

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 LD₅₀) 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, \pm 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 ED₅₀s 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 ED₅₀ for β -lactam/AAI101 was lower than the corresponding ED₅₀ for β -lactam/Tazo.
- For *E. coli* strains MRO 10006 and MRO 10007, and for *K. pneumoniae* MRO 11008, ED₅₀s for Pip/AAI101 were 22%, 58%, and 65% lower, respectively, than the corresponding ED₅₀s for Pip/Tazo.
- For *C. freundii* MRO 12301, the ED₅₀ for Cro/AAI101 was 90% lower than the ED₅₀ for Cro/Tazo, whereas the ED₅₀ for Fep/AAI101 was 76% lower than that for Fep/Tazo.

Table. ED₅₀ values for β -lactams \pm BLIs in mice infected with ESBL-producing Enterobacteriaceae

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