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ePoster Viewing
New and old beta-lactamase inhibitors

EFFICACY OF EXTENDED SPECTRUM BETA-LACTAMASE INHIBITOR AAI101 COMBINED WITH BETA-LACTAMS IN MURINE MODELS OF SYSTEMIC GRAM-NEGATIVE INFECTION.

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Objectives: New therapeutic modalities are needed for patients suffering from multidrug-resistant Gram-negative infections. AAI101 is an extended spectrum beta-lactamase inhibitor (BLI) of the penicillanic acid sulfone class, currently in clinical development for the treatment of such infections. This study examined the impact of AAI101 or tazobactam coadministered with various beta-lactams on the 7-day survival in mice infected with ESBL-producing clinical isolates.

Methods: Immunocompetent female Swiss albino mice (18-22 g; 5-6 animals per cohort) were injected intraperitoneally with lethal doses (LDs) of ESBL-producing Enterobacteriaceae (obtained from university hospitals in Bangalore and Pune, India) suspended in physiological saline containing 5% hog gastric mucin. At 0.5 h post-infection, single doses of piperacillin (Pip), ceftriaxone (Cro), or cefepime (Fep), alone or combined with AAI101 or tazobactam at an antibiotic/BLI (w/w) ratio of 4/1, were administered subcutaneously (5 mL/kg body weight). Animals were monitored twice daily, and drug doses (mg/kg body weight) enabling 50% survival (ED50) by 7 days for each treatment group calculated by the method of Reed and Muench.

Results: All animals in untreated cohorts succumbed to the infection within 48 h of bacterial inoculation. The beta-lactams examined, their MICs towards the strains surveyed, and ED50s for the beta-lactams in the absence and presence of BLIs, are presented in the table. For each bacterial strain examined, the ED50 for beta-lactam + AAI101 is lower than that for beta-lactam + tazobactam. For *Escherichia coli* strains MRO10006 and MRO10007, and for *Klebsiella pneumoniae* MRO11008, ED50s for Pip combined with AAI101 were, respectively, 22%, 58%, and 65% lower than the corresponding ED50s for Pip combined with tazobactam. For *Citrobacter freundii* MRO12301, the ED50 for Cro + AAI101 was 90% lower than the ED50 for Cro + tazobactam, whereas the ED50 for Fep + AAI101 was 76% lower than that for Fep + tazobactam.

Conclusion: When administered with Pip, Cro, or Fep, AAI101 proved more effective than equiproportionate ratios of tazobactam at restoring the activity of the beta-lactams tested and improving the survival of mice given lethal doses of ESBL-producing Enterobacteriaceae. AAI101, in combination with an established beta-lactam, is a promising new therapeutic modality for the treatment of infections caused by drug-resistant Gram-negative pathogens.

Strain	Challenge dose, CFU/mouse (multiple of LD_{50})	β-Lactam MIC (mg/L)	ED_{50} (mg/kg)
E. coli MRO 10006	2.9×10^4 (26)	Pip alone, >128 Pip + 4 mg/L AAI101, 1 Pip + 4 mg/L tazobactam, 1	Pip alone, >128 Pip/AAI101 (4:1), 42.2 Pip/tazobactam (4:1), 53.8
E. coli MRO 10007	7.5×10^2 (8)	Pip alone, >128 Pip + 4 mg/L AAI101, 0.5 Pip + 4 mg/L tazobactam, 1	Pip alone, >128 Pip/AAI101 (4:1), 24.9 Pip/tazobactam (4:1), 58.8
K. pneumoniae MRO 11008	5.6×10^5 (6)	Pip alone, >128 Pip + 4 mg/L AAI101, 4 Pip + 4 mg/L tazobactam, 4	Pip alone, not determined Pip/AAI101 (4:1), 34.9 Pip/tazobactam (4:1), 99.5
C. freundii MRO 12301	5.0×10^6 (83)	Cro alone, >64 Cro + 4 mg/L AAI101, 0.06 Cro + 4 mg/L tazobactam, 0.25	Cro alone, >40 Cro/AAI101 (4:1), 2.3 Cro/tazobactam (4:1), 22.5
C. freundii MRO 12301	4.3×10^6 (72)	Fep alone, 16 Fep + 4 mg/L AAI101, 0.03 Fep + 4 mg/L tazobactam, 0.03	Fep alone, >10 Fep/AAI101 (4:1), 1.7 Fep/tazobactam (4:1), 7.1