P0284 Plazomicin is associated with fewer post-baseline infectious complications compared with colistin in patients with serious infections due to carbapenem-resistant Enterobacteriaceae (CRE): results from the randomized, controlled CARE study

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Background: Bloodstream infections (BSIs) and hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) due to CRE have poor outcomes. Despite increased use of combination therapy and the approval of new antibiotics, continued high mortality and the emergence of resistance reinforce the need for additional treatments. Plazomicin is a next-generation aminoglycoside with bactericidal activity against multidrug-resistant Enterobacteriaceae. The CARE study evaluated the efficacy and safety of plazomicin versus colistin as part of definitive combination therapy for serious infections due to CRE. Here we report secondary outcomes of postbaseline infections and resistance.

Materials/methods: CARE enrolled 2 cohorts: cohort 1 (C1), a randomised comparison of plazomicin versus colistin, and cohort 2 (C2), a single-arm study of plazomicin in patients ineligible for C1. Patients in C1 received plazomicin (15 mg/kg q24h) or colistin (300-mg load [colistin base activity] then 5 mg/kg/d) plus tigecycline or meropenem. Patients in C2 received plazomicin plus investigator's choice of adjunctive agent. Treatment was for 7-14 days. Outcomes were assessed in patients with confirmed CRE who received ≥1 dose of study drug (microbiological modified intent-to-treat population). Postbaseline infections were defined as pathogen(s) other than baseline CRE isolated during treatment (superinfection) or after study drug discontinuation (new infection) associated with signs/symptoms of infection. Decreased susceptibility was defined as a ≥4-fold increase from baseline minimum inhibitory concentration. Resistance was defined as a change from susceptible at baseline to nonsusceptible postbaseline.

Results: Of 37 patients in C1, 29 had BSI and 8 had HABP/VABP. A higher proportion of colistin-treated patients developed superinfections and new infections versus plazomicin-treated patients (Table). Emergence of decreased susceptibility/resistance to study drug or adjunctive agents occurred only in colistin-treated patients.

Among 23 plazomicin-treated patients in C2 (BSI and HABP/VABP), superinfections and new infections occurred in 5 (21.7%) and 4 (17.4%), respectively. No pathogens met criteria for decreased susceptibility/resistance to plazomicin; 1 Klebsiella pneumoniae isolate developed resistance to tigecycline.

Conclusions: The high incidence of subsequent infections was as expected in this acutely ill, hospitalised population. Plazomicin was associated with a reduced incidence of postbaseline infectious complications versus colistin. No emergence of decreased susceptibility to plazomicin was detected in this study.
<table>
<thead>
<tr>
<th>Outcomes in Cohort 1 (mMITT Population)</th>
<th>Plazomicin N=17 n/N (%)</th>
<th>Colistin N=20 n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superinfection</td>
<td>5 (29.4)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>New infection</td>
<td>1 (5.9)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Decreased susceptibility/resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug</td>
<td>0 (0.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Adjunctive agents</td>
<td>0 (0.0)</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>

Decreased susceptibility is defined as a postbaseline MIC of >4 µg/mL for plazomicin, >2 for colistin, >2 for tigecycline, or >8 for meropenem, plus ≥4-fold increase in MIC from baseline. Resistance is defined as an increase in plazomicin MIC from ≤4 µg/mL at baseline to >4 µg/mL postbaseline, or from an interpretation of susceptible at baseline to nonsusceptible at postbaseline for colistin or tigecycline according to EUCAST and FDA criteria, respectively. By definition, all CRE pathogens met the definition of resistance to meropenem at baseline, so development of resistance is not applicable.

EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; mMITT, microbiological modified intent-to-treat.