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BRIEF REPORT

Efficacy and Safety of Meropenem–Vaborbactam Versus Best Available Therapy for the Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections in Patients Without Prior Antimicrobial Failure: A Post Hoc Analysis

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ABSTRACT

Introduction: Infections due to *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* are associated with increased morbidity and high mortality. Meropenem–vaborbactam (MV) is a novel β-lactam/β-lactamase inhibitor combination active against KPC-producing *Enterobacteriaceae*. The aim of this post hoc analysis of the TANGO-II randomized controlled trial was to assess the efficacy of MV versus best available therapy (BAT) in the subgroup of patients without prior antimicrobial failure.

Methods: The primary outcome measure was clinical cure at the test of cure (TOC). Secondary outcome measures included (1) clinical cure at the end of therapy (EOT), (2) microbiological cure at TOC, (3) microbiological cure at EOT, and (4) 28-day all-cause mortality.

Results: First-line MV was associated with a 42.9% absolute increase in clinical cure rate at TOC (95% confidence intervals [CI] 13.7–72.1) in comparison with first-line BAT. A 49.3% absolute increase in clinical cure rate at EOT (95% CI 20.8–77.7), a 42.6% absolute increase in microbiological cure rate at EOT (95% CI 13.4–71.8), and a 36.2% absolute increase in microbiologic cure rate at TOC (95% CI 5.9–66.6) were also observed, in addition to a 29.0% absolute reduction in mortality (95% CI − 54.3 to − 3.7). Overall, fewer adverse events were observed in the MV group than in the BAT group.

Conclusion: MV was superior to BAT in the subgroup of patients with serious carbapenem-resistant *Enterobacteriaceae* (CRE) infections and no prior antimicrobial failure, with very high rates of clinical success, and was well tolerated. Post approval and real-world studies remain essential to clearly define the most appropriate population for early, empirical MV coverage, in accordance with antimicrobial stewardship principles.

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INTRODUCTION

Antimicrobial resistance is increasing worldwide, and serious infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) have been associated with increased morbidity and high mortality [1–8]. In the last decade, the treatment of serious CRE infections was frequently based on the combination of last-resort agents associated with nephrotoxicity, possible subtherapeutic concentrations, and/or intermediate in vitro activity due to limited options and resistance to several classes of antimicrobials [1–3, 9].

Meropenem–vaborbactam (MV) is the combination of a well-known carbapenem with a first-in-class, boron-based, β-lactamase inhibitor, able to inhibit *Klebsiella pneumoniae* carbapenemase (KPC), which is one of the most frequent carbapenemases responsible for CRE [10]. MV has been approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, based on the TANGO-I randomized controlled trial (RCT), comparing efficacy and safety of MV to piperacillin–tazobactam [11]. Furthermore, MV has also been recently approved by the European Medicines Agency (EMA) for cUTI and pyelonephritis, complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options. Results of the TANGO-II RCT, in which MV monotherapy was compared with best available therapy (BAT) for the treatment of adults with serious infections due to CRE, have also been recently published [12]. In TANGO-II, MV was associated with increased clinical cure and decreased mortality in comparison with BAT, and less nephrotoxicity [12]. However, patients with prior antimicrobial failure (PAF), who are expected to have a lower response also to salvage therapy, were enrolled only in the MV arm [12]. Therefore, the advantage of MV over BAT could be expected to be even higher than observed in the TANGO-II RCT when both MV and BAT are employed as first-line therapies.

The aim of this post hoc analysis of the TANGO-II RCT was to assess the efficacy of MV versus BAT in the subgroup of patients without prior antimicrobial failure.

METHODS

This was a post hoc analysis of a phase 3, multicenter, multinational, randomized, open-label, active-controlled study comparing MV monotherapy to BAT for the treatment of serious infections suspected or known to be caused by CRE in patients aged 18 years or older, from November 2014 to June 2017 (NCT02168946) [12]. Serious CRE infections included cUTI and acute pyelonephritis (AP), hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), bacteremia, or cIAI [12].

Only patients without PAF and belonging to the microbiologic-CRE-modified intent-to-treat (mCRE-MITT) population were included in this analysis and were divided in two groups: (1) patients who received MV monotherapy as first-line therapy; (2) patients who received BAT as first-line therapy. The primary outcome measure was clinical cure at the test of cure (TOC). Secondary outcome measures included (1) clinical cure at the end of therapy (EOT), (2) microbiological cure at TOC, (3) microbiological cure at EOT, and (4) 28-day all-cause mortality.

The protocol of the TANGO-II trial and the informed consent form were approved by the sites' institutional review boards/independent ethics committees. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study or from their guardian/legal representative.

Population and Definitions

The mCRE-MITT population was defined as patients receiving at least one dose of study drug and with a baseline isolate confirmed as CRE by local or central laboratories. The safety population consisted of patients receiving at least one dose of study drug. BAT was defined as an antibiotic therapy including any of the following, alone or in combination: carbapenems, aminoglycosides, polymyxin B, colistin, tigecycline, or monotherapy ceftazidime–avibactam. Prior antimicrobial failure was defined as clinical evidence of prior failure as ascertained by the study investigator at screening and randomization. Clinical cure was defined as complete resolution of symptoms of the index infection such that no further antimicrobial therapy (and/or surgical intervention for cIAI) was required. Microbiologic cure was defined as microbial eradication or presumed eradication (i.e., clinical cure in absence of culture samples collected at the respective visit [EOT or TOC]). Outcomes at TOC were assessed at 7 ± 2 days after EOT.

Intervention

Meropenem–vaborbactam monotherapy (2 g/2 g) was administered for 7–14 days as a 3-h intravenous infusion every 8 h. BAT was selected according to institutional standards of care [12]. Detailed information on treatments received by BAT patients are available in the supplementary material of the original TANGO-II publication [12].

Statistical Analysis

Descriptive demographic and clinical characteristics of patients are reported with number and percentages for categorical variables, and with mean and standard deviation (SD) for continuous variables. Absolute percentage differences in primary and secondary outcome measures between subgroups are presented with their 95% confidence intervals (CI) [12].

RESULTS

Demographic and clinical characteristics of patients are reported in Table 1. There was a high proportion of patients with systemic inflammatory response syndrome (17/38, 44.7%) and/or immunocompromised status (15/38, 39.5%).

As shown in Table 2, first-line MV was associated with a 42.9% absolute increase in clinical cure rate at TOC (95% CI 13.7–72.1) in comparison with first-line BAT. A 49.3% absolute increase in clinical cure rate at EOT (95% CI 20.8–77.7), a 42.6% absolute increase in microbiological cure rate at EOT (95% CI 13.4–71.8), and a 36.2% absolute increase in microbiologic cure rate at TOC (95% CI 5.9–66.6) were also observed, in addition to a 29.0% absolute reduction in mortality (95% CI − 54.3 to − 3.7). Overall, fewer adverse events were observed in the MV group than in the BAT group (Table S1).

Additional comparisons between MV-treated patients with and without prior antimicrobial failure are available as supplementary material (Tables S2, S3). No comparison was made between MV-treated patients with PAF and patients treated with first-line BAT because of the small subgroups.

DISCUSSION

In patients without PAF, MV showed increased efficacy (clinical cure at TOC) and reduced 28-day all-cause mortality compared to BAT (+ 42.9% and − 29.0%); these changes were greater than those observed in the original TANGO-II RCT (+ 32.7% and − 17.7%), in which the MV group included patients with prior antimicrobial failure [12].

As a result of the small sample size, definitive conclusions could not be drawn (connected to the early study termination of the TANGO-II RCT due to superiority of MV at an interim analysis); however, these results, in comparison with those of the original trial, are suggestive of an additional advantage of MV over BAT when both are administered as a first-line therapy. This raises an important point of discussion, that is the need for a correct balance between

Table 1 Baseline demographics and clinical characteristics of patients without prior antimicrobial failure in the mCRE-MITT population

	Meropenem–vaborbactam (*n* = 23)	**Best available therapy (*n* = 15)**	**Total (*n* = 38)**
Age, mean (SD)	62.3 (14.6)	60.2 (13.0)	61.5 (13.9)
Female gender	12 (52.2)	5 (33.3)	17 (44.7)
White race	19 (82.6)	12 (80.0)	31 (81.6)
Region			
North America	6 (26.1)	7 (46.7)	13 (34.2)
Europe	11 (47.8)	8 (53.3)	19 (50.0)
Israel, Colombia, Brazil, Argentina	6 (26.1)	0 (0)	6 (15.8)
BMI, mean (SD)	27.0 (7.7)	25.8 (7.6)	26.5 (7.6)
Infection type			
Bacteremia	10 (43.5)	8 (53.3)	18 (47.4)
cUTI/AP	9 (39.1)	4 (26.7)	13 (34.2)
HABP/VABP	3 (13.0)	1 (6.7)	4 (10.5)
cIAI	1 (4.3)	2 (13.3)	3 (7.9)
Baseline pathogen[a]			
Klebsiella pneumoniae	22 (95.7)	12 (80.0)	34 (89.5)
Escherichia coli	2 (8.7)	1 (6.7)	3 (7.9)
Enterobacter cloacae species complex	0 (0)	2 (13.3)	2 (5.3)
Proteus mirabilis	0 (0)	2 (13.3)	2 (5.3)
Serratia marcescens	1 (4.3)	1 (6.7)	2 (5.3)
Creatinine clearance (mL/min)			
$\geq$ 50	17 (73.9)	9 (60.0)	26 (68.4)
30–49	3 (13.0)	2 (13.3)	5 (13.2)
20–29	1 (4.3)	2 (13.3)	3 (7.9)
$<$ 20	1 (4.3)	0 (0)	1 (2.6)
Missing	1 (4.3)	2 (13.3)	3 (7.9)
Charlson comorbidity index			
$\leq$ 2	3 (13.0)	1 (6.7)	4 (10.5)
3–4	2 (8.7)	2 (13.3)	4 (10.5)
5	6 (26.1)	1 (6.7)	7 (18.4)
$\geq$ 6	12 (52.2)	11 (73.3)	23 (60.5)

Table 1 continued

	Meropenem–vaborbactam (*n* = 23)	Best available therapy (*n* = 15)	Total (*n* = 38)
Diabetes mellitus	8 (34.8)	7 (46.7)	15 (39.5)
SIRS	11 (47.8)	6 (40.0)	17 (44.7)
ICU admission	3 (13.0)	3 (20.0)	6 (15.8)
Immunocompromised[b]	7 (30.4)	8 (53.3)	15 (39.5)

Results are reported as *n* (%) unless otherwise indicated

AP acute pyelonephritis, *BMI* body mass index, *cIAI* complicated intra-abdominal infection, *cUTI* complicated urinary tract infection, *HABP* hospital-acquired bacterial pneumonia, *ICU* intensive care unit, *VABP* ventilator-associated bacterial pneumonia, *PAF* prior antimicrobial failure, *SD* standard deviation, *SIRS* systemic inflammatory response syndrome

[a] Only baseline pathogens occurring in 2 or more subjects are shown

[b] Defined as receipt of immunosuppressive medications or bone marrow ablative chemotherapy, underlying lymphoma or leukemia (not in remission), previous transplantation, splenectomy, or presence of neutropenia

Table 2 Efficacy results in patients without prior antimicrobial failure in the mCRE-MITT population

Efficacy endpoints (mCRE-MITT)	Meropenem–vaborbactam (*n* = 23)	Best available therapy (*n* = 15)	Absolute difference (95% CI)
Clinical cure at TOC	16 (69.6)	4 (26.7)	+ 42.9 (+ 13.7 to + 72.1)
Clinical cure at EOT	19 (82.6)	5 (33.3)	+ 49.3 (+ 20.8 to + 77.7)
Microbiologic cure[a] at EOT	19 (82.6)	6 (40.0)	+ 42.6 (+ 13.4 to + 71.8)
Microbiologic cure[a] at TOC	16 (69.6)	5 (33.3)	+ 36.2 (+ 5.9 to + 66.6)
Day 28 mortality	1 (4.3)	5 (33.3)	− 29.0 (− 54.3 to − 3.7)

CI confidence intervals, *EOT* end of therapy, *mCRE-MITT* microbiologic carbapenem-resistant *Enterobacteriaceae* modified intent-to-treat, *TOC* test of cure

[a] Microbiologic cure was defined as microbial eradication or presumed eradication

limiting the use of novel agents to delay emergence of further resistance and, at the same time, guaranteeing the most active early therapy in case of severe infection. This is particularly important for CRE, by considering together the following reasons: (1) CRE infections are endemic in several countries [8], (2) there is a frequent delay of active therapy in patients with CRE infections [8], and (3) there is lower survival of patients with severe infections when active therapy is delayed [1].

Innovative, pathogen-focused trials enrolling vulnerable patients are essential to understanding the efficacy and safety of novel agents in real target populations. This is also important when a reference therapy standard is not established and multidrug-resistant (MDR) organisms are prevalent, as in the TANGO-II

trial, since difficult-to-treat vulnerable populations could be exposed to less effective and more toxic agents because of the paucity of active options. The TANGO-II trial included both immunocompromised patients and patients with prior antimicrobial failure, who are usually excluded from RCTs [12]. In addition, there still is the need for updated knowledge of the local, molecular, microbiological epidemiology as well as the patients' medical history (e.g., colonization, previous infections and antibiotic therapies, travel in countries or regions endemic for KPC-producing CRE) to make informed treatment decisions.

This post hoc analysis has some limitations. The most important is that this is a subgroup analysis of small sample size which prevents definitive conclusions, as well as further subgrouping (e.g., according to continent/country of enrollment, causative organism, baseline characteristics). However, it is noteworthy that the independent data safety monitoring board recommended to stop randomization to BAT because the risk/benefit analysis did not support further BAT randomization at an interim analysis [12], which, together with the present post hoc analysis, supports the suggestion of a potential advantage of MV as first-line therapy, to be explored further in post-approval studies. Another limitation is the heterogeneity in BAT, which is nonetheless consistent with the real-life approach to KPC-producing CRE infections at the time of the study, when there was not a unique standard reference.

CONCLUSIONS

MV was superior to BAT in the subgroup of patients with serious CRE infections and no PAF, with very high rates of clinical success, and was well tolerated. Post approval and real-world studies remain essential to clearly define the most appropriate population for early, empirical MV coverage, in accordance with antimicrobial stewardship principles.

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