Meropenem-vaborbactam vs. standard of care for multidrug resistant carbapenem-resistant *Enterobacterales*

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ABSTRACT

Background
Antimicrobial resistance to gram negative organisms is an increasing issue worldwide, particularly with regard to extended-spectrum B-lactamase (ESBL) and carbapenem-resistant Enterobacterales (CRE). Meropenem/vaborbactam (M-V) is an approved antimicrobial for treatment of CRE infections. This study compares the outcomes of patients with CRE infections who were treated with M-V to standard of care (SoC) therapy.

Methods
A retrospective chart analysis was performed which analyzed 25 patients in the M-V group and 25 patients in the SoC group at an 800-bed tertiary care hospital in Southeast Michigan. Patients were matched by type of infection. Variables included basic demographics, infection source, bacterial species, as well as 30-day readmission, ICU admission, and creatinine levels pre- and post-treatment. The primary outcome of interest was 30-day mortality and clinical outcome (cure/improved/failure). Secondary outcomes included microbiological outcome (eradication/presumed eradication/persistence/presumed persistence) and acute kidney injury (AKI) on therapy. The data was analyzed using SPSS version 14.0.

Results
The most commonly used antibiotics in the SoC group were ceftazidime-avibactam (64%) and cefepime (32%). In both groups, the most common infection source was intra-abdominal (56%). The most commonly isolated pathogen in each group was *Klebsiella pneumoniae* (52% in M-V and 48% in SoC). Mortality and re-admission at 30 days did not differ statistically between the two groups. However, patients who received M-V were found to be more likely to achieve clinical cure, although this did not achieve statistical significance. Patients who were treated with SoC were significantly more likely to achieve an improved clinical outcome and presumed microbiological eradication (p=0.001 and 0.01 respectively). Of the 50 patients, only 26 patients (52%) met criteria to analyze for AKI. Patients who received M-V were more likely to have AKI (16% compared to 8%) but this did not reach statistical significance.

Conclusion
M-V is an important option for care of patients with infections due to MDR gram-negative bacteria. However, further studies are warranted to determine whether its use is associated with reduced mortality and improved clinical outcomes.

INTRODUCTION

Resistance to gram-negative organisms, particularly carbapenem-resistant Enterobacterales (CRE) is a growing concern. In 2019, the Center for Disease Control and Prevention (CDC) listed CRE as an urgent threat to be addressed (1). Meropenem-vaborbactam (M-V) was approved by the U.S Food & Drug Administration (FDA) in 2017 for the treatment of complicated urinary tract infections, including pyelonephritis (3). Since its approval, the antimicrobial has proven to be associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared to best available therapy in randomized clinical trials (4). However, there is little research done on comparing both clinical and microbiological cure with M-V versus other standard of care (SoC) treatment for multidrug resistant bacteria.

OBJECTIVE

The primary objective of this study was to assess and evaluate the clinical and microbiologic efficacy of M-V in the form of either a cure, improvement, failure or non-evaluable outcome.

METHODS

Study Design: This is a single-center, retrospective, observational matched cohort study conducted at an 800-bed tertiary care hospital located in a metropolitan city in the Southeast Michigan area. The study period was from 2016 – 2019 and was approved by the institution's investigational review board with waiver of consent.

Data Collection: Epidemiological, clinical and laboratory data were captured via the electronic medical records. Individual patient information collected included demographics, comorbidities, length of hospital stay, infection source, isolated organism, antibiotic use, 30-day readmission, ICU admission, clinical and microbiological outcome and serum creatinine pre- and post-treatment.

Statistical Analysis: Descriptive analysis and bivariate analyses were used when appropriate. For all bivariate analysis, Wilcoxon-Mann-Whitney, Fisher's exact, and t-test were used to assess ordinal, categorical, and continuous variables, respectively. The data analysis was performed using SPSS, Version 22.0 (IBM Corporation, Armonk, NY)

Table 1. Variable Definitions

Term	Definition
Cure	Clinical signs and symptoms are resolved, clinician documentation of cure, and/or no additional antibiotic therapy is necessary for the treatment of the infection.
Improvement	Partial resolution of clinical signs and symptoms and no additional antibiotic therapy is necessary for the treatment of the infection.
Failure	Inadequate resolution, or new or worsening clinical signs and symptoms, such that additional antibiotic therapy is necessary for treatment of the infection.
Eradication	Documentation of a negative bacterial culture from the same site as the initial positive baseline culture at least 5 days after the last dose of M/V or SoC.
Presumed eradication	The absence of follow up microbiological data/information in a patient with a clinical response of cure or improved.
Persistence	Bacterial growth from the same site as the initial positive baseline culture at least 4 days after the last M/V or SoC dose.
Presumed persistence	The absence of follow up microbiological data/information in a patient with a clinical response of failure.

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RESULTS

Table 2. Comparative Analysis of M-V and SoC

	M-V group N=25	SoC group N=25	P value
Mean age	63	66	0.526
Female	36%	60%	0.156
Mean length of stay (days)	33	32	0.899
Infection Source			
Intraabdominal	56%	56%	
Pneumonia	24%	24	
Genitourinary	16%	16	-
Skin/Soft tissue	4%	4	
Pathogen isolated			
Klebsiella pneumoniae	52%	48%	
Escherichia coli	20%	20%	
Enterobacter sp.	20%	16%	-
Citrobacter freundii	4%	8%	
Serratia marcescens	0%	4%	
Other *Klebsiella sp.*	4%	4%	
30-day mortality	48%	32%	0.387
30-day re-admission	20%	16%	1
Clinical Outcome			
Cure	52%	28%	0.148
Improved	0%	40%	**0.001**
Failure	48%	32%	0.098
Non-evaluable	0%	0%	-
Microbiological Outcome			
Eradication	24%	4%	0.098
Presumed eradication	28%	68%	**0.01**
Persistence	8%	6%	1
Presumed persistence	40%	24%	0.364
	Treated with M-V N=25	Treated with SoC N=25	P value
Acute Kidney Injury*	16%	8%	1

*AKI was defined as an occurrence of post-baseline creatinine > 1.5 times the baseline serum creatinine, from 48 hours post-therapy completion. A total of 14 patients were excluded in the M-V group and 10 patients in the SoC group due to baseline creatinine > 2.0.

CONCLUSION

- M-V is an important option for care of patients with infections due to MDR gram-negative bacteria.
- Further studies are warranted to determine whether its use is associated with reduced mortality and improved clinical outcomes.

LIMITATIONS

- Single study site
- Retrospective study design
- Small sample size

FINANCIAL DISCLOSURES

This project was funded through a grant awarded by Melinta Therapeutics.