The antibacterial effect (ABE) of ceftolozane (TOL)/tazobactam (TAZ) plus amikacin (AMI) against *Pseudomonas aeruginosa* (PA) using simulated human dosing

**Background**
- Ceftolozane/tazobactam (TOZ/TAZ) has been approved for clinical use in Europe and is noteworthy for its potency in vitro against PA - including many multi-drug resistant strains.
- The debate of combination versus monotherapy has not been fully elucidated though combination antimicrobial chemotherapy is widely used as both empiric and definitive therapy to treat PA.
- With many anti-pseudomonal antibiotics, emergence of resistance (EoR) is a significant issue and the risk may be reduced by use of combination chemotherapy.

**Objective**
To determine the effect of adding AMI to TOL/TAZ in terms of bacterial killing and suppression of EoR against 3 strains of *P.aeruginosa*

**Materials and methods**
- A one compartment IVPKM was used to simulate free drug serum concentrations associated with TOL/TAZ 2G/1G (Cmax 112/32mg/L; TOL t½ 2.5h, TAZ t½ 1h) alone and plus AMI 15mg/kg (OD Cmax 50mg/L; BD Cmax 25mg/L; t½ 2.5h).
- Dosing of TOL/TAZ was q8hly for 7 days and AMI q24hly or q12hly for 7 days. TOL and TAZ concentrations were measured using HPLC methodology, LLOQ 1.0mg/L for both compounds; amikacin concentrations were measured competitive inhibition immunoassay using Indiko Plus® QMS system (LLOQ 1.5mg/L).
- Three strains of PA (55759 and 55762 (AmpC) and 47237 (AmpC and OprD) were used.
- EoR was assessed by changes in population analysis profiles on x2, x4 and x8 MIC plates 24hly over 7days.

**Results**
- The MICs of TOL/TAZ (4mg/L) were on the EUCAST clinical breakpoint for 2/3 PA strains tested (strain 3 MIC 2mg/L).
- For the TOL/TAZ dose simulation viable counts were reduced by >4 log by 4-6h; addition of AMI resulted in >4 log reduction in bacterial load by 2h.
- Regrowth occurred with TOL/TAZ alone by 12-72h (2-4log10); however, addition of AMI OD resulted in delayed regrowth for all 3 strains; 24-96h, (2-5log10) . The two TOL/TAZ+AMI dosing regimens had the same ABE as measured by AUBKC.
- Comparison of AUBKC_24 and AUBKC_168 indicated greater ABE for TOL/TAZ+AMI compared to TOL/TAZ alone (p<0.05).

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**Table 1: Antibacterial effect of TOL/TAZ, AMI OD and AMI BD**

<table>
<thead>
<tr>
<th>Strain</th>
<th>TOL/TAZ MIC</th>
<th>AMI MIC</th>
<th>AUBKC (logCFU/mL) at 72h</th>
<th>T0</th>
<th>T24</th>
<th>T72</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA 47237</td>
<td>4</td>
<td>4</td>
<td></td>
<td>2.55</td>
<td>1.36</td>
<td>0.27</td>
</tr>
<tr>
<td>PA 55759</td>
<td>4</td>
<td>4</td>
<td></td>
<td>2.38</td>
<td>0.71</td>
<td>0.27</td>
</tr>
<tr>
<td>PA 55762</td>
<td>4</td>
<td>4</td>
<td></td>
<td>2.31</td>
<td>0.71</td>
<td>0.27</td>
</tr>
</tbody>
</table>

**Table 2: EoR for TOL/TAZ plus AMI OD or AMI BD at TOL/TAZ and T72h**

<table>
<thead>
<tr>
<th>Strain</th>
<th>TOL/TAZ MIC</th>
<th>AMI MIC</th>
<th>EoR at 24h logCFU/mL</th>
<th>T72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA 47237</td>
<td>4</td>
<td>4</td>
<td>-2.02</td>
<td>-2.80</td>
</tr>
<tr>
<td>PA 55759</td>
<td>4</td>
<td>4</td>
<td>0.55</td>
<td>2.38</td>
</tr>
<tr>
<td>PA 55762</td>
<td>4</td>
<td>4</td>
<td>0.55</td>
<td>2.38</td>
</tr>
</tbody>
</table>

**Conclusions**
- There was no EoR to TOL/TAZ alone (growth on MICx4 plates) with any simulation.
- Growth was noted with strain 55761 with TOL/TAZ + AMI simulations (AMI MIC x2 and MIC x4 plates (2/3 exps; 4.6logcfu/mL; TOL/TAZ and AMI MIC 4mg/L) however no changes in AMI MIC was seen. No growth was observed on x8MIC plates.