Efficacy of the extended spectrum β-lactamase inhibitor, AAI101, combined with β-lactams in murine models of systemic Gram-negative infection

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Introduction

AAI101 is a novel zwitterionic extended-spectrum β-lactamase inhibitor (BLI) belonging to the penicillanic acid sulfone class, currently in Phase I trials.

A major challenge confronting antibacterial chemotherapy is the emergence and global dissemination of extended-spectrum β-lactamases (ESBLs). These enzymes deactivate β-lactam antibiotics (including penicillins, cephalosporins, and monobactams) before they can access their targets in the periplasmic space or inner wall zone, thereby restricting treatment options for infections attributable to ESBL-producing pathogens.

Development of BLIs such as tazobactam (Tazo) has helped preserve the clinical value of β-lactam antibiotics by protecting them against hydrolysis. For treatment of community-onset sepsis, clinicians often prefer third-generation cephalosporins (*e.g.* ceftriaxone [Cro]); for patients with a high-burden of healthcare-associated factors or febrile neutropenia, cefepime (Fep) or piperacillin (Pip)/Tazo is preferred.[1] However, the efficacy of these treatments is being compromised by appearance and spread of aggressive β-lactamases not susceptible to existing BLIs.[2]

This study was designed to assess the efficacy in mice of AAI101 vs. Tazo in combination with Pip, Cro, or Fep for treatment of systemic infections caused by ESBL-producing Enterobacteriaceae.

Materials and Methods

- ESBL-producing Enterobacteriaceae were obtained from St. John's Medical College Hospital, Bangalore, India, and from the Sassoon General Hospital affiliated with the B. J. Medical College, Pune, India; ESBL production was confirmed by broth microdilution and disc diffusion as previously described by the CLSI.[3]
- Broth microdilution minimum inhibitory concentrations (MICs) (mg/L) were obtained for β-lactams, β-lactams + AAI101 4 mg/L, and β-lactams + Tazo 4 mg/L, respectively, using CLSI protocols, as follows:
  - *Escherichia coli* MRO 10006, Pip: >128, 1, 1
  - *E. coli* MRO 10007, Pip: >128, 0.5, 1
  - *Klebsiella pneumoniae* MRO 11008, Pip: >128, 4, 4
  - *Citrobacter freundii* MRO 12301, Cro: >64, 0.06, 0.25
  - *C. freundii* MRO 12301, Fep: 16, 0.03, 0.03.
- Immunocompetent female Swiss albino mice (18-22 g, obtained from a GLP-certified breeding facility at Orchid Chemicals & Pharmaceuticals, Ltd., Chennai, India; 5-6 animals per cohort) were injected i.p. with lethal doses of bacteria (6-82 x LD_{50}) suspended in physiological saline containing 5% ($^w/_v$) hog gastric mucin.[4]

References

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Materials and Methods (contd.)

- At 0.5 h post-infection, single doses of Pip, Cro, or Fep, ± AAI101 or Tazo at an antibiotic/BLI ($^w/_w$) ratio of 4:1, were administered s.c. (5 mL/kg of body weight).
- Animals were monitored twice daily for 7 days, and drug doses corresponding to ED_{50}s for each treatment group were calculated by the method of Reed & Muench.[5]

Results

- All β-lactam-untreated animals succumbed to the pathogen within 48 h of infection.
- For each bacterial strain examined, the ED_{50} for β-lactam/AAI101 was lower than the corresponding ED_{50} for β-lactam/Tazo.
- For *E. coli* strains MRO 10006 and MRO 10007, and for *K. pneumoniae* MRO 11008, ED_{50}s for Pip/AAI101 were 22%, 58%, and 65% lower, respectively, than the corresponding ED_{50}s for Pip/Tazo.
- For *C. freundii* MRO 12301, the ED_{50} for Cro/AAI10 was 90% lower than the ED_{50} for Cro/Tazo, whereas the ED_{50} for Fep/AAI101 was 76% lower than that for Fep/Tazo.

Table. ED_{50} values for β-lactams ± BLIs in mice infected with ESBL-producing Enterobacteriaceae

Strain	ED_{50} (mg/kg)
E. coli MRO 10006	Pip alone, >128 Pip/AAI101 (4:1), 42.2 Pip/Tazo (4:1), 53.8
E. coli MRO 10007	Pip alone, >128 Pip/AAI101 (4:1), 24.9 Pip/Tazo (4:1), 58.8
K. pneumoniae MRO 11008	Pip alone, not determined Pip/AAI101 (4:1), 34.9 Pip/Tazo (4:1), 99.5
C. freundii MRO 12301	Cro alone, >40 Cro/AAI101 (4:1), 2.3 Cro/Tazo (4:1), 22.5
C. freundii MRO 12301	Fep alone, >10 Fep/AAI101 (4:1), 1.7 Fep/Tazo (4:1), 7.1

Conclusions

- When administered with Pip, Cro, or Fep, AAI101 proved more efficacious than equiproportionate ratios of Tazo at improving survival in mice treated with lethal doses of ESBL-producing Enterobacteriaceae.
- AAI101, in combination with an established β-lactam, is a promising new therapeutic modality for the treatment of infections caused by ESBL-producing Enterobacteriaceae.

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