae*	Sputum	Respiratory	95	14	48	MEM	None	Yes, day 21	No	Yes	0.06	MEM: 2 IMP: 4	0.25
2	62 F	*Klebsiella pneumoniae*	Wound	Skin and soft tissue	82	6	80	None	None	Yes, day 9	No	Yes	4	N/A	3
3	50 M	*Enterobacter cloacae*	Blood	Unknown	162	3	N/A	Cefepime, ceftriaxone, colistin, TMP-SMX	TMP-SMX	Yes, day 27	No	No	N/A	MEM: ≥16	N/A
4	62 F	*Klebsiella pneumoniae*	Urine	Urinary	145	15	N/A	None	None	No	Yes	Yes	0.032	None	2
5	45 M	*Klebsiella pneumoniae*	Sputum	Respiratory	99	17	N/A	CZA	CZA	No	Yes	Yes	0.064	MEM:1	
6	58 F	*Klebsiella pneumoniae*	Sputum	Respiratory	51	10	52	C/T	None	No	Yes	Yes	0.064	ETP: ≥8 MEM: ≥16	1.5
7	63 F	*Klebsiella pneumoniae*	Tissue	Intra-abdominal	56	22	111	CZA, aztreonam, amikacin	CZA	No	Yes	No	2	ETP: ≥8 MEM: ≥16	2
8	60 M	*Enterobacter cloacae* and *Klebsiella pneumoniae*	Wound	Skin and soft tissue	80	17	186	Cefepime	None	No	Yes	No	0.047[a]	ETP[3]: ≤0.5 MEM[3]: ≤0.25	1.5[3]

Abbreviations: CBP, carbapenem; CZA, ceftazidime-avibactam; CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; C/T, ceftolozane-tazobactam; cUTI, complicated urinary tract infection; DOR, doripenem; ETP, ertapenem; F, female; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMP, imipenem; MEV, meropenem-vaborbactam; MIC, minimum inhibitory concentration; M, male; MEM, meropenem; N/A, nonapplicable; VABP, ventilator-associated bacterial pneumonia.

[a]Minimum inhibitory concentrations are for *Enterobacter cloacae*.

[b]Minimum inhibitory concentrations are for *Klebsiella pneumoniae*.

DISCUSSION

MEV was used in 40 patients with complicated MDR infections and was successful in 70.0% (28/40). Clinical failure was largely attributed to failure to resolve signs and symptoms of infection (22.5%, 9/40). With careful consideration of the small sample size, our experience is an initial investigation promising clinical outcomes for MEV as a novel CRE agent in a real-world setting.

Improvement in outcome was achieved despite a high index illness severity, infections with high bacterial burden, CRE predominance, and delayed time to appropriate therapy [9]. Additionally, clinical outcomes remained consistent regardless of disease indicators, dose adjustment, or infection source. Notably, all of our study patients had an infectious disease consult, and many underwent source control (9/40). These factors impact microbiological workup and improve patient survival [10, 11].

High APACHE II scores, inactive initial antibiotics, and lack of carbapenem combination therapy are associated with higher 30-day mortality [12, 13]. In our cohort, most 30-day nonsurvivors had high APACHE II scores, did not receive active initial antibiotics, and did receive combination therapy.

MEV was generally well tolerated; 1 patient experienced a severe dermatological adverse reaction possibly related to MEV. Although carbapenems are not commonly associated with SJS/TEN, this reaction is well documented with β-lactam antibiotics, including β-lactamase inhibitor combinations [14]. More research focusing on the immunogenicity of boronic acid β-lactamase inhibitors would be valuable. No patients experienced *Clostridioides difficile*–associated diarrhea or acute kidney injury. These are important findings as the management of nephrotoxicity and *C. difficile* is a major challenge in critically ill patients with serious GNB infections.

Exceeding the TANGO II trial, we present the largest study to date evaluating the efficacy and safety of MEV for serious GNB infections, particularly CRE [5]. Our study's results are affirmative to recent real-world reports regarding MEV clinical success [15]. In our cohort, the distribution of patients among 7 geographically distinct medical centers in a real-world setting provides early clinical evidence that describes the role of MEV outside of randomized controlled trials. Conversely, this has caused variations in the laboratory diagnostics used, and we were therefore unable to detect types of carbapenemases, test for MEV susceptibility at a center location, and/or monitor emergence of resistance across the entire cohort. Although GNB are less common in SST infections, we did observe a few cases in our cohort. It would be of future interest to specify the type of SST involvement. Additionally, our study was limited by its retrospective design, lack of a control group, size of the study population, and inability to track AEs as closely as a clinical trial. Although it may be challenging to make definitive decisions about MEV's place in therapy at this time, our experience supports current evidence demonstrating positive clinical and safety outcomes in GNB infections treated with MEV.

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References

1. Doi Y, Bonomo RA, Hooper DC, et al; Gram-Negative Committee of the Antibacterial Resistance Leadership Group (ARLG)a. Gram-negative bacterial infections: research priorities, accomplishments, and future directions of the antibacterial resistance leadership group. Clin Infect Dis **2017**; 64:30–5.
2. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant *Enterobacteriaceae*: epidemiology and prevention. Clin Infect Dis **2011**; 53:60–7.
3. Jorgensen SCJ, Rybak MJ. Meropenem and vaborbactam: stepping up the battle against carbapenem-resistant *Enterobacteriaceae*. Pharmacotherapy **2018**; 38:444–61.
4. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. JAMA **2018**; 319:788–99.
5. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant *Enterobacteriaceae* infections: the TANGO II randomized clinical trial. Infect Dis Ther **2018**; 7:439–55.
6. 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.
7. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al; Investigators from the REIPI/ESGBIS/INCREMENT Group. A predictive model of mortality in patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae*. Mayo Clin Proc **2016**; 91:1362–71.
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. Lodise TP, Zhao Q, Fahrbach K, et al. A systematic review of the association between delayed appropriate therapy and mortality among patients hospitalized with infections due to *Klebsiella pneumoniae* or *Escherichia coli*: how long is too long? BMC Infect Dis **2018**; 18:625.
10. Martínez ML, Ferrer R, Torrents E, et al; Edusepsis Study Group. Impact of source control in patients with severe sepsis and septic shock. Crit Care Med **2017**; 45:11–9.
11. Viale P, Tedeschi S, Scudeller L, et al. Infectious diseases team for the early management of severe sepsis and septic shock in the emergency department. Clin Infect Dis **2017**; 65:1253–9.
12. Tzouvelekis LS, Markogiannakis A, Piperaki E, et al. Treating infections caused by carbapenemase-producing *Enterobacteriaceae*. Clin Microbiol Infect **2014**; 20:862–72.
13. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis **2012**; 55:943–50.
14. Lin YF, Yang CH, Sindy H, et al. Severe cutaneous adverse reactions related to systemic antibiotics. Clin Infect Dis **2014**; 58:1377–85.
15. Shields RK, McCreary EK, Marini RV, et al. Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant *Enterobacteriaceae* infections. Clin Infect Dis. https://doi.org/10.1093/cid/ciz1131