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Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing *Klebsiella pneumoniae*: a multicentre study

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Objectives: To explore the real-life performance of meropenem/vaborbactam for treating serious KPC-producing *Klebsiella pneumoniae* infections, including those resistant to ceftazidime/avibactam.

Methods: A retrospective observational cohort study was conducted in 12 Italian hospitals. Enrolled patients had *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-*Kp*) infections (59.5% of which were ceftazidime/avibactam resistant). Patients who received ≥72 h of meropenem/vaborbactam therapy (with or without other antimicrobials) in a compassionate-use setting were included.

Results: The 37 infections (all hospital-acquired) were mainly bacteraemic (BSIs, $n=23$) or lower respiratory tract infections (LRTIs, $n=10$). Clinical cure was achieved in 28 (75.6%) cases and microbiologically confirmed in all 25 with follow-up cultures. Three (10.7%) of the 28 clinical cures (all BSIs, 2/3 microbiologically confirmed) were followed by in-hospital recurrences after meropenem/vaborbactam was discontinued (median interval: 18 days). All three recurrences were susceptible to meropenem/vaborbactam and successfully managed with meropenem/vaborbactam combined with colistin or fosfomycin. Nine patients (24.3%) (all with BSIs or LRTIs) died in hospital with persistent signs of infection. Most were aged over 60 years, with high comorbidity burdens and INCREMENT scores ≥8. Only one had received meropenem/vaborbactam monotherapy. Six began meropenem/vaborbactam therapy >48 h after infection onset. Outcomes were unrelated to the isolate's ceftazidime/avibactam susceptibility status. The single adverse event observed consisted of severe leukopenia with thrombocytopenia.

Conclusions: With the well-known limitations of real-life retrospective studies, our results support previous findings indicating that meropenem/vaborbactam therapy will be a safe, effective tool for managing serious KPC-*Kp* infections, including the increasing proportion displaying resistance to ceftazidime/avibactam.

Introduction

The fixed-dose antimicrobial agent meropenem/vaborbactam combines the broad-spectrum antimicrobial meropenem with a novel cyclic boronic acid β-lactamase inhibitor, vaborbactam, which restores meropenem's activity against bacteria producing *Klebsiella pneumoniae* carbapenemase (KPC) and several other serine β-lactamases. Meropenem/vaborbactam is inactive against bacteria that produce MBLs or oxacillinases with carbapenemase activity.[1] The drug was approved in 2017 by the FDA for treating complicated urinary tract infections (cUTIs) and in 2018 by the EMA for treating cUTIs, complicated intra-abdominal infections, hospital-acquired pneumonia and aerobic Gram-negative infections in adults with limited treatment options.[1]

The approvals were based on data from two randomized Phase 3 clinical trials: TANGO I, which documented meropenem/vaborbactam's non-inferiority to piperacillin/tazobactam for treating cUTIs,[2] and TANGO II, which showed the new drug to be safer and more effective than best available therapies for managing infections caused by carbapenem-resistant Enterobacterales (CRE).[3] Evidence on the real-life use of meropenem/vaborbactam is limited and based exclusively on observational studies, which confirm its efficacy and safety in the treatment of CRE infections[4–6] and suggest that they are similar to those of ceftazidime/avibactam.[7] The latter is now widely used as first-line treatment of CRE infections[8–11] despite increasing reports of the emergence during treatment of *in vitro* and *in vivo* resistance.[12–15]

To expand the real-life treatment evidence base for use of meropenem/vaborbactam in treating CRE infections, we conducted a retrospective observational study of patients with KPC-producing *K. pneumoniae* (KPC-*Kp*) infections treated with meropenem/vaborbactam, including a large number caused by isolates that were resistant to ceftazidime/avibactam.

Methods

The study cohort comprised 37 inpatients from 12 Italian hospitals, who received ≥72 h of meropenem/vaborbactam therapy for KPC-*Kp* infections between 1 September 2020 and 30 April 2021. The drug was administered within a compassionate-use programme activated by A. Menarini IFR before meropenem/vaborbactam was commercially available in Italy. The company had no further involvement in the study. The protocol was approved by the Research Ethics Committee of the coordinating centre, and the informed consent requirement was waived because of the study's retrospective, non-interventional nature.

Cohort eligibility was open to patients aged ≥18 years, with monomicrobial culture-confirmed KPC-*Kp* infections, who received meropenem/vaborbactam therapy (with or without other antimicrobials). Candidates were excluded if they had *K. pneumoniae* isolates producing KPCs plus other carbapenemases, and in any case the isolates were resistant to meropenem/vaborbactam. Isolates were identified with the Vitek 2 (bioMérieux, Marcy-l'Étoile, France) or MALDI-TOF MS (MALDI Biotyper, Bruker Daltonics GmbH, Leipzig, Germany, or Vitek-MS, bioMérieux). Each hospital conducted susceptibility testing according to its own protocols (mainly using bioMérieux's Vitek 2 system or broth microdilution). Meropenem/vaborbactam MICs were determined with gradient diffusion tests. Susceptibility findings were classified according to EUCAST breakpoints (https://eucast.org). Carbapenemases were identified with the NG-Test CARBA 5 (NG Biotech, Guipry, France); RESIST-3 O.O.K. K-SeT (Coris BioConcept, Gembloux, Belgium); eazyplex® SuperBug CRE assay (Amplex Diagnostics GmbH, Germany); or the Xpert Carba-R assay (Cepheid, Buccinasco, Italy). Meropenem/vaborbactam infusions [4 g (meropenem 2 g + vaborbactam 2 g) q8h] were delivered over a 3 h period, and dosage was adjusted for renal impairment, as per manufacturer's recommendations.

Data collected included patients' demographic characteristics and comorbidities; clinical and microbiological features of the infection; and meropenem/vaborbactam treatment details (including adverse effects). Primary efficacy outcomes were clinical cure and all-cause in-hospital mortality. Secondary outcomes included in-hospital recurrence of the infection and adverse events. (See Table 1 for detailed definitions.)

Results

During the study period, 37 adults hospitalized in the participating centres received meropenem/vaborbactam for a KPC-*Kp* infection (Table 1). All infections were hospital-acquired, almost 90% were bloodstream or lower respiratory tract infections (BSI and LRTI, respectively), and 70% were diagnosed in an ICU. All 37 isolates were resistant to penicillins, extended-spectrum cephalosporins, ciprofloxacin and meropenem, and 22 were resistant to ceftazidime/avibactam. All displayed *in vitro* susceptibility to meropenem/vaborbactam. Some were also susceptible to fosfomycin, colistin, gentamicin, tigecycline or amikacin.

The median interval from infection onset to the initiation of meropenem/vaborbactam therapy was 5 days. The median duration of treatment was 13.5 days (Table 1). In over 60% of the cases, the meropenem/vaborbactam regimen included at least 48 h of treatment with one or more other active antibacterial agents. The 14 patients who received meropenem/vaborbactam alone had BSIs ($n = 10$), cUTIs ($n = 2$), LRTI ($n = 1$) or acute bacterial skin and skin structure infection ($n = 1$).

Clinical cure was observed in 28 of the 37 cases, and 25 of those cures were microbiologically confirmed (Table 1). (Follow-up cultures were not done in the remaining 12 cases of the cohort.) Three of the 28 infections (all BSIs) classified as clinically cured (including 2 with negative follow-up cultures), all initially treated with combination regimens, recurred after meropenem/vaborbactam treatment was discontinued (median interval: 18 days). In all three cases, the KPC-*Kp* isolates remained susceptible to meropenem/vaborbactam, and microbiological and/or clinical cures were achieved after re-treatment with meropenem/vaborbactam plus colistin (two cases) or meropenem/vaborbactam plus fosfomycin (one case). The in-hospital mortality rate was 24.3%. In Figure 1 within patients with BSIs or LRTIs, mortality data are shown for patients who received meropenem/vaborbactam alone versus with other active antimicrobials and with subgroups defined by the ceftazidime/avibactam susceptibility status of the KPC-*Kp* isolate.

All nine patients who died (Table 2) had BSIs or LRTIs, and none had achieved clinical cure. Most were over 60 years of age, had Charlson Comorbidity Indexes (CCIs) ≥4, and/or INCREMENT scores ≥8, and all but one received meropenem/vaborbactam with another active antimicrobial. Six had been started on meropenem/vaborbactam >48 h after infection onset (although, during that interval, four of the six had received another active antibacterial).

As shown in Table 1, the 15 patients with ceftazidime/avibactam-susceptible KPC-*Kp* infections were generally older

Table 1. Baseline characteristics, treatment features and outcomes of the KPC-*Kp* infections treated with meropenem/vaborbactam, stratified according to the isolate's ceftazidime/avibactam susceptibility status

Variables	All infections ($n=37$)	CZA^{a}_{RES} ($n=22$)	CZA_{SUSC} ($n=15$)	*P* value CZA_{RES} vs CZA_{SUSC}
Patient variables				
Males	22 (59.5)	13 (59.1)	9 (60.0)	0.95
Age, years, median (IQR)	65 (31–71)	61 (43–66)	69 (53–74)	0.07
CCI ≥4	19 (51.3)	8 (36.4)	11 (73.3)	0.02
Pre-infection healthcare interventions				
Previous hospitalization[b]	19 (51.3)	12 (54.5)	7 (46.7)	0.64
Previous antibiotic therapy[c]	34 (91.9)	21 (95.4)	13 (86.7)	0.33
Previous CZA therapy[c]	13 (35.1)	12 (54.5)	1 (6.7)	0.002
Infection characteristics				
Hospital acquired[d]				
BSI	23 (62.2)	15 (68.2)	8 (53.3)	0.36
LRTI	10 (27.0)	5 (22.7)	5 (33.3)	0.47
IAI	1 (2.7)	1 (4.5)	0	0.40
cUTI	2 (5.4)	1 (4.5)	1 (6.7)	0.78
ABSSI	1 (2.7)	0	1 (6.7)	0.22
Severity of illness at onset				
INCREMENT score ≥8	19 (51.3)	8 (36.4)	11 (73.3)	0.03
Septic shock	7 (18.9)	1 (4.5)	6 (40.0)	0.007
Ward submitting index culture				
Medical	7 (18.9)	4 (18.2)	3 (20.0)	0.89
Surgical	4 (10.8)	3 (13.6)	1 (6.7)	0.51
ICU	26 (70.3)	15 (68.2)	11 (73.3)	0.73
MEM/VAB treatment variables				
Days before MEM/VAB treatment, median (IQR)[e]	5 (2–8)	4 (1–8)	5 (2–9)	0.91
Monotherapy regimens	14 (37.8)	10 (45.5)	4 (26.7)	0.24
Combination regimens[f]	23 (62.2)	12 (54.5)	11 (73.3)	0.24
MEM/VAB + 1 other active antimicrobial:	17 (45.9)	9 (40.9)	8 (53.3)	0.46
Fosfomycin	6 (16.2)	2 (9.1)	4 (26.7)	0.15
Tigecycline	3 (8.1)	3 (13.6)	0	0.14
Gentamicin	1 (2.7)	1 (4.5)	0	0.40
Colistin	6 (16.2)	3 (13.6)	3 (20.0)	0.61
Amikacin	1 (2.7)	0	1 (6.7)	0.22
MEM/VAB + ≥2 active antimicrobials	6 (16.2)	3 (13.6)	3 (20.0)	0.61
Days of treatment, median (IQR)	13.5 (8.5–15.5)	14 (12–16)	12.5 (7–15)	0.41
Dose adjusted for renal function	14 (37.8)	10 (45.5)	4 (26.7)	0.25
Outcomes				
Clinical cure[g]	28 (75.6)	18 (81.8)	10 (66.6)	0.29
Microbiological eradication[h]	25 (89.3)	16 (88.9)	9 (90.0)	0.93
Microbiological data N/A[h]	3 (10.7)	2 (11.1)	1 (10.0)	0.93
In-hospital infection recurrence[h,i]	3 (10.7)	1 (5.5)	2 (20.0)	0.24
Adverse reactions[j]	1 (2.7)	0	1 (6.7)	0.22
In-hospital mortality	9 (24.3)	4 (18.2)	5 (33.3)	0.29

Unless otherwise stated, data are expressed as *n* (%).

ABSSI, acute bacterial skin and skin structure infection; CZA_{RES}, ceftazidime/avibactam resistant; CZA_{SUSC}, ceftazidime/avibactam susceptible; IAI, intra-abdominal infection; MEM/VAB, meropenem/vaborbactam N/A, not available.

[a]Ceftazidime/avibactam MIC ≥16 mg/L.

[b]During the 12 months preceding infection onset.

[c]During the 6 months preceding infection onset.

[d]Index culture collected ≥48 h after hospital admission.

[e]From collection of index culture to first dose of meropenem/vaborbactam.

[f]Regimens that included ≥48 h of treatment with one or more other drugs with *in vitro* activity against the KPC-*Kp* isolate.

[g]Resolution of all signs and symptoms of infection followed by discontinuation of meropenem/vaborbactam therapy.

[h]Percentages of microbiological eradication and microbiological data. N/A outcomes have been computed within cases that achieved clinical cures (28).

[i]Diagnosed microbiologically during the index hospitalization after the original infection had been classified as microbiologically and/or clinically cured.

[j]Severe leukopenia with thrombocytopenia, which developed after 10 days of meropenem/vaborbactam therapy.

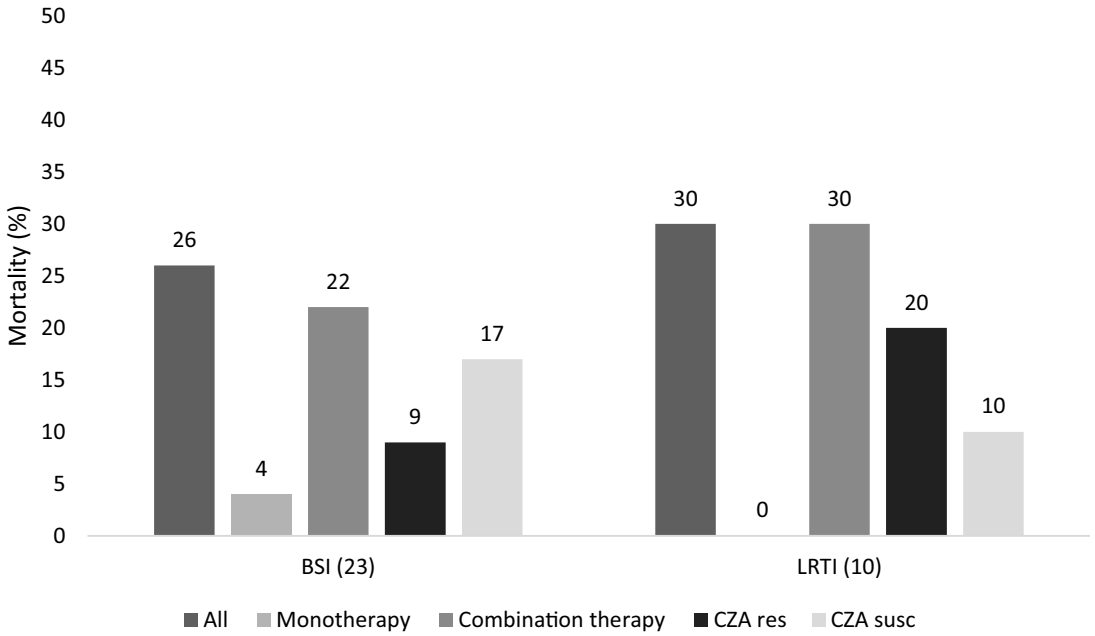

Figure 1. In-hospital mortality. All deaths occurred in patients with BSIs or LRTIs. Within each group, data are shown for patients who received meropenem/vaborbactam alone versus with other active antimicrobials and with subgroups defined by the ceftazidime/avibactam susceptibility status of the KPC-*Kp* isolate. CZA res, ceftazidime/avibactam resistant; CZA susc, ceftazidime/avibactam susceptible.

Table 2. Features of cases characterized by all-cause in-hospital mortality

Patient	Age/Sex	CCI	Infection type	INCR score	MIC (mg/L)		MEM/VAB treatment start (days)[a]	Active concomitant antimicrobials	Dose adjustment for renal function	MEM/VAB treatment duration (days)	Clinical cure[b]	Time of death (days)[a]
					MEM/VAB	CZA						
1	31/M	3	BSI	6	0.5	≥16	5	Tigecycline	Yes	5	No	10
2	66/M	5	BSI	8	1	≥16	4	—	No	8	No	12
3	75/M	6	BSI	15	0.5	4	6	Colistin	No	4	No	10
4	61/F	4	LRTI	10	0.5	2	9	Colistin	Yes	6	No	15
5	69/F	2	BSI	13	1	1	1	Colistin	No	9	No	10
6	73/F	5	BSI	10	1	2	8	Fosfomycin	No	11	No	19
7	52/M	10	BSI	12	1	8	1	Fosfomycin	Yes	7	No	8
8	61/F	3	LRTI	10	1	≥16	1	Colistin	No	15	No	16
9	64/F	4	LRTI	13	0.25	≥16	3	Colistin	No	18	No	21

CZA, ceftazidime/avibactam; INCR, INCREMENT; MEM/VAB, meropenem/vaborbactam.
[a]Calculated from date of index culture.
[b]Resolution of all signs and symptoms of infection while on meropenem/vaborbactam.

and more likely to have a CCI >4, an INCREMENT score >7 and/or septic shock. Their clinical cure and in-hospital survival rates were somewhat lower than those of their counterparts with ceftazidime/avibactam-resistant isolates, but neither difference was statistically significant.

Discussion

The last decade has seen striking worldwide increases in the incidence of CRE infections, particularly those caused by KPC-*Kp*. These infections are associated with high mortality rates and a dearth of treatment options.[16–19] Meropenem/vaborbactam is a potentially powerful addition to clinicians' armamentarium for treating these infections.[20] Since the TANGO I and TANGO II trial results were reported,[2,3] meropenem/vaborbactam's efficacy and safety for treating serious Gram-negative bacterial infections have been assessed mainly in small retrospective observational studies.[4,5,7] Promising findings have also emerged, however, from a larger multicentre study of 126 severe Gram-negative bacterial infections, 99 (78.6%) of which were caused by CRE,

most represented by *K. pneumoniae* ($n = 53$).[6] Real-world studies conducted after the initial approval of a new drug are provide invaluable information on the drug's performance in the treatment of specific conditions and/or patient populations. Unlike conventional randomized controlled trials, real-world studies tend to include patients who are older, more critically ill, more severely immunocompromised and/or more likely to have chronic end-organ damage (e.g. renal insufficiency).[6]

Consistent with the findings cited above,[4,5,7] our multicentre cohort study found meropenem/vaborbactam to be an effective, well-tolerated option for treating BSIs, LRTIs and other serious infections caused by *K. pneumoniae* producing only KPC β-lactamases. Clinical cure was recorded in over three-quarters of the cases (28/37), and all but three of those were microbiologically confirmed. Equally important, 3 of the 28 clinical cures were followed by in-hospital recurrences, but all three recurrences remained susceptible to meropenem/vaborbactam and were successfully eradicated with a second course of meropenem/vaborbactam plus another active drug.

The fact that our patients received meropenem/vaborbactam in a compassionate-use programme largely explains the fairly long period between infection onset and the initiation of meropenem/vaborbactam therapy (median: 5 days—appreciably longer than the intervals reported in a post-marketing setting).[6] Although our cohort is too small to allow reliable conclusions on predictors of negative responses to meropenem/vaborbactam, six of the nine patients who died in hospital had initiated meropenem/vaborbactam ≥48 h after the index culture, a finding consistent with those of Alosaimy *et al.*[6] and with the growing body of evidence highlighting the importance of prompt initiation of effective antimicrobial therapy in multiresistant Gram-negative infections.

Importantly, almost 60% of the KPC-*Kp* infections in our cohort were caused by ceftazidime/avibactam-resistant isolates, and in most of these cases, meropenem/vaborbactam treatment—alone or with other active drugs—produced favourable responses in terms of both clinical cure and in-hospital survival rates. The fact that clinical cure and in-hospital survival were appreciably (but not significantly) less common among the 15 patients with ceftazidime/avibactam-susceptible isolates is almost certainly related to the severity of their infections (see Table 1) and their baseline comorbidity burdens. Almost none of these 15 infections was treated with ceftazidime/avibactam prior to the administration of meropenem/vaborbactam. Consequently, it is impossible to tell whether outcomes in this subgroup would have been more favourable if they had received ceftazidime/avibactam instead of meropenem/vaborbactam.

Meropenem/vaborbactam's performance against ceftazidime/avibactam-resistant KPC-*Kp* isolates is encouraging given the reports of resistance to the latter drug during treatment.[12,14] Meropenem/vaborbactam retains activity against strains producing KPC mutants that confer resistance to ceftazidime/avibactam. Moreover pharmacodynamic aspects of vaborbactam are more effective than avibactam, which often needs to be maintained at a high concentration to be effective against KPC.[1] Meropenem/vaborbactam resistance was not observed in any of our patients (including three with in-hospital recurrence, all of which were still susceptible to meropenem/vaborbactam). This finding is fully consistent with previous reports.[6] However, follow-up cultures were not collected in most of the cases we analysed, and larger studies are undoubtedly necessary to reliably estimate the actual frequency of resistance.

Despite these limitations, however, our findings expand the growing body of real-life data pointing to meropenem/vaborbactam as a valuable option for treating serious infections in hospitals where KPC-*Kp* are endemic. Further study, particularly clinical trials, should be performed to devise strategies for the optimal use of this important new drug in the treatment of KPC-*Kp* infections and provide strong evidence for the real-life practice.

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Transparency declarations

None to declare.

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