IDWeek 2022 | Poster #P1686

Antimicrobial Activity of Aztreonam-Avibactam, Ceftazidime-Avibactam, and Comparator Agents against *Pseudomonas aeruginosa* from Cystic Fibrosis Patients

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INTRODUCTION

- *Pseudomonas aeruginosa* is the most common cultured respiratory pathogen in individuals with cystic fibrosis (CF) and is associated with a more rapid decline in lung function.
- Aztreonam-avibactam (ATM-AVI) is under clinical development for the treatment of serious infections caused by Gram-negative bacteria, including metallo-ß-lactamase (MBL) producers.
- Four other ß-lactamase inhibitor combinations (BL/BLI) have been recently approved by the US FDA: ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), meropenem-vaborbactam (MEM-VAB), and imipenem-relebactam (IMI-REL).
- We evaluated the *in vitro* activity of these 5 BL/BLIs and comparators against *P. aeruginosa* causing CF pulmonary exacerbation.

METHODS

- Isolates were collected as part of SENTRY Antimicrobial Surveillance Program.
- Medical centers were asked to collect consecutive bacterial isolates from lower respiratory tract sites of CF patients in 2018–2021.
- Each participant center could contribute up to 40 *P. aeruginosa* isolates.
- Only isolates from invasive sampling, including transtracheal aspiration, bronchoalveolar lavage, protected brush samples, or qualified sputum samples, were accepted.
- The isolate collection included 383 *P. aeruginosa* isolates (1/patient) from 35 medical centers in the US (*n*=187) and 12 centers in Europe (EU; *n*=196; Figure 1).
- Isolates were categorized as multidrug-resistant (MDR) or extensively drug-resistant (XDR) according to criteria defined in 2012 by the joint European and US Centers for Disease Control:
  - MDR: nonsusceptible to ô1 agent in ô3 antimicrobial classes.
  - XDR: susceptible to ô2 classes.
- Isolates were susceptibility tested by the CLSI broth microdilution method (M100; 2022).
- MIC results were interpreted according to CLSI and/or US FDA breakpoints when available.
- A provisional aztreonam-avibactam PK/PD breakpoint of ô8 mg/L was applied for comparison.
- MEM-VAB is not approved for *P. aeruginosa* treatment in the US; thus, MEM-VAB breakpoints published for Enterobacterales (ô4/8/ó16 mg/L for S/I/R) by CLSI were applied for comparison.

RESULTS

- ATM-AVI ($MIC_{50/90}$, 4/>16 mg/L) inhibited 83.4% and 85.2% of isolates from the US and EU at ô8 mg/L, respectively (Figure 2).
- CAZ-AVI ($MIC_{50/90}$, 2/8 mg/L; 96.3%/95.4% susceptible [S] in US/EU) was the most active BL/BLI agent, followed by IMI-REL (94.7%/92.5%S in US/EU) and C-T (89.8%/91.3%S in US/EU; Figure 2).
- MEM-VAB ($MIC_{50/90}$, 0.5/8 mg/L; not approved for *P. aeruginosa* in the US) and MEM ($MIC_{50/90}$, 0.5/16 mg/L) showed similar potency (data not shown).
- Tobramycin (TOB)-S rates were 73.3% and 85.7% in US and EU, respectively (Figure 2).
- Among TOBïnon-S (NS) isolates, 84.6% were CAZ-AVIïS and 73.1% were inhibited at ATM-AVI MIC of ô8 mg/L (Figure 3).
- CAZ-AVI retained good activity against C-TïNS (61.1%S), IMI-RELïNS (62.1%S), piperacillin-tazobactam (PIP-TAZ)ïNS (86.7%S), meropenem (MEM)ïNS (86.6%S), and ciprofloxacin (CIP)ïNS (92.1%S) isolates (Figure 3).
- ATM-AVI and TOB showed similar coverage against *P. aeruginosa*–resistant subsets (Figure 3).
- MDR and XDR phenotypes were observed among 40.1%/30.1% and 24.6%/16.8% of isolates from the US and EU, respectively (Figure 4).
- Among MDR isolates, 88.1% were CAZ-AVIïS, 65.7% were inhibited at ô8 mg/L of ATM-AVI, and 57.5% were TOB-S (Figure 3).
- ATM-AVI and TOB retained activity against 54.4% and 49.4% of XDR isolates, whereas 82.3% of these isolates were CAZ-AVIïS (Figure 3).