Poster T-05

Pharmacodynamic Targets of Enmetazobactam, Combined with Cefepime, against ESBL-Producing Isolates of *K. pneumoniae* in a Murine Thigh Infection Model

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Abstract (revised)

Background Enmetazobactam (EMT, formerly AAI101) is a novel ESBL inhibitor developed in combination with cefepime (FEP) as carbapenem-sparing option for the treatment of serious Gram-negative infections. FEP/EMT has entered phase 3 trials in patients with cUTI/AP. Here, the magnitude of the fraction of free drug above a threshold concentration (%*f*T > C_T), the PK-PD index for EMT, was assessed in a murine thigh infection model.

Methods Nine FEP-resistant, ESBL-producing isolates of *K. pneumoniae* with FEP/EMT MICs ranging from 0.06 to 2 µg/ml were tested in a neutropenic mouse thigh infection model. EMT dosages of 1, 3.16, 10, 31.6 and 100 mg/kg were administered intravenously q4h. FEP was administered concomitantly at a fixed, non-effective dose q4h, determined separately for each isolate. Terminal bioburden was quantified 26 h post infection. PK parameters of EMT were determined in infected animals, and the exposure-response (E-R) relationship was simulated for the combined set of isolates with the threshold concentration C_T fixed at 2 µg/ml.

Results EMT restored the efficacy of FEP against all ESBL-producing isolates of *K. pneumoniae*. Sigmoid curve fitting by regression analysis across the combined set of isolates identified PK-PD targets for stasis and 1-$\log_{10}$ reduction in bioburden of 2% and 16% *f*T > 2 µg/ml for the global fit, and 8% and 44% *f*T > 2 µg/ml for the 75th percentile, respectively.

Conclusion The PK-PD targets identified here will assist in dose-selection and breakpoint-setting for FEP/EMT.

Background

- Infections from the **WHO list of critical priority pathogens** rank highest for third-generation cephalosporin (3GC)-resistant Enterobacteriaceae (1, 2):
  a) **77.2% 3GC-resistant Enterobacteriaceae** (*E. coli* and *K. pneumoniae)*
  b) **13.1% Carbapenem (CP)-resistant *P. aeruginosa***
  c) **5.8% CP-resistant *A. baumannii***
  d) **3.9% CP-resistant Enterobacteriaceae** (*E. coli* and *K. pneumoniae)*
- 3GC-resistance is mediated by extended-spectrum beta-lactamases (ESBLs). Mainstay therapies against ESBL-producing Enterobacteriaceae, including piperacillin-tazobactam, are losing activity (3).
- Carbapenems are now recommended as definitive therapy for infections caused by ESBL-producing Enterobacteriaceae. Widespread carbapenem use, however, promotes carbapenem resistance, which is associated with increased mortality (4, 5).
- Enmetazobactam is a novel extended-spectrum beta-lactamase inhibitor with a mechanism different from tazobactam (6).
- The safety and efficacy of cefepime 2 g-enmetazobactam 0.5 g vs piperacillin 4 g-tazobactam 0.5 g administered every 8 h as 2 h iv infusion is currently being investigated in a randomized, double-blind, non-inferiority Ph3 study in adults with cUTI or AP.
- Enmetazobactam, in combination with cefepime, is intended as an empiric carbapenem-sparing option in settings where ESBL-producing Enterobacteriaceae are prevalent.
- The objective of this study was to determine the magnitude of the PK-PD index of enmetazobactam, when combined with cefepime, in a neutropenic mouse thigh model infected with cefepime-resistant, ESBL-producing isolates of *K. pneumoniae*.

Methods

Susceptibility testing Cefepime-enmetazobactam MICs were determined in quintuplicate by broth microdilution following CLSI guidelines with enmetazobactam fixed at 8 µg/ml.

Neutropenic murine thigh infection model Thighs of immunocompromised mice were infected intramuscularly. Treatment was initiated 2 h post-infection by intravenous injection. Animals of pre-treatment groups were euthanized 2 h post infection and animals of treatment groups 26 h post infection. Colony forming units were converted to the $\log_{10}$ of the group geometric mean and the terminal bioburden was expressed as the difference between pre-treatment and treatment groups ($\Delta\log_{10}$(CFU/g)).

Exposure-response modelling The terminal bioburden as $\Delta\log_{10}$(CFU/g) was modelled as a function of enmetazobactam exposure (*f*Ex) expressed as *f*T > C_T, *f*AUC / C_T, or *f*C_{max} / C_T by fitting a sigmoid curve to the equation:

$$\Delta log_{10}(CFU/g) = -E_{min} + (E_{max} - E_{min})\frac{f\mathrm{Ex}^{\gamma}}{f\mathrm{Ex}^{\gamma} + \mathrm{EC}_{50}{}^{\gamma}}$$

Results

Table 1. Susceptibility of ESBL-producing *K. pneumoniae* isolates used in this study.

Identifier	Genotyped beta-lactamases	MIC (µg/ml)			
		FEP	FEP-EMT(8)	MEM	PTZ
#1280740	CTX-M-15; DHA-1	>32	0.06	0.12	>128
#B454	CTX-M-15	64	0.12	0.03	16
#1093554	CTX-M-15	>32	0.25	0.06	128
#1237221	CTX-M-15	>32	0.25	0.06	>128
#1061285	CTX-M-14; OXA-48	>32	0.5	2	>128
#900679	CTX-M-2; CTX-M-28	>32	0.5	6	>128
#1273479	SHV-12	32	1	0.25	>128
#1077711	CTX-M-15	>32	1	4	>128
#1046194	CTX-M-15	>32	2	>8	>128

Figure 1. Chemical structures of enmetazobactam and tazobactam.

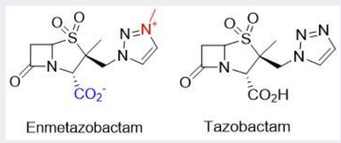

Table 2. Terminal bioburden resulting from an enmetazobactam (EMT) dose-response study, combined with a fixed dose of cefepime (FEP), administered q4h in a 26 h murine thigh infection model challenged with ESBL-producing isolates of *K. pneumoniae*.

Identifier	Bioburden as $\Delta\log_{10}$(CFU/g)						fixed FEP backbone (mg/kg) q4h
	vehicle	EMT (mg/kg) in combination with fixed FEP backbone administered q4h					
		0	1	3.16	10	31.6	100	
#1280740	3.1	2.1	-0.5	-1.4	-1.5	-2.6	-2.7	25
#B454	3.9	2.1	-0.5	-1.1	-1.7	-2.2	-1.6	25
#1093554	0.9	-0.3	-0.4	-0.6	-1.9	-2.3	-1.7	25
#1237221	4.0	2.5	-0.6	-1.0	-1.1	-1.1	-1.2	100
#1061285	2.6	1.5	0.8	0.3	-1.0	-1.2	-1.5	100
#900679	2.8	1.9	1.5	0.8	-0.1	-0.4	-1.2	50
#1273479	2.8	2.9	2.5	2.2	-0.9	-1.3	-0.5	100
#1077711	2.7	2.5	1.7	0.7	-0.6	-1.5	-2.2	100
#1046194	0.8	-0.4	-1.3	-1.5	-0.9	-1.5	-2.3	200

Figure 2. Combined enmetazobactam exposure-response relationship in a 26 h murine thigh infection model of nine ESBL-producing isolates of *K. pneumoniae*. The Y-axis shows the bioburden as $\log_{10}$(CFU/g) difference between pre-treatment and treatment groups. The X-axis show the enmetazobactam exposure as *f*T > 2 µg/ml.

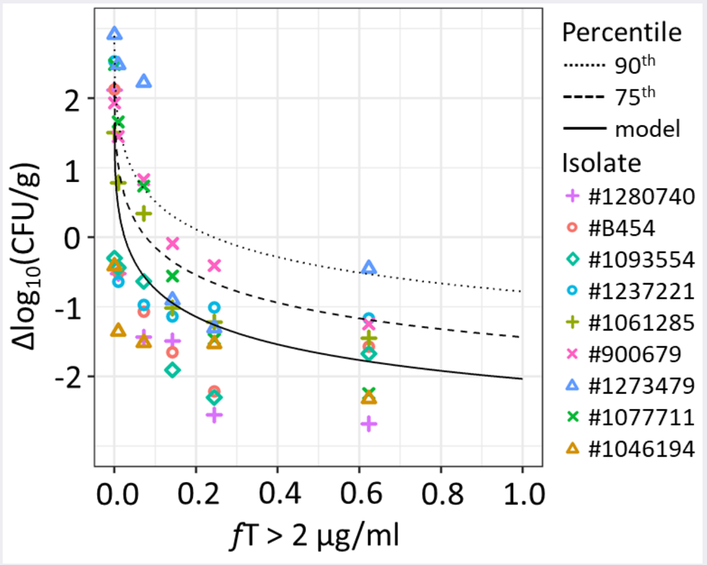

Table 3. Simulated individual and combined enmetazobactam magnitudes required for stasis and 1-$\log_{10}$ reduction in bioburden.

Identifier	Simulated enmetazobactam fT > 2 µg/ml required for:	
	stasis	1-$\log_{10}$ reduction
#1280740	0%	3%
#B454	1%	1%
#1093554	0%	8%
#1237221	0%	1%
#1061285	8%	14%
#900679	15%	46%
#1273479	10%	>100%
#1077711	10%	20%
#1046194	0%	1%
mean	5%	22%
model (global fit)	2%	16%
75th percentile	8%	44%
90th percentile	24%	>100%

Summary

- **Enmetazobactam restored the *in vitro* activity and *in vivo* efficacy of cefepime against cefepime-resistant, clinical isolates of *K. pneumoniae* expressing a variety of beta-lactamases, including CTX-M and SHV ESBLs, OXA-48 and DHA-1 (Table 1 and Table 2).**
- **PK-PD modelling identified an enmetazobactam target of 44% *f*T > 2 µg/ml, in combination with cefepime, representing the 75th percentile of the global fit for all isolates tested required for a 1-$\log_{10}$ reduction in bioburden (Figure 2 and Table 3).**

References

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