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MEROPENEM-VABORBACTAM VERSUS BEST AVAILABLE THERAPY FOR INFECTIONS DUE TO CARBAPENEM-RESISTANT ENTEROBACTERIACEAE IN TANGO II: IMPACT OF PRIOR ANTIBIOTIC FAILURE ON CLINICAL OUTCOMES

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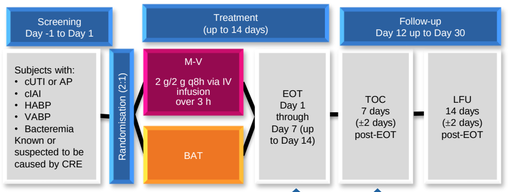
INTRODUCTION

- Increasing antimicrobial resistance among gram-negative pathogens, particularly carbapenem resistance, is associated with increased risk of inappropriate initial antimicrobial therapy.[1]
- Inappropriate initial antimicrobial therapy, in turn, is a known risk factor for mortality.[1]
- Enterobacteriaceae are common pathogens in pneumonia, urinary tract infections, and sepsis, and are often treated empirically before carbapenem resistance is identified, making initial appropriate antibiotic therapy problematic.[1]
- The current best available therapy involves treatment with one or more of a limited pool of antibiotics that have been associated with poor clinical outcomes, high levels of toxicity, and high mortality rates.[2]
- Meropenem-vaborbactam is a novel beta-lactam/beta-lactamase inhibitor combination developed for the treatment of serious gram-negative infections, including carbapenem-resistant Enterobacteriaceae (CRE).[3]
- TANGO II is a Phase 3, multi-center, open-label comparative trial of the efficacy and safety of meropenem-vaborbactam (M-V) versus best available therapy (BAT) in the treatment of serious infections due to known or suspected CRE pathogens. Patients who failed prior antimicrobial therapy, including treatment with in vitro active antimicrobial regimens, were eligible for inclusion in TANGO II.
- Here, we examine the effect of excluding patients with prior antibiotic failure for serious gram-negative infections on outcomes in TANGO II.

METHODS

- Phase 3, multi-center, randomised, open-label study of adults with infections due to known or suspected CRE, including complicated urinary tract infection (cUTI), acute pyelonephritis (AP), hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), bacteremia, or complicated intra-abdominal infection (cIAI).
- Eligible patients were randomised 2:1 to monotherapy with M-V or BAT for 7-14 days (**FIGURE 1**).

FIGURE 1.



- BAT included (alone or in combination): a carbapenem, aminoglycoside, polymyxin B, colistin, tigecycline, (monotherapy only) ceftazidime-avibactam.
- Enrollment was stratified by infection type and geographic region.
- Key inclusion criteria: known or suspected (evidence of CRE in culture or molecular testing within past 90 days) CRE pathogen, requirement of ≥ 7 days IV therapy, confirmed cUTI/AP, HABP/VABP, bacteremia, or cIAI.
- Key exclusion criteria: receipt of more than 24 hours of potentially effective antimicrobials (unless documented clinical failure), immediate life-threatening disease, known infection due to NDM, VIM, IMI or OXA-encoded beta-lactamase.
- Efforts to reduce bias included blinded investigator (BI), blinded adjudication committee (BAC), and a source control adjudication committee (for cIAI).
- Clinical cure: defined as complete resolution of signs/symptoms such that no further antimicrobial therapy was required and was assessed by the BI and primary investigator (PI) at two time points: end of therapy (EOT) and test of cure (TOC). In cases where the assessment by the BI and PI differed, clinical cure was adjudicated by the BAC.
- Prior antibiotic failure: defined as documented clinical evidence of failure (i.e., clinical deterioration, failure to improve) despite at least 48 hours of treatment with an antimicrobial agent to which the known CRE is susceptible or (for suspected CRE) an empiric agent with gram-negative coverage. Presence of prior antibiotic failure (yes/no) was ascertained at baseline by the unblinded investigator.
- Difference estimates, 95% confidence intervals and *P*-values were obtained by Fisher's Exact test.

RESULTS

- 72 patients were enrolled. 43 (28 M-V; 15 BAT) had a baseline qualifying CRE pathogen (mCRE-MITT).
- Within the mCRE-MITT, 20 patients had bacteremia, 15 had cUTI/AP, 5 had HABP/VABP, and 3 had cIAI.
- Within the mCRE-MITT, 9 patients had baseline investigator-ascertained failure of prior antimicrobials, all of which were randomised to M-V.
- Baseline demographics and clinical characteristics were similar in patients with and without prior antibiotic failures and across treatment groups (**TABLE 1**).
- Antimicrobial regimens associated with prior antimicrobial failure are shown in **TABLE 2**.

TABLE 1.

Baseline Demographics and Patient Characteristics	M-V No PAF[1] (n=19)	M-V All (n = 28)	BAT All[2] (n = 15)	Total (N = 43)
Age, mean (SD)	62.6 (14.7)	63.9 (14.0)	60.2 (13.0)	62.6 (13.6)
Female gender, n (%)	9 (47.4)	15 (53.6)	5 (33.3)	20 (46.5)
White race, n (%)	15 (78.9)	24 (85.7)	12 (80.0)	36 (83.7)
Region, n (%)				
North America	5 (26.3)	6 (21.4)	7 (46.7)	13 (30.2)
Europe	9 (47.4)	17 (60.7)	8 (53.3)	25 (58.1)
Israel, Colombia, Brazil, Argentina	5 (26.3)	5 (17.9)	0 (0)	5 (11.6)
Body mass index, mean (SD)	27.6 (8.2)	28.4 (9.4)	25.8 (7.6)	27.5 (8.8)
Infection type, n (%)				
Bacteremia	8 (42.1)	12 (42.9)	8 (53.3)	20 (46.5)
cUTI/AP	8 (42.1)	11 (39.3)	4 (26.7)	15 (34.9)
HABP/VABP	3 (15.8)	4 (14.3)	1 (6.7)	5 (11.6)
cIAI	0 (0)	1 (3.6)	2 (13.3)	3 (7.0)
Baseline pathogen, n (%)[3]				
Klebsiella pneumoniae	18 (94.7)	25 (89.3)	12 (80.0)	37 (86.0)
Escherichia coli	1 (5.3)	2 (7.1)	1 (6.7)	3 (7.0)
Enterobacter cloacae spp.	0 (0)	1 (3.6)	2 (13.3)	3 (7.0)
Proteus mirabilis	0 (0)	0 (0)	2 (13.3)	2 (4.7)
Serratia marcescens	1 (5.3)	1 (3.6)	1 (6.7)	2 (4.7)
Creatinine clearance, mL/min, n (%)				
>50	15 (78.9)	22 (78.6)	9 (60.0)	31 (72.1)
30–49	2 (10.5)	3 (10.7)	2 (13.3)	5 (11.6)
20–29	1 (5.3)	1 (3.6)	2 (13.3)	3 (7.0)
<20	0 (0)	1 (3.6)	0 (0)	1 (2.3)
Missing	1 (5.3)	1 (3.6)	2 (13.3)	3 (7.0)
CCI, n (%)				
≤2	3 (15.8)	4 (14.3)	1 (6.7)	5 (11.6)
3–4	2 (10.6)	3 (10.7)	2 (13.3)	5 (11.6)
5	5 (26.3)	10 (35.7)	1 (6.7)	11 (25.6)
≥6	9 (47.4)	11 (39.3)	11 (73.3)	22 (51.2)
Diabetes mellitus, n (%)	5 (26.3)	9 (32.1)	7 (46.7)	16 (37.2)
SIRS, n (%)	8 (42.1)	12 (42.9)	6 (40.0)	18 (41.9)
ICU admission (at baseline)	3 (15.8)	5 (17.9)	2 (13.3)	7 (16.3)
Immunocompromised[4], n (%)	6 (31.6)	10 (35.7)	8 (53.3)	18 (41.9)

PAF, prior antibiotic failure; CCI, Charlson Comorbidity Index; SIRS, systemic inflammatory response syndrome.
[1] Excludes the 9 patients enrolled after failure of prior antimicrobials, all of whom were randomised to M-V.
[2] No patients with prior antimicrobial failure were randomised to BAT, thus none were excluded.
[3] Only baseline pathogens occurring in 2 or more patients (mCRE-MITT) are shown.
[4] Underlying active leukemia, lymphoma, prior transplant or splenectomy on medical history; any active receipt of immunosuppressive drugs including selective immunosuppressants, calcineurin inhibitors, or high-dose systemic steroids (equivalent to ≥20 mg/day of prednisone for ≥2 weeks); or neutropenia (ANC <1000 cells/mm^3) at any point during the study period.

TABLE 2.

Subject No.	Infection Type	Antimicrobial Regimen[1]	Baseline Pathogen[2]; MIC	Days of Treatment
300-001-601	Bacteremia	Meropenem	*K. pneumoniae*; meropenem MIC >64	3
376-001-601	Bacteremia	Colistin + Meropenem	*K. pneumoniae*; colistin MIC >4, meropenem MIC >64	7
300-001-610	AP	Tigecycline[3]	*K. pneumoniae*; tigecycline MIC >4	6
300-002-604	cUTI	Piperacillin-Tazobactam	*K. pneumoniae*; piperacillin-tazobactam MIC >64	2
300-001-616	Bacteremia	Colistin + Meropenem	*K. pneumoniae*; colistin MIC 0.25, meropenem MIC >64	4
376-001-605	Bacteremia	Imipenem + Gentamicin	*E. coli*; imipenem 2[4], gentamicin MIC 2	6
840-020-603	VABP	Tigecycline	*K. pneumoniae*; tigecycline MIC 2	3
376-001-606	cIAI	Meropenem + Amikacin	*E. cloacae*; amikacin MIC 16, meropenem MIC 32	6
376-003-601	cUTI	Colistin	*K. pneumoniae*; colistin MIC 4	4

[1] Only the gram-negative intravenous antimicrobial regimen immediately prior to study day 1 is shown. For an antimicrobial regimen to be shown as a combination, antimicrobials had to overlap by ≥72 hours.
[2] Minimum inhibitory concentration (MIC) data is from the central microbiology laboratory (JMI) unless otherwise indicated.
[3] Used for a respiratory tract infection.
[4] Data obtained from local microbiology laboratory.

- A statistically significant increase in clinical cure rate at EOT and TOC was observed in patients treated with M-V (Kaye K, et al, Poster 1862, IDWeek 2017)
- In patients without prior antibiotic failure, treatment of serious infections due to CRE pathogens was associated with (**TABLE 3**):
  - increase in clinical cure rate at EOT and TOC
  - increase in microbiologic cure rate at EOT and TOC
  - decrease in Day 28 mortality

TABLE 3.

Efficacy Endpoints	M-V No PAF[1] (N = 19) n (%)	M-V All (N = 28) n (%)	BAT All[2] (N = 15) n (%)	Difference[3] (95% CI)	*P*-value[3]
Clinical cure at EOT	16 (84.2)	18 (64.3)	5 (33.3)	+50.9 (21.9 to 79.8)	<.001
Clinical cure at TOC	13 (68.4)	16 (57.1)	4 (26.7)	+41.8 (11.1 to 72.4)	<.01
Microbiologic cure at EOT	16 (84.2)	18 (64.3)	6 (40)	+44.2 (14.5 to 73.9)	<.01
Microbiologic cure at TOC	13 (68.4)	14 (50)	5 (33.3)	+35.1 (3.4 to 66.8)	0.03
Day 28 mortality	1 (5.3)	5 (17.9)	5 (33.3)	-28.1 (-54.0 to -2.2)	0.03

[1] Excludes the 9 patients enrolled after failure of prior antimicrobials, all of whom were randomised to M-V.
[2] No patients with prior antimicrobial failure were randomised to BAT, thus none were excluded.
[3] Data represent the difference in percentages for M-V No PAF and BAT All (95% CI, *P* for that difference).

- The adverse event profile of M-V was similar among patients with and without prior antibiotic failure. In both patients with and without prior antibiotic failure, receipt of M-V was associated with fewer drug-related adverse events, severe adverse events, and serious adverse events than BAT (**TABLE 4**).
- Both instances of renal-related adverse events occurred in patients with prior antibiotic failure. Patients who received M-V experienced less nephrotoxicity than patients who received BAT regardless of prior antibiotic failure (**TABLE 4**).

TABLE 4.

Adverse Events (Safety Population, MITT)	M-V No PAF[1] (N=35) n (%)	M-V All (N= 45) n (%)	BAT All[2] (n = 25) n (%)	Total (N = 70) n (%)
TEAEs				
Any	28 (80.0)	38 (84.4)	23 (92.0)	61 (87.1)
Drug-related	9 (25.7)	11 (24.4)	11 (44.0)	22 (31.4)
TEAEs by maximum severity				
Mild	7 (20.0)	9 (20.0)	4 (16.0)	13 (18.6)
Moderate	9 (25.7)	11 (24.4)	5 (20.0)	16 (22.9)
Severe	4 (11.4)	6 (13.3)	7 (28.0)	13 (18.6)
Life-threatening	2 (5.7)	2 (4.4)	1 (4.0)	3 (4.3)
Death	6 (17.1)	10 (22.2)	6 (24.0)	16 (22.9)
SAEs				
All	9 (25.7)	15 (33.3)	11 (44.0)	26 (37.1)
Drug-related	0 (0)	0 (0)	2 (8.0)	2 (2.9)
Study drug discontinuations due to TEAEs	2 (5.7)	5 (11.1)	3 (12.0)	8 (11.4)
Study discontinuations due to TEAEs	4 (11.4)	8 (17.8)	5 (20.0)	13 (18.6)
Renal-related safety endpoints				
Renal-related TRAEs (Preferred Term)	2 (10.5)	2 (4.4)	6 (24.0)	8 (11.4)
Renal failure acute	1 (2.9)	1 (2.2)	3 (12.0)	4 (5.7)
Renal impairment	1 (2.9)	1 (2.2)	2 (8.0)	3 (4.3)
Renal failure	0 (0)	0 (0)	1 (4.0)	1 (1.4)
Any post-baseline RIFLE[3] Criteria[4]	1 (2.9)	1 (2.3)	2 (8.3)	3 (4.5)
Maximum post-baseline creatinine increase[5]				
>0.5 mg/dL	4 (11.8)	5 (11.9)	6 (27.3)	11 (17.2)

[1] Excludes the 9 patients enrolled after failure of prior antimicrobials, all of whom were randomised to M-V.
[2] No patients with prior antibiotic failure were randomised to BAT, thus none were excluded.
[3] See reference 4.
[4] Subjects with missing baseline creatinine values censored (2 in M-V All, 1 in BAT All).
[5] Subjects with missing baseline creatinine values censored (1 in M-V No PAF, 3 in M-V All, 3 in BAT All).

CONCLUSIONS

- In patients with infection due to confirmed CRE, receipt of meropenem-vaborbactam was associated with increase in clinical cure and microbiologic cure and decreased mortality compared with best available therapy.
- Consistent with the known importance of early appropriate antimicrobial therapy, the effect of meropenem-vaborbactam over best available therapy was maximised when meropenem-vaborbactam was used as primary therapy for CRE, rather than as salvage therapy.
- Meropenem-vaborbactam is a promising new option for the treatment of CRE infections.

DISCLOSURES

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