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COMMENTARY

The Place of Meropenem–Vaborbactam in the Management of Carbapenem-Resistant Gram-Negative Infections

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Key Summary Points

This Topical Collection of four papers discuss the different aspects of cephalosporin-resistant Enterobacterales (CRE) including the biology of this group of pathogens, the microbiological activity of meropenem–vaborbactam (M-V), the pharmacodynamic profile of the combination, and the clinical implications of using M-V.

These articles describe the growing problem of antibiotic resistance among Gram-negative bacteria, CRE, and the development of a new carbapenem-β-lactamase inhibitor, and a novel clinical trial designed to test the experimental drug against the best available treatment.

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DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14046302.

EDITORIAL

Antimicrobial resistance is an existential threat to human health. In 2017 the World Health Organization identified three key species as targets for research for new compounds to manage carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem and extended-spectrum cephalosporin-resistant Enterobacterales (CRE).

In this Topical Collection, four papers discuss the different aspects of CRE including the biology of this group of pathogens, the microbiological activity of meropenem–vaborbactam (M-V), the pharmacodynamic profile of the combination, and the clinical implications of using M-V.

Hansen [1] describes the history of β-lactams, their discovery, and resistance development, drawing attention to the global emergence of carbapenem resistance. CRE incidence is increasing with over 50,000 cases reported

annually in the USA. The paper describes the breadth of enzymes observed within the four Ambler classes A–D. The epidemiology of various enzymes such as *Klebsiella pneumoniae* carbapenemase (KPC) is discussed along with the activity of various β-lactam-β-lactamase inhibitors against an array of enzymes. The distribution of resistance is illustrated with several useful figures which help portray the extent of the growing problem.

Bhowmick and Weinstein [2] describe the novel boron-based β-lactamase inhibitor vaborbactam. This molecule was specifically developed to be effective against a range of resistant species including those with KPC enzymes. Vaborbactam has no antibacterial activity, but in combination with meropenem creates a molecule with enhanced activity against a wide range of Gram-negative bacilli, including those producing Ambler class A and C. M-V has been shown to be highly active against KPC 2 and KPC 3, but as with other β-lactam/β-lactamase inhibitors is inactive against class B or OXA-48. The authors report several examples of large surveillance programs which illustrated the benefit of vaborbactam. Various in vitro and in vivo studies demonstrated a low potential to develop resistance to M-V which was also shown in the TANGO clinical program.

The challenges and complexities of developing a combination antimicrobial are discussed by Wenzler and Scoble [3]. The pharmacokinetic profiles of meropenem and vaborbactam are well matched with an optimized dosing regimen of 4 g every 8 h given as a 3-h infusion. This regimen yields a proven and reliable probability target attainment against most CRE. Furthermore, pharmacodynamic data provide evidence that pharmacokinetic/pharmacodynamic (PK/PD) targets for both bactericidal activity and prevention of resistance in pathogens with a minimum inhibitory concentration of no greater than 8 mg/l. Appropriate animal models which studied CRE in phase III clinical trials on complicated urinary tract infection (UTI), acute pyelonephritis, and hospital and ventilator-associated pneumonia were conducted.

The balance of designing and completing trials for regulatory purposes and the daily clinical challenges created by multidrug-resistant pathogens is difficult to achieve. Thus, more broad range, real-world settings help clinicians understand the efficacy of an antibiotic-resistant strain such as KPC infections. There are many hurdles to designing a trial which yields data on vital clinical subsets such as prior antibiotic exposure, renal failure, immunosuppressed patients, and other complexities which are usually excluded by phase III programs. Equally the conventional studies can only recruit patients whose infecting organism is susceptible to the comparator drug, thus negating studies against resistant pathogens which would be unethical. An elegant case presentation describes a typical daily case which would not be enrolled in a regulatory type study because of comorbidities and complications. The TANGO II study was designed to compare patients who received M-V versus the best available therapy (BAT) as per clinician choice. Clearly these studies are not designed to show any statistical differences but some interesting trends were reported [4].

This collection of papers describes the growing problem of antibiotic resistance among Gram-negative bacteria, CRE, and the development of a new carbapenem-β-lactamase inhibitor, and a novel clinical trial designed to test the experimental drug against BAT. M-V is active against the key KPC-producing Enterobacterales in complicated urinary tract and other types of infections, and in difficult to study, complex patients. To date the drug appears to be safe and well tolerated.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

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