Meropenem-Vaborbactam (VABOMERE) vs. Best Available Therapy for Carbapenem-Resistant Enterobacteriaceae Infections in TANGO II: Primary Outcomes by Site of Infection

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Abstract

Introduction

Carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a major challenge for healthcare systems globally due to the increasing frequency of infections with CRE strains and the lack of effective treatment options. While the Carbapenem Healthcare Alliance (CHA) has developed a variety of antibiotic combinations in clinical trials, no agent has met the current standard of care (SOC) for treatment of CRE infections.

Methods

Meropenem-vaborbactam (M-V; VABOMERE) is a novel beta-lactam/beta-lactamase inhibitor combination with potent activity against KPC-producing CRE. In a double-blind, randomized, Phase 2b trial, 47 patients with confirmed CRE infections were randomized (2:1) to receive M-V or the best available therapy (BAT). Patients were stratified by site of infection in cUTI/AP, 28-day all-cause mortality included in the assessment of clinical cure (CC), antibiotic success (AS), and mortality outcomes compared to BAT (mCRE-MITT). Failure was defined as a complete or partial resolution of signs/symptoms, and mortality outcomes were assessed at 30 days.

Results

8/11 (72.7%) of patients receiving M-V achieved the primary endpoint of conditional success (CS) compared to 2/4 (50%) of those receiving BAT (p = 0.052). The most common CS failures in the BAT group were due to CRE (n = 2/4). In cUTI/AP, 28-day all-cause mortality in the combined HABP/VABP and bacteremia infections.

Conclusions

The results of TANGO II provide the first proof of concept for a novel antibiotic against CRE. Comparative studies in M-V in vitro and in vivo suggest that M-V is a promising candidate for the treatment of CRE infections.

Background

Increasing resistance to carbapenem antibiotics among Enterobacteriaceae pathogens has been recognized by the CDC and WHO as an urgent global threat. Penicillins, cephalosporins, and carbapenems are the drugs of choice in the treatment of Carbapenem-resistant enterobacteriaceae (CRE). However, there is a lack of approved drugs for the treatment of CRE infections.

Table 1. Baseline Demographic and Clinical Characteristics (n=34)

| Characteristic | M-V Group (n=20) | BAT Group (n=14) | P-Value
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<tr>
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<tbody>
<tr>
<td>Gender, n (%)</td>
<td>Male: 15 (75.0)</td>
<td>Male: 10 (71.4)</td>
<td>0.518</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>62.3 (14.6)</td>
<td>59.7 (16.1)</td>
<td>0.598</td>
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| Baseline characteristics for the mCRE-MITT population are shown in Table 1. There was no consensus BAT regimen. BAT ranged from 1 to >4 drug combinations, which included combinations of carbapenems, aminoglycosides, and beta-lactams.

Table 2. Efficacy Among Patients with Confirmed CRE Infections by Infection Type (n=34)

| Infection Type | M-V Group (n=20) | BAT Group (n=14) | P-Value
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<thead>
<tr>
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<tbody>
<tr>
<td>cUTI</td>
<td>10 (50.0)</td>
<td>3 (21.4)</td>
<td>0.052</td>
</tr>
<tr>
<td>cIAI</td>
<td>1 (5.0)</td>
<td>1 (7.1)</td>
<td>0.598</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>9 (45.0)</td>
<td>9 (64.3)</td>
<td>0.110</td>
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Discussion

The results of TANGO II provide the first proof of concept for a novel antibiotic against CRE. Comparative studies in M-V in vitro and in vivo suggest that M-V is a promising candidate for the treatment of CRE infections.

References


Disclosures

This project was funded by a grant from The Medicines Company to the Project Management Office. The design of the protocol was governed by the Project Management Office. The Project Management Office was not involved in the conduct of this study or the review and approval of this manuscript.

References


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Table 3. Efficacy Among Patients with Confirmed CRE Infections by Infection Type (n=34)

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Table 4. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections (n=34)

| Variable | M-V Group (n=20) | BAT Group (n=14) | P-Value
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<td>CS</td>
<td>10 (50.0)</td>
<td>3 (21.4)</td>
<td>0.052</td>
</tr>
<tr>
<td>AS</td>
<td>15 (75.0)</td>
<td>11 (78.6)</td>
<td>0.444</td>
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<tr>
<td>Mortality</td>
<td>5 (25.0)</td>
<td>3 (21.4)</td>
<td>0.598</td>
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Figure 1. Study Schema

Figure 2. Percentage (%) of Patients with confirmed CRE Infections by Infection Type

Figure 3. Efficacy Among Patients with Confirmed CRE Infections by Infection Type

Figure 4. Efficacy Among Patients with Confirmed CRE Infections by Infection Type

Figure 5. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 6. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 7. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 8. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 9. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 10. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 11. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 12. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 13. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 14. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 15. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 16. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 17. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections

Figure 18. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections