Semi-mechanistic pharmacodynamics modeling of aztreonam-avibactam combination to understand its antimicrobial activity against multidrug-resistant Gram(-) bacteria

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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.[1] developed a semi-mechanistic PD model for ATM-AVI combination in which 3 effects for AVI were characterized : inhibition of ATM degradation; intrinsic bactericidal effect and enhancement of ATM bactericidal activity.
- The aims of this study were to apply this 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 MDR *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 using NONMEM 7.4[2] (Fig 1).
  - ✓ The proportion of pre-existing resistant bacteria was determined by plating the initial inoculum onto agar plates supplemented with ATM-AVI and used to define the initial conditions of S and R.
  - ✓ 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) according to an exponential function, and AVI concentration according to a fractional inhibitory Emax model (**inhibitory effect**).
  - ✓ ATM bactericidal effect was modeled as an increase in the killing rate for both subpopulations, according to a sigmoidal Emax model with a higher EC_{50} for the resistant state explaining regrowth. Whereas **AVI bactericidal effect**, characterized by a sigmoidal Emax model, was incorporated in the model only for the susceptible subpopulation.
  - ✓ The **enhancement of ATM bactericidal activity by AVI** was modeled as a decrease of ATM EC_{50} with increasing AVI concentrations using a bi-exponential function:

$$EC_{50,ATM} = Ae^{-\alpha AVI} + Be^{-\beta AVI}$$

  Where A and B (µg/mL) are model constants that added together correspond to the ATM EC50 value when AVI concentration is zero; α and β (mL/µg) are exponential constants that describe the relationship between AVI concentration and ATM potency.
- 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[3,4]).
- The maximum effect of the combination was defined as the difference between the AUBC[5] of the control ($AUBC_{control}$) and the AUBC when all effects (ATM effect + the 3 AVI effects) were taken into account ($AUBC_{full}$). The percentage of the maximum effect induced by each AVI effect was then calculated, as follow:

$$\%\ \text{maximum effect} = \frac{(AUBC_{control} - AUBC_i)}{(AUBC_{control} - AUBC_{full})} \times 100$$

Where i corresponded to the AVI effect considered.

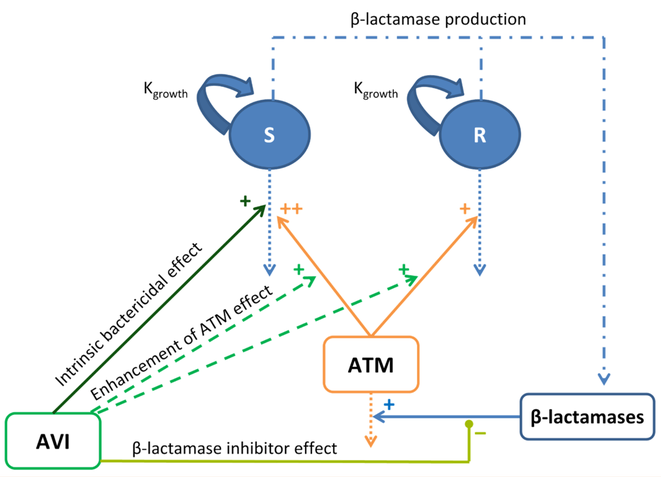

Fig 1. PD model for ATM-AVI effect on drug-susceptible (S) and resistant (R) bacteria.

RESULTS

- The 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. Thus, for this strain, only the bactericidal and the enhancing effects of AVI could be characterized.

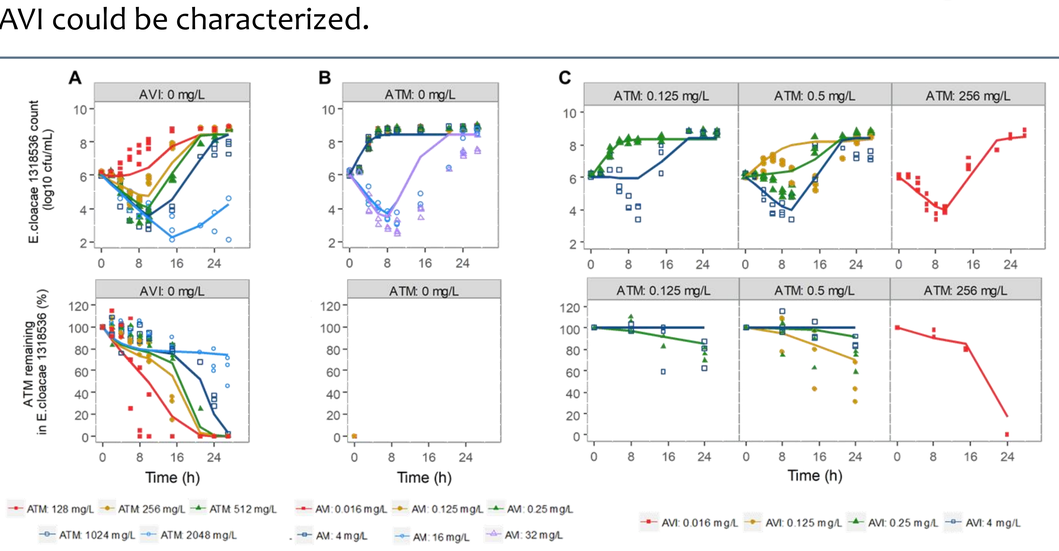

Fig 2. Model-prediction and observed static time-kill curves of A) ATM alone, B) AVI alone and C) ATM-AVI in combination against *E. cloacae* 1318536 over 27 h (top panels) and the percentage of the initial ATM concentration remaining in the system during the time-kill experiments (bottom panels). The symbols represent the experimental data (n=3) and the color-matched lines the predictions from the PD model.

- AVI can prevent ATM degradation (Fig 2, panel C) although this effect alone is not able to explain the bacterial killing due to the drug combination (Fig 3).
- According to the simulation results (Fig 3), among the 3 AVI effects, the enhancing effect is the most important, which by itself yielded a similar bacterial killing to the one obtained with the full model whatever the concentration level (between 71.3 and 100% of the maximum effect).
- The inhibitory and bactericidal effects of AVI poorly contributed to total effect and resulted in a percentage of maximum effect close to that obtained with ATM alone.

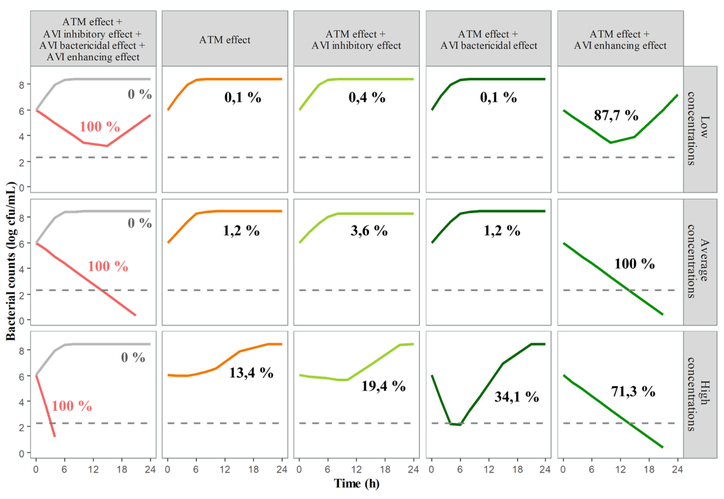

Fig 3. Simulations of the different effects of AVI on bacterial counts in *E. cloacae* 1318536 in response to different constant concentrations of ATM-AVI: low (5-0.9 mg/L), average (25-4.5 mg/L) and high (125-22.5 mg/L) concentrations. Dashed lines correspond to the limit of quantification. Grey curve represents the control (0% effect) and red curve the maximum effect in bacterial killing (100%) predicted when all effects (ATM effect + the 3 AVI effects) are taken into account. The percentage of the maximum effect induced by ATM and each AVI effect is indicated for each simulated profile.

CONCLUSIONS

- The 3 previously reported effects of AVI could be well characterized by the 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.

References:

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Conflict of interest: de Jonge BLM is a former employee of Pfizer

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