Clinical Infectious Diseases

BRIEF REPORT

Early Experience With Meropenem-Vaborbactam for Treatment of Carbapenem-resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,2,3] Erin K. McCreary,[3] Rachel V. Marini,[3] Ellen G. Kline,[1] Chelsea E. Jones,[1] Binghua Hao,[1,2] Liang Chen,[4] Barry N. Kreiswirth,[4] Yohei Doi,[1] Cornelius J. Clancy,[1,2,5] and M. Hong Nguyen[1,2,3]

[1]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, [2]Extensively Drug-Resistant Pathogen Laboratory, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, [3]Antibiotic Management Program, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, [4]Hackensack-Meridian Health Center for Discovery and Innovation, Nutley, New Jersey, USA, and [5]Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA

Twenty patients with carbapenem-resistant Enterobacteriaceae infections were treated with meropenem-vaborbactam. Thirty-day clinical success and survival rates were 65% (13/20) and 90% (18/20), respectively. Thirty-five percent of patients had microbiologic failures within 90 days. One patient developed a recurrent infection due to meropenem-vaborbactam–nonsusceptible, *ompK36* porin mutant *Klebsiella pneumoniae*.

Keywords. meropenem; vaborbactam; KPC; resistance; porin.

Meropenem-vaborbactam is a carbapenem-boronic acid β-lactamase inhibitor combination that demonstrates potent in vitro activity against *Klebsiella pneumoniae* carbapenemase (KPC)–producing Enterobacteriaceae [1]. The agent was approved by the US Food and Drug Administration (FDA) for treatment of complicated urinary tract infections in August 2017 [2]. Meropenem-vaborbactam was studied in 47 patients with microbiologically confirmed carbapenem-resistant Enterobacteriaceae (CRE) infections in a multinational, open-label, randomized clinical trial (TANGO-II) [3]. Clinical cure rates were significantly higher among patients receiving meropenem-vaborbactam (21/32 [65.6%]) compared to best available therapy (BAT; 5/15 [33.3%]) at end of treatment ($P = .03$) and test of cure (TOC; $P = .02$) evaluations. Meropenem-vaborbactam was associated with fewer severe treatment-emergent adverse events (TEAEs; 7/50 [14%] vs 7/25 [28%]) and renal-related TEAEs (2/50 [4%] vs 6/25 [24%]) than BAT. While these findings provide important preliminary efficacy and safety data to support use of meropenem-vaborbactam against CRE infections, their applicability to clinical practice is limited as only 15.6% of patients were in the intensive care unit (ICU) at the time of infection, BAT regimens were highly variable, and few patients with pneumonia were included in the trial [3]. The objective of this study is to report our experience with the use of meropenem-vaborbactam in clinical practice for the treatment of infections due to CRE, including long-term clinical and microbiologic outcomes.

METHODS

We conducted a prospective, observational study of patients with CRE infections who were treated with meropenem-vaborbactam for >48 hours at the University of Pittsburgh Medical Center between December 2017 and April 2019. During this time, meropenem-vaborbactam was recommended as the front-line therapy for infections caused by suspected or confirmed KPC-producing organisms. CRE was defined according to Centers for Disease Control and Prevention criteria by phenotypic resistance to any carbapenem or the presence of a carbapenemase hydrolyzing enzyme. Types of CRE infection were classified according to National Healthcare Safety Network criteria [4]. A standard dosing of 4 g intravenously every 8 hours was used, with adjustments for renal impairment made according to manufacturer recommendations. One patient receiving continuous renal replacement therapy (CRRT) was prescribed 2 g intravenously every 8 hours. Clinical success was defined as a composite of survival, resolution of signs and symptoms of infection, and absence of recurrent infection or microbiologic failure at 30 days following the onset of infection [5]. Microbiologic failure was defined as isolation of the same bacterial species following ≥7 days of meropenem-vaborbactam treatment. Minimum inhibitory concentrations (MICs) were determined using reference broth microdilution methods and interpreted according to Clinical and Laboratory Standards Institute criteria [6]; vaborbactam was tested at a fixed concentration of 8 μg/mL. All isolates were tested for the presence or absence of β-lactamases by multiplex polymerase chain reaction (PCR) [7]. Among *K. pneumoniae* isolates, gene mutations in *ompK35* and *ompK36* were further explored by PCR and Sanger DNA sequencing [7]. Outcome comparisons between groups were made using Fisher exact and Mann-Whitney *U* tests for categorical and continuous variables, respectively. Significance was defined as $P < .05$ (2-tailed).

RESULTS

Twenty consecutive patients were included in the study. Median age was 56 years (range, 31–83 years); 60% (12/20) of patients were men, and the median Charlson comorbidity index was

Received 16 August 2019; editorial decision 12 November 2019; accepted 15 November 2019; published online November 18, 2019.

Correspondence: R. K. Shields, University of Pittsburgh Department of Medicine, 3601 Fifth Ave, Falk Medical Bldg, Suite 5B, Pittsburgh, PA 15213 (shieldsrk@upmc.edu).

Clinical Infectious Diseases® 2020;71(3):667–71

DOI: 10.1093/cid/ciz1131

4 (range, 0–11). At the onset of infection, 70% (14/20) of patients were in the ICU and 35% (7/20) required renal replacement therapy (RRT; intermittent hemodialysis [n = 6] or CRRT [n = 1]). Median Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation (APACHE-II) scores were 5 (range, 1–14) and 20 (range, 7–40), respectively. CRE infection types included bacteremia (n = 8), pneumonia (n = 5/6 [83%] ventilator-associated), tracheobronchitis (n = 1/2 [50%] ventilator-associated), skin/soft tissue (n = 2), pyelonephritis (n = 1), and peritonitis with intra-abdominal abscess (n = 1). *Klebsiella pneumoniae* was the predominant pathogen (n = 14), followed by *Klebsiella oxytoca* (n = 2), *Escherichia coli* (n = 2), *Enterobacter cloacae* (n = 1), and *Citrobacter freundii* (n = 1). Ninety-five percent (19/20) of isolates were resistant to ertapenem; the lone exception was a *K. pneumoniae* isolate harboring a KPC-3 variant enzyme with a tyrosine for aspartic acid substitution at Ambler amino acid position 179 (D179Y; KPC-31, accession number MAPH01000113), which confers ceftazidime-avibactam resistance and restores carbapenem susceptibility [8]. Median meropenem and meropenem-vaborbactam MICs were 32 μg/mL (range, 0.25–128) and 0.03 μg/mL (range, 0.015–0.12), respectively. Ninety percent (18/20) of isolates produced KPC (KPC-3 [n = 10], KPC-2 [n = 7], or KPC-31 [n = 1]). All KPC-producing *K. pneumoniae* isolates (n = 14) harbored mutant *ompK35* genes with a premature stop codon and wild-type *ompK36* at baseline. The 2 non-KPC-producing isolates were an *E. coli* isolate with bla_{CMY} and a *K. oxytoca* isolate with $bla_{ACC,}$ $bla_{CMY,}$ and bla_{DHA} (ertapenem MIC = 2 μg/mL for both).

Meropenem-vaborbactam was administered as monotherapy in 80% (16/20) of patients; 4 patients received a second agent with in vitro activity against the infecting isolate for >48 hours (inhaled gentamicin [n = 2], intravenous and inhaled gentamicin [n = 1], and intravenous ciprofloxacin [n = 1]). The median duration of treatment was 8 days (range, 3–28 days). Thirty- and 90-day survival rates were 90% (18/20) and 80% (16/20), respectively. Clinical success was achieved in 65% (13/20) of patients. Failures were due to death (n = 2), worsening symptoms (n = 2), recurrent infection (n = 2), or persistent bacteremia for 10 days (n = 1). Success rates were 63% (5/8) and 67% (4/6) for bacteremia and pneumonia, respectively. Rates were not statistically different among patients who did (3/7 [43%]) or did not (10/13 [77%]) require RRT (P = .17). Median APACHE-II scores were higher among patients failing therapy compared to those experiencing clinical success (29 vs 15; P = .06). No other clinical or microbiologic factors were predictive of treatment response. Severe TEAEs were limited to 1 patient (5%) who developed eosinophilia following 19 days of meropenem-vaborbactam.

Microbiologic failures occurred in 35% (6/20) of patients due to relapsing CRE infections (n = 3), respiratory colonization (n = 1), breakthrough infection during treatment (n = 1), or persistent bacteremia (n = 1) (Table 1). The median time to microbiologic failure was 38.5 days (range, 12–67 days). Fifty percent (3/6) of recurrent isolates demonstrated a ≥8-fold meropenem-vaborbactam MIC increase (Table 1). One recurrent isolate was categorized as nonsusceptible to meropenem-vaborbactam (MIC = 8 μg/mL).

DISCUSSION

Our early experience with meropenem-vaborbactam for treatment of CRE infections supports the findings of TANGO-II and extends those observations to critically ill patients. Indeed, 70% of patients included in our cohort were in the ICU at the time of infection and the median APACHE-II score was 20. Overall clinical success and survival rates at 30 days were 65% and 90%, respectively, which are similar to rates of cure at the TOC visit and survival reported in TANGO-II (59% and 84%, respectively) [3]. Clinical success and 30-day survival rates with meropenem-vaborbactam were higher than, but not statistically different from, those we previously reported for ceftazidime-avibactam against CRE infections (59% and 76%, respectively) [9]. Our study also provides new insights into the efficacy of meropenem-vaborbactam against CRE pneumonia, an underrepresented infection type in TANGO-II that we previously identified as a risk factor for ceftazidime-avibactam clinical failures [3, 5]. Here, clinical success was achieved in 67% (4/6) of patients with CRE pneumonia and 100% (2/2) of patients with tracheobronchitis; all 8 patients with respiratory tract infections survived at 30 days. Likewise, none of the 4 patients with CRE pneumonia treated with meropenem-vaborbactam in TANGO-II died at 28 days, the regulatory guidance-based endpoint for hospital-acquired and ventilator-associated pneumonia. Among healthy volunteers, ratios of epithelial lining fluid to plasma concentrations are 65% and 79% for meropenem and vaborbactam, respectively [10]. Corresponding ratios for both ceftazidime and avibactam are approximately 30% [11]. Taken together, the preliminary data supporting use of meropenem-vaborbactam for CRE infections, including pneumonia, are encouraging, but must be validated in future studies.

Microbiologic failures were noted in more than one-third of patients treated with meropenem-vaborbactam, as CRE were reisolated within 90 days following treatment initiation. One failure occurred in a patient with bacteremia due to a ceftazidime-avibactam resistant *K. pneumoniae* isolate (MIC = 256 μg/mL) harboring KPC-31; the meropenem-vaborbactam MIC was 0.12 μg/mL. On day 12 of meropenem-vaborbactam treatment, a new abdominal wall abscess was identified. Abscess cultures grew *K. pneumoniae* with a meropenem-vaborbactam MIC of 8 μg/mL. Whole genome sequence (Illumina) analysis identified an IS*5* insertion in the *ompK36* promoter of the recurrent isolate that was not present at baseline; a single copy of bla_{KPC} on an IncFIA pBK30683-like plasmid that encoded KPC-31 was unchanged. The baseline and recurrent isolates were of sequence type 258, in which core

Table 1. Description of Cases Associated With Microbiologic Failure Following Treatment With Meropenem-Vaborbactam

Age, y (Sex)	Underlying Disease	CRE Pathogen	Type of Initial Infection	Initial Treatment Regimen (Duration, d)	Clinical Outcome at 30 d	Time to Microbiologic Failure, d[a]	Cause of Microbiologic Failure	MVB MIC Pre-Tx, µg/mL	MVB MIC Post-Tx, µg/mL
45 (F)	PUD w/ esophageal perforation s/p esophagectomy	KPC-3 *Klebsiella pneumoniae*	Primary bacteremia	MVB (19) plus IV gentamicin (1)	Failure	12	Abdominal wall abscess[b]	0.12	8[c]
76 (M)	Esophageal-pulmonary fistula s/p stent placement	KPC-3 *K. pneumoniae*	Primary bacteremia	MVB (14)	Success	49	Pneumonia	0.03	0.03
36 (M)	ESRD, CAD, s/p gastric sleeve procedure	KPC-3 *K. pneumoniae*	VAP	MVB (24) plus INH gentamicin (12)	Failure	41	Bacteremia	0.06	1
65 (M)	Disseminated peritoneal mucinous cancer	*Escherichia coli*	Peritonitis and abdominal abscess drained prior to Tx initiation	MVB (8)	Failure	67	Intra-abdominal abscess	0.03	0.5
83 (F)	ESRD, CRF	KPC-3 *K. pneumoniae*	Primary bacteremia	MVB (28)	Failure	10	Persistent bacteremia due to indwelling CVC	0.03	0.06
38 (F)	Respiratory failure due to influenza	KPC-3 *K. pneumoniae*	VAP	MVB (7) plus INH gentamicin (14)	Success	36	Respiratory colonization	0.03	0.03

Abbreviations: CAD, coronary artery disease; CRE, carbapenem-resistant Enterobacteriaceae; CRF, chronic respiratory failure; CVC, central venous catheter; ESRD, end-stage renal disease; F, female; INH, inhaled; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; M, male; MIC, minimum inhibitory concentration; MVB, meropenem-vaborbactam; PUD, peptic ulcer disease; s/p, status-post; Tx, treatment; VAP, ventilator-associated pneumonia.

[a]From the start of meropenem-vaborbactam treatment.

[b]The abscess was drained surgically and treatment was changed to intravenous ciprofloxacin, doxycycline, and metronidazole.

[c]Associated with an IS*5* promoter insertion in *ompK36* that was not present in the baseline isolate.

genomes differed by 2 single-nucleotide polymorphisms; both isolates harbored bla_{SHV-11} and bla_{TEM-1}. To our knowledge, this is the first case of meropenem-vaborbactam nonsusceptibility to be reported during or following treatment. Two additional patients experienced microbiologic failures due to isolates demonstrating at least an 8-fold MIC increase. We previously showed that meropenem-vaborbactam MICs were approximately 8-fold higher against KPC-producing *K. pneumoniae* isolates that harbored *ompK36* mutant genes than isolates with wild-type *ompK36* [7]. Findings here corroborate a prior in vitro study showing that meropenem-vaborbactam passage-selected *K. pneumoniae* contained partially functional or completely inactive *ompK36* genes [12]. In TANGO-II, a single isolate (1/32 [3%]) collected after randomization demonstrated a 4-fold meropenem-vaborbactam MIC increase (0.25 to 1 µg/mL); however, patients were only followed until a TOC visit 5–9 days after treatment completion. Our study design allowed for patients to be monitored at least 90 days after treatment initiation, and all recurrent isolates were tested for reduced susceptibility.

The clinical efficacy of meropenem-vaborbactam against infections caused by CRE isolates that demonstrate reduced susceptibility is unknown. In vitro data generated in a hollow-fiber infection model showed rapid bactericidal killing at the FDA-approved dose for isolates exhibiting MICs up to 8 µg/mL; however, experiments were only conducted for 32 hours [13]. Pooled data from these experiments, which included 3 isolates with MICs ≥8 µg/mL, suggest that vaborbactam 24-hour free drug area under the curve (AUC):MIC ratio >24 suppresses the emergence of resistance [14]. When the vaborbactam AUC:MIC ratio was <24, resistant mutants were selected that demonstrated a 4-fold MIC increase compared to baseline. As clinical experience grows, it will be imperative to define the efficacy of meropenem-vaborbactam against isolates harboring porin mutations that demonstrate higher MICs, and the frequency with which they are selected following treatment. Moreover, the impact of various porin mutations requires careful consideration and further characterization. The 2 most common mutations we have identified among KPC-producing *K. pneumoniae* clinical isolates have varying effects on the outer cell membrane. Mutant *ompK36* with a glycine–aspartic acid insertion at position 134 results in a constricted inner porin channel whereas an IS*5* promoter insertion results in decreased *ompK36* expression [1, 7, 15].

To date, only 3 other cases of meropenem-vaborbactam treatment against CRE infections have been reported outside of clinical trials [16–18]. Two of 3 patients were treated successfully following failure of ceftazidime-avibactam, including 1 case in which the isolate was ceftazidime-avibactam resistant [16, 17]. At this point it is unclear if meropenem-vaborbactam will be more effective than ceftazidime-avibactam for treatment of serious CRE infections. While the emergence of ceftazidime-avibactam resistance due to bla_{KPC} mutations is

well-documented [5, 16], it is unknown if resistance will emerge less frequently with meropenem-vaborbactam based on the limited in vitro data that are available [12]. Ceftazidime-avibactam has in vitro characteristics that offer potential advantages over meropenem-vaborbactam, including broader activity against OXA-48–producing Enterobacteriaceae and carbapenem-resistant *Pseudomonas aeruginosa* [19, 20]. Centers may prioritize 1 agent over the other based on their local epidemiology and clinical experience. Both agents are clearly safer and more effective than polymyxin-based combinations and other salvage regimens used to treat CRE infections historically [3, 21, 22]. Nevertheless, 2018 United States prescription data indicate that intravenous polymyxins were used more commonly than meropenem-vaborbactam and ceftazidime-avibactam to treat CRE infections [23]. In countries such as the United States where new anti-CRE agents are available, they should be prioritized unambiguously over polymyxins for treatment of CRE infections. Studies to elucidate potential clinical outcome and/or pharmacokinetic differences between ceftazidime-avibactam, meropenem-vaborbactam, and the recently FDA-approved imipenem-cilastatin-relebactam are needed.

We acknowledge that our study is limited by its single-center design and sample size. Nevertheless, this is the first systematic study of meropenem-vaborbactam in routine clinical practice. The data presented here harken a new era in which clinicians have a choice of effective antibiotics against CRE infections. Our findings speak to the need for future comparative-effectiveness studies that define advantages and disadvantages of newly approved CRE treatment options.

Notes

Financial support. This work was supported by an investigator-initiated grant from Melinta Pharmaceuticals. The following authors are supported by the National Institutes of Health (NIH): R. K. S. (grant numbers K08AI114883 and R03AI144636); B. N. K. (grant numbers R01AI090155, R2AI135250, and U19AI142731); Y. D. (grant numbers R01AI104895 and R21AI135522); C. J. C (grant numbers R21AI126157, R21AI142049, and R21AI144390); M. H. N. (grant number R21AI128338).

Potential conflicts of interest. R. K. S. has received grant support from Accelerate Diagnostics, Achaogen, Allergan, Merck, Melinta, Roche, Shionogi, Tetraphase, and VenatoRx, and the NIH; has served on advisory boards for Accelerate Diagnostics, Achaogen, Allergan, Entasis, Merck, Nabriva, Shionogi, and VenatoRx; and has received speaking honoraria from Allergan, Menarini, Pfizer, and T2Biosystems. R. V. M. has received an investigator-initiated grant from Merck. Y. D. has received grant support from Pfizer, MSD, Shionogi, Astellas, Kanto Chemical, the NIH, the Japan Society for the Promotion of Science, and the Japan Agency for Medical Research and Development; has served on advisory boards for Roche, Pfizer, Tetraphase, Recida, Fedora, VenatoRx, and Entasis; and has received speaking honoraria from Pfizer, Merck, and Shionogi. C. J. C. has been awarded investigator-initiated research grants from Astellas, Merck, Melinta, and Cidara for projects unrelated to this study; served on advisory boards or consulted for Astellas, Entasis, Merck, The Medicines Company, Cidara, Scynexis, Shionogi, Qpex, and Needham & Company; and has spoken at symposia sponsored by Merck and T2Biosystems. M. H. N. has been awarded investigator-initiated research grants from Astellas, Merck, Melinta, and Cidara for projects unrelated to this study and has served on advisory boards for Astellas, Merck, The Medicines Company, Scynexis, and Shionogi. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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