Semi-mechanistic pharmacokinetic/pharmacodynamics modeling of aztreonam-avibactam combination against multidrug resistant Gram(-) organisms

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INTRODUCTION

- Aztreonam-avibactam (ATM-AVI) is a combination, currently in development by Pfizer, intended to treat serious infections caused by multi-drug resistant (MDR) pathogens including those producing metallo-β-lactamases (MBLs).
- Sy et al. developed a semi-mechanistic PK/PD model for ATM-AVI combination in which 3 effects for AVI were characterized : inhibition of ATM degradation; enhancement of ATM bactericidal activity and bactericidal effect.
- The aims of this study were to apply this PK/PD model for 4 additional MDR strains with different β-lactamase profiles, including isolates of other species, and to investigate the individual contribution of each of the 3 AVI PD effects.

METHODS

- 4 *Enterobacteriaceae* strains (1 *E. coli*, 1 *C. freundii* and 2 *E. cloacae*) expressing MBLs and other β-lactamases were evaluated in *in vitro* static time-kill studies using wide concentration ranges of ATM and AVI alone and in combination.
- A common structural model with 2 sub-populations, slightly different from the one developed by Sy et al., was applied for all strains (Fig 1).
  - ✓ ATM degradation by β-lactamases was taken into account by measuring the actual concentrations of ATM by LC-MS/MS and was modeled depending on the bacteria density (S+R), remaining ATM in the system and AVI concentration (inhibitory effect).
  - ✓ ATM bactericidal effect was modeled as an increase in the killing rate for both subpopulations with a higher EC_{50} for the resistant state. Whereas AVI bactericidal effect was incorporated in the model only for the susceptible subpopulation.
  - ✓ The enhancing effect of AVI was characterized by a reduction of the ATM EC_{50} in a concentration-dependent manner.

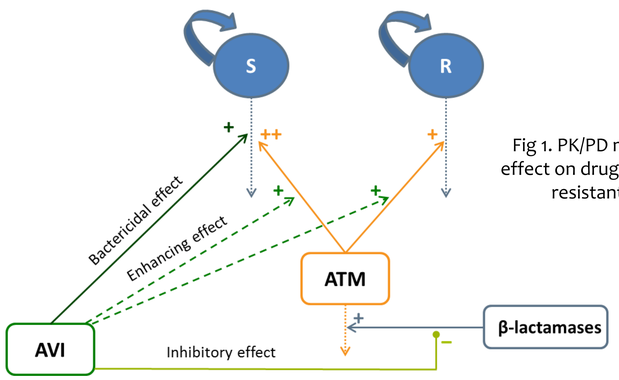

Fig 1. PK/PD model for ATM-AVI effect on drug-susceptible (S) and resistant (R) bacteria.

- Final model was used to simulate the 3 AVI effects separately in order to evaluate the impact of each effect at clinical ATM and AVI concentrations (C_{avg} = 25 and 4.5 µg/mL respectively, corresponding to a dosing regimen of 2g and 0.5g q8h in human[2,3]).

RESULTS

- All strains were resistant to ATM alone although the susceptibility was restored in the presence of 4 µg/mL of AVI (Table 1)
- The PK/PD model succeeded in capturing the bacterial growth, regrowth and killing kinetics and ATM degradation profiles for all strains as shown in Fig 2, using *E. cloacae* 1318536 as an example.
- No ATM degradation, even in the absence of AVI, was observed for *E. coli* 1266865 (Fig 3). Thus, for this strain, only the bactericidal and the enhancing effects of AVI could be characterized.

Table 1. Susceptibility and β-lactamase content of the MDR strains

Strain	β-lactamases	MIC (mg/L)	
		ATM	ATM-AVI[a]
E. coli 1266865	NDM-5, TEM-OSBL(b), CMY-42	32	4
C. freundii 974673	NDM-1, SHV-12(2be), TEM-OSBL(2b), CTX-M-3, CMY-34	512	0.125
E. cloacae 1285905	NDM-1, CTX-M-15	64	0.25
E. cloacae 1318536	NDM-1, CTX-M-15	512	0.125

[a]AVI at 4 mg/L

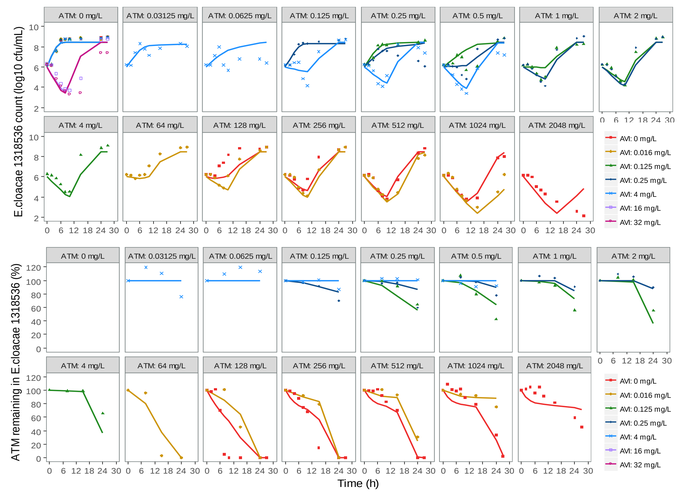

Fig 2. Model-prediction and observed static time-kill curves of ATM and AVI against *E. cloacae* 1318536 (top) and ATM concentration remaining in the system (bottom). The points show the experimental data and the lines the predictions from the model.

- AVI can prevent ATM degradation although this effect alone is not able to explain the bacterial killing due to the drug combination (Fig 3, light green triangles).
- When killing is observed, the lower number of bacteria, and consequently the lower quantity of β-lactamases produced, leads to a slower ATM degradation (Fig 3, green squares).
- According to the simulation results, among the 3 AVI effects, the enhancing effect is the most important.
- The way that the AVI effects are affected by different ATM-AVI concentrations within a clinical range was investigated (Fig 4). The inhibitory and bactericidal effects of AVI contribute to a faster killing rate only at high concentration (5 x C_{avg}).

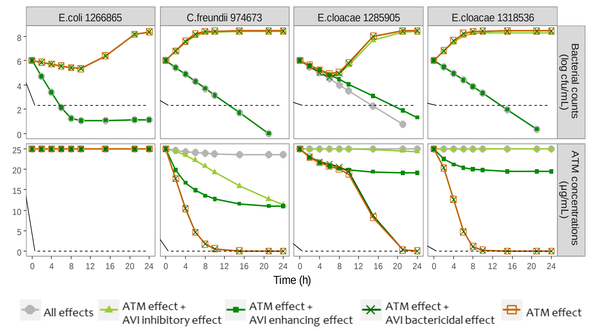

Fig 3. Model simulations of static time-kill curves and ATM concentrations for ATM-AVI combination of 25-4.5 µg/mL. Each color represents the simulated profile for the different effects of AVI and ATM against the 4 investigated strains. Dashed lines correspond to the limit of quantification.

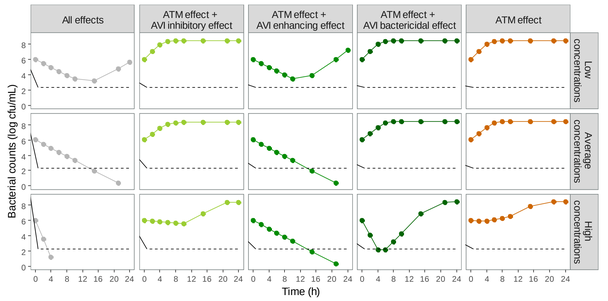

Fig 4. Simulations of the different effects of AVI and ATM against E. cloacae 1318536 in response to different constant concentrations of ATM-AVI:
low concentrations (5-0.9 µg/mL),
average concentrations (25-4.5 µg/mL)
and high concentrations (125-22.5 µg/mL).
Dashed lines correspond to the limit of quantification.

CONCLUSIONS

- The 3 previously reported effects of AVI could be well characterized by the PK/PD model for the additional MDR strains evaluated in this study.
- However, within the clinical range of ATM and AVI concentrations, even though AVI prevents ATM degradation, the combined bactericidal activity was mostly explained by AVI enhancing effect.
- These findings should be further investigated in hollow-fiber experiments where bacteria are exposed to dynamic antibiotic concentrations.

Conflict of interest: de Jonge BLM is currently an employee of Pfizer

References:

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