Official journal of the Spanish Society of Chemotherapy

New antimicrobial alternatives in the treatment of pneumonia

María Forteza Guillot[1]
María Martín Cerezuela[2]
Paula Ramírez[1]

New evidence in severe pneumonia: meropenem-vaborbactam

[1]Servicio de Medicina Intensiva. Hospital Universitario la Fe, Valencia, Spain.
[2]Servicio de Farmacia Hospitalaria. Hospital Universitario la Fe, Valencia, Spain.

Revista Española de Quimioterapia
doi:10.37201/req/s01.10.2022

ABSTRACT

The appearance and spread of new mechanisms of bacterial resistance to antibiotics is a serious health problem. One of the most difficult resistance mechanisms to treat is the production of carbapenemases. Carbapenemase KPC is one of those mechanisms with few therapeutic options. Meropenem-vaborbactam has shown great efficacy against this type of microorganism, both from a clinical and microbiological point of view. Its good pharmacokinetics, including in the lung, and its safety profile make meropenem-vaborbactam an excellent therapeutic option. Finally, the absence of resistance genesis during treatment seems to indicate that its efficacy will be long-lasting.

Keywords: Gram-negative bacteria, multiresistant *Enterobacteriaceae*, ceftazidime-avibactam, meropenem-vaborbactam,

INTRODUCTION

The combination of carbapenem (meropenem) with the beta-lactamase inhibitor vaborbactam is one of the latest therapeutic novelties available on the market. Meropenem-vaborbactam (MV) represents an important therapeutic advance due to its wide antimicrobial spectrum that includes the dreaded carbapenemase KPC, its clinical efficacy, its correct pharmacokinetic profile and its large safety margin.

MICROBIOLOGY

In addition to the usual coverage of beta-lactams, MV is effective against type A and C beta-lactamases. Among them, the KPC type carbapenemase (class A) is one of the most frequent and difficult to treat threats among the resistances developed by Gram-negative bacteria. This type of resistance is widely distributed in the United States and multiple papers from that area demonstrate the ability of MV to treat KPC producing *Enterobacteriaceae* [1,2].

Clinical experience with MV has shown the absence of resistance development with exposure to the drug. Lomonovskaya assessed patients treated with MV in Tango II clinical trial and found only 1 of 50 patients treated an increase in MIC from 0.25/8 to 1/8 mg/L (within the susceptibility range). This aspect is of great interest in contrast to the findings detected with the treatment of KPC enterobacteria with ceftazidime-avibactam. In vitro exposure to this drug causes a mutation in the "omega loop" of the KPC enzyme that manages to increase its hydrolysis capacity on ceftazidime and overcomes the effect of avibactam. In parallel, a recovery of susceptibility to meropenem is observed, but not in a lasting way. This resistance phenomenon has been observed in the clinical practice [3-8] (Table 1).

Table 1 **Development of resistance to ceftazidime-avibactam.**

Study (year)	Development of resistance to ceftazidime-avibactam
Shields et al, 2016 [3]	8.1% (3/37) after 10-19 days of treatment
Lomonovskaya et al, 2017 (from Tango II study) [4]	25% (1/4)
Giddins et al, 2018 [5]	1 clinic case
Gaibani et al, 2018 [6]	
Athans et al, 2019 [7]	1 clinic case
Tumbarello et al, 2022 [8]	59,5% of strains resistant to ceftazidime-avibactam

Correspondence:
Paula Ramírez
Servicio de Medicina Intensiva
Hospital Universitario y Politécnico la Fe, Valencia, Spain.
E-mail: paula.ramirez.galleymore@gmail.com

Vaborbactam, for the time being in union with meropenem, administered together with aztreonam has been shown to be effective in the *in vitro* treatment of metallo-beta-lactamases that coincide with a beta-lactamase that otherwise would inhibit the efficacy of aztreonam [9].

PHARMACOKINETICS/PHARMACODYNAMICS

Preclinical and clinical data have shown good pharmacokinetic parallelism between the two components of MV, and a predictable PK that maintains correct plasma concentrations with the dose of 4 g (2g/2g) of MV administered every 8h in a 3 hour infusion for all strains with a MIC equal to or lower than 8 mg/l (10). Intravenous dose adjustment is recommended in patients with renal insufficiency (eGFR < 50 ml/min/1,73 m^2 or ACr ≤ 39 ml/min). In case of critically ill patients treated with continuous hemodialysis the MV dose will be 2 g (1 meropenem + 1 vaborbactam) in 3 h infusion every 8h [11].

One of the most frequent infectious focus in the critically ill patient, and one that also poses a pharmacokinetic challenge, is the lung. MV was evaluated in 10 healthy subjects with plasma and alveolar epithelial fluid sampling and a plasma/alveolar fluid ratio of 65% and 79% was obtained for the two components of MV, respectively [12]. Therefore MV is a correct choice for the treatment of pneumonia from the Pk point of view.

CLINICAL EXPERIENCE

Tango I and Tango II clinical trials provided MV indication for: complicated urinary tract infection (including pyelonephritis), complicated intraabdominal infection, in-hospital pneumonia (including ventilator-associated pneumonia), bacteremia occurring in conjunction with, or suspected to be associated with, any of the above infections, and the treatment of infections due to aerobic gram-negative microorganisms in adults with limited treatment options [4,13].

The results of the Tango II trial are of particular interest for the critically ill patient. Both clinical and microbiological responses were better in the MV-treated group compared to patients treated with best available therapy. Although not statistically significant, survival was also superior in the MV group. Since the control group included the use of aminoglycosides and/or colistin, renal adverse effects were more frequent in this group [4]. Basetti *et al* performed a post hoc analysis of the subgroup of patients treated with MV or best available therapy in the first line of treatment; this analysis showed a potentiation of the positive results of MV [14].

Three recent publications have shown clinical outcomes with MV used in care. In 2020 Shields *et al* published a prospective series including 20 patients, most of them (70%) were admitted to ICU and most of the strains (90%) were *Enterobacteriaceae* with KPC. MV was administered as monotherapy in 80% of the cases. Clinical and microbiological response was obtained in 65% of cases. Mortality in the series was strikingly low; 10% at day 30 and 20% at day 90 of evolution. Only one case of serious adverse event was described: eosinophilia that responded to treatment cessation [15].

In 2020 Alosaimy *et al* published a retrospective registry that included 40 patients (70% of them in ICU). Most strains were carbapenem-resistant enterobacteria (86,7%). MV was administered as monotherapy in 62% of cases and as rescue treatment in 27,5%. A correct clinical response was achieved in 70% of patients. It is of interest that the lack of response could be related to a late onset of MV (>72 h). One case of Steven-Johson syndrome was described as an adverse effect [16].

Finally in 2022 Tumbarello *et al* published the results of a retrospective registry on the compassionate use of MV in 12 Italian hospitals. 37 cases were collected; 23 bacteremias, 10 respiratory infections, 2 urinary tract infections, 1 soft tissue infection, 1 abdominal infection. Again 70% of the patients were admitted to the ICU. MV was used in monotherapy in 14 patients (38%) and the median time between clinical onset and treatment was 5 days. An interesting fact is the frequent presence of resistance to ceftazidime-avibactam observed, even without previous exposure to the drug (59,5%). Clinical cure was obtained in 28 of the treated cases (75,6%). Three patients suffered a recurrence of infection that was successfully treated with a second course of MV treatment. Nine patients died (24,3%); six of these patients started treatment with MV with a lag time of more than 48h from the onset of the clinic. There were no cases of development of resistance to MV during treatment [8].

CONCLUSIONS

MV is a highly effective option for the treatment of all types of infectious focus, especially when the etiological agent is a KPC-producing. Its pharmacokinetic and safety profile make the drug an excellent option for the critically ill patient. Compared to ceftazidime-avibactam MV does not induce the development of intra-treatment resistance.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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