ePP440

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

H. Chalhoub[1], M. Tunney[2], S. Elborn[2], A. Vergison[3], O. Denis[4], P. Plésiat[5], B.C. Kahl[6], F. Van Bambeke[1], P.M. Tulkens[1]

[1]Louvain Drug Research Institute, *Université catholique de Louvain*, Brussels, Belgium; [2]CF & Airways Microbiology Research Group, Queen's University Belfast, Belfast, United Kingdom; [3]*Unité des maladies infectieuses*, *Hôpital Universitaire des Enfants Reine Fabiola*, Brussels, Belgium; [4]*Laboratoire de microbiologie*, *Hôpital Erasme*, Brussels, Belgium; [5]*Laboratoire de bactériologie*, *Hôpital Jean Minjoz*,Besançon, France; [6]Medical Microbiology, University Hospital Münster, Münster, Germany.

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-lactamases. 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 Pharmacopoiea (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 interpretive 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).

References

1. Davies JC (2002) Pseudomonas aeruginosa in cystic fibrosis: pathogenesis and persistence. *Paediatr Respir Rev* 3: 128-134. PubMed: PM:12297059.
2. Zobell JT , Young DC, Waters CD, Stockmann C, Ampofo K, Sherwin CM and Spigarelli MG (2012) Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: I. aztreonam and carbapenems. *Pediatr Pulmonol* 47: 1147-58. PubMed: PM: 22911974.
3. Performance Standards for Antimicrobial Susceptibility Testing; 23d Informational Supplement. CLSI document M100-S23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
4. European Committee on Antimicrobial Suscpetibility Testing. Breakpoint tables for interpretation of MICs and zone diameters – version 4.0. 2014 – http://www.eucast.org

Acknowledgements

HC is Boursier of the Belgian *Fonds de la recherche dans l'industrie et l'agriculture* (FRIA) and FVB is Maître de Recherches of the Belgian *Fonds de la Recherche Scientifique* (F.R.S.-FNRS). This work was supported in part by the Belgian *Région Wallonne*. We thank AstraZeneca for providing us with avibactam.

This poster will be available after the meeting at http://www.facm.ucl.ac.be/posters

Results

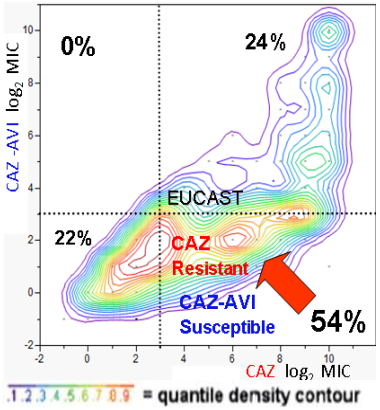
Table 1 : MICs (mg/L) and percentage of susceptible and resistant isolates for CAZ and CAZ-AVI as compared between EUCAST and CLSI susceptibility breakpoints for CAZ [3,4].

Drug	MIC_{50}	MIC_{90}	Range		EUCAST [a]		CLSI [b]		
			min	max	% S	%R	% S	%I	%R
CAZ	32	512	0.5	>512	36	64	36	9	55
CAZ-AVI	4	64	0.03	>512	76	24	76	5	19

[a] EUCAST CAZ bkpts: S≤8, R>8; [b] 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.**

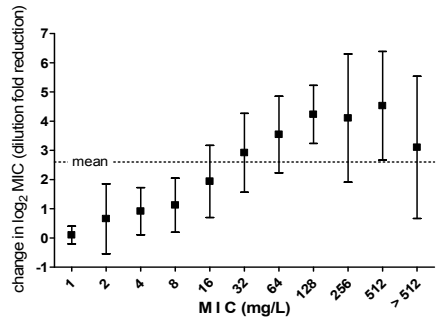
Fig. 1 : correlation between MICs of individual isolates for CAZ vs. CAZ-AVI.



➔ The colour gives information of the proportion of strains in each zone of the diagram.

➔ **Half of isolates resistant to CAZ alone become susceptible to CAZ-AVI.**

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



➔ The decrease in MICs of CAZ brought by AVI is proportional to the MIC of CAZ alone (if ≤ 128 mg/L).

➔ **AVI (4 mg/L) effectively neutralizes β-lactamase activity up to a large expression threshold.**

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