COMPARATIVE IN VITRO ACTIVITY OF CEFTAZIDIME (CAZ) AND CEFTAZIDIME-AVIBACTAM (CAZ-AVI) IN A EUROPEAN COLLECTION OF PSEUDOMONAS AERUGINOSA FROM CYSTIC FIBROSIS (CF) PATIENTS.

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Introduction
Multidrug resistance in Pseudomonas aeruginosa (Pa) is causing increasing concern for CF patients, especially when having received multiple antibiotic treatments [1]. Carbapenems are now increasingly used in this setting, promoting the risk of selecting strains resistant to this “last line” therapy [2]. In this context, avibactam (AVI), a novel, broad-spectrum β-lactamase inhibitor, could prove of value in restoring activity of antipseudomonal cephalosporins such as CAZ when strains express extended spectrum β-lactamas. Our aim was to examine the shift of MIC distribution in a European collection of Pa isolates from CF patients if AVI is added to CAZ.

Materials and Methods
Antimicrobial test agent. Avibactam (potency 91.7%; batch no. AFCH005151) was kindly provided by AstraZeneca Pharmaceuticals, Waltham, MA, USA. Commercially available ceftazidime was procured as the clinical form of the corresponding branded product (Glazidim®) authorized for human use in Belgium and complying with the provisions of the European Pharmacopoeia (pentahydrate plus sodium bicarbonate; potency: 74.8 %, batch no. 8009) from GlaxoSmithKline Consumer Health Care s.a., Genval, Belgium.

Bacterial isolates. 342 Pa isolates were collected in Belgium, Germany, United Kingdom and France from CF patients who had received multiple antibiotic therapies.

Susceptibility testing. MICs were determined by microdilution in cation-adjusted Muller Hinton broth with or without AVI (4 mg/L), following CLSI recommendations [3]. P. aeruginosa ATCC27853 served as quality control strain for ceftazidime. Extended-spectrum-β-lactamase-producing K. pneumoniae K6 ATCC700603 was used as quality control strain for ceftazidime-avibactam studies.

Data analysis. MIC distributions and correlations between MICs were analysed by basic statistics and susceptibility/resistance patterns assessed using both EUCAST and CLSI interpretative criteria for CAZ [3,4]. The correlation between MICs of CAZ and CAZ-AVI against individual strains was examined using quantile density contour analysis (JMP® versions 10.0.2, SAS Institute Inc, Cary, NC).

Results

Table 1: MICs (mg/L) and percentage of susceptible and resistant isolates for CAZ and CAZ-AVI as compared between EUCAST and CLSI susceptibility breakpoints for CAZ [3,4].

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC50</th>
<th>MIC90</th>
<th>Range</th>
<th>EUCAST a</th>
<th>CLSI b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min</td>
<td>max</td>
<td>% S</td>
<td>%R</td>
<td>% S</td>
</tr>
<tr>
<td>CAZ</td>
<td>32</td>
<td>512</td>
<td>0.5</td>
<td>&gt;512</td>
<td>36</td>
</tr>
<tr>
<td>CAZ-AVI</td>
<td>4</td>
<td>64</td>
<td>0.03</td>
<td>&gt;512</td>
<td>76</td>
</tr>
</tbody>
</table>

* EUCAST CAZ bkpts: S≤8, R>8; * CLSI CAZ bkpts: S≤8, I=16, R≥32 (see refs. 3 and 4)

About 2/3 of the strains are resistant to CAZ alone. AVI increases the susceptibility to CAZ. Based on CLSI breakpoints, the presence of AVI also resulted in a smaller proportion of intermediate isolates than were observed for CAZ alone.

Fig. 1: correlation between MICs of individual isolates for CAZ vs. CAZ-AVI.

Fig. 2: CAZ MIC change upon addition of AVI as function of the original CAZ MIC.

Conclusions
- AVI restores CAZ activity in a large proportion of European Pa isolates.
- CAZ-AVI may represent a useful part of our future therapeutic armamentarium in documented pseudomonal infections in CF patients.

Acknowledgements

References