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In vitro activities of AAI101, a novel extended-spectrum β-lactamase inhibitor, and tazobactam, in combination with cefepime, against extended-spectrum β-lactamase producing *Klebsiella pneumoniae* clinical isolates

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ABSTRACT

Background: AAI101, a novel penicillanic acid sulfone β-lactamase inhibitor (BLI; **Figure 1**) active against ESBLs and other β-lactamase types, has completed Phase 2 clinical development in combination with cefepime. Emergence and spread of aggressive β-lactamases amongst Enterobacteriaceae has compromised the clinical utility of marketed BLIs such as tazobactam. This study sought to compare *in vitro* efficacies of AAI101 with those of tazobactam against ESBL-producing *Klebsiella pneumoniae*, regarded as amongst the most clinically challenging Enterobacteriaceae.

Materials/methods: The efficacies of AAI101 and tazobactam were compared for a geographically diverse panel of *K. pneumoniae* (n = 120, 94.2% cefepime-resistant; MIC_{90} >128 mg/L), using cefepime as a β-lactam partner. Each isolate tested produced one or more ESBL ± an OXA-48 carbapenemase or a plasmid-encoded AmpC cephalosporinase (**Figure 2**). Most isolates also encoded OSBL (original-spectrum β-lactamase)-TEMs and/or OSBL-SHVs. The ability of AAI101 or tazobactam, each at a fixed concentration of 4 or 8 mg/L, to restore cefepime activity towards the isolates was determined by broth microdilution. Imipenem and ertapenem were included as comparators.

Results: MIC_{90} data are presented in **Table 1**. Against ESBL-only-producing *K. pneumoniae* cefepime/AAI101 was 16-fold more potent than cefepime/tazobactam at BLI concentrations of 4 mg/L or 8 mg/L. Towards ESBL-producing isolates co-producing an OXA-48 or an AmpC, cefepime/AAI101 was >8-fold more potent than cefepime/tazobactam. In the presence of 8 mg/L of AAI101, cefepime was as potent as imipenem towards ESBL-only producers, and more potent than imipenem towards isolates co-producing an OXA-48 or an AmpC. The MIC_{90} for ertapenem was >8 mg/L.

Conclusion: AAI101 is a much more effective β-lactamase inhibitor than tazobactam. Against a challenge panel of ESBL-producing *K. pneumoniae* with or without an OXA-48 or an AmpC, AAI101 restored the activity of cefepime to the CLSI susceptible, and susceptible-dose-dependent breakpoint, respectively. In contrast, tazobactam did not restore cefepime activity. Cefepime/AAI101 activity was at least comparable to imipenem and superior to ertapenem. These data support further clinical investigation of cefepime/AAI101 for treatment of infections by *K. pneumoniae* producing ESBLs with or without an OXA-48 carbapenemase or an AmpC cephalosporinase.

INTRODUCTION

Allecra Therapeutics is developing AAI101 (**Figure 1**), a novel extended-spectrum β-lactamase inhibitor belonging to the penicillanic acid sulfone class, in combination with the 4th-generation cephalosporin cefepime. The mechanism of action of AAI101 towards β-lactamases is distinguishable from that of tazobactam (1). The combination cefepime/AAI101 has been granted Qualified Infectious Disease Product and Fast Track designations by the FDA.

The purpose of this study was to obtain additional data on the activity of cefepime/AAI101 *vs.* comparators towards a "challenge panel" of *Klebsiella pneumoniae* clinical isolates.

MATERIALS & METHODS

A collection of 120 isolates of *K. pneumoniae* from 22 countries were tested. MIC were performed by broth microdilution in line with CLSI susceptibility testing standards (2, 3) CLSI breakpoints for cefepime were applied also to cefepime/AAI101 and cefepime/tazobactam combinations for comparative purposes.

RESULTS

Figure 1. Chemical structure of AAI101

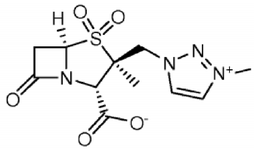


Figure 2. ESBL combinations in the *K. pneumoniae* isolates investigated

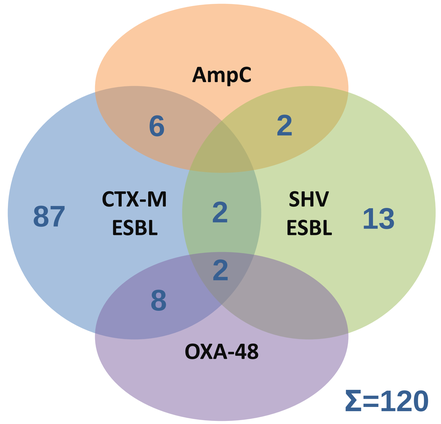


Table 1. Summary MIC_{90} of AAI101 and tazobactam, combined with cefepime, and comparators

K. pneumoniae isolates	MIC_{90} (mg/L)						
	cefepime	ertapenem	imipenem	cefepime combined with BLI fixed at			
				4 mg/L		8 mg/L	
				AAI101	tazobactam	AAI101	tazobactam
ESBL-only (n = 102)	>128	>8	1	2	32	1	16
ESBL + OXA-48 or AmpC (n = 18)	>128	>8	>8	8	>64	8	>64
all (n = 120)	>128	>8	2	4	64	1	32

Key: susceptible; susceptible dose-dependent; intermediate; resistant according to 2017 CLSI criteria

Figure 3. MIC distribution: ESBL-only *K. pneumoniae* (n = 102)

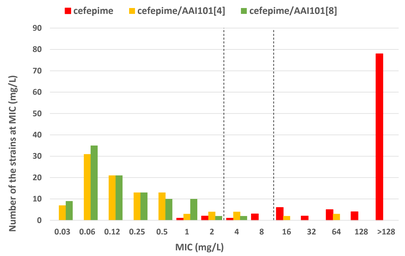


Figure 4. Cumulative % MIC distribution for ESBL-only *isolates* (n = 102)

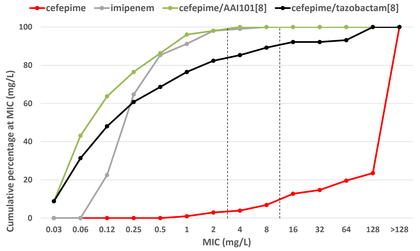


Figure 5. MIC distribution: ESBL and AmpC or OXA-48 positive isolates (n = 18)

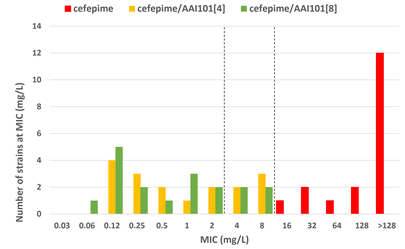


Figure 6. Cumulative % MIC distribution for ESBL and OXA-48 or AmpC-positive isolates (n = 18)

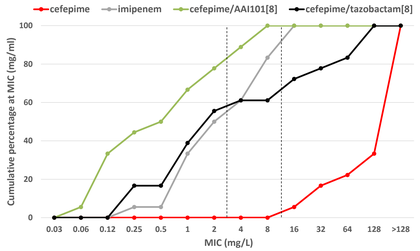


Figure 7. MIC distribution: all *K. pneumoniae* isolates (n = 120)

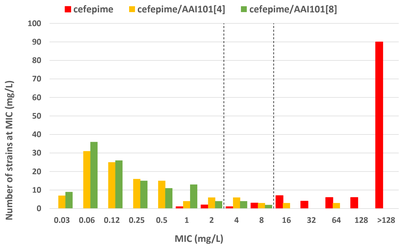
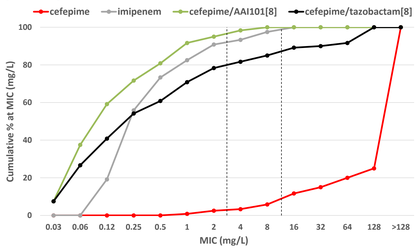


Figure 8. Cumulative % MIC distribution for all isolates (n = 120)



cefepime breakpoints for susceptible (2 mg/L) and susceptible-dose-dependent (8 mg/L) categories acc. to CLSI

RESULTS

- The combination of ESBL, AmpC, and OXA-48 β-lactamases encoded in the *K. pneumoniae* isolates investigated is shown in **Figure 2**. The majority of isolates encoded a single ESBL, followed by combinations of ESBLs with a plasmid-encoded AmpC or the OXA-48 carbapenemase. Many isolates also encoded OSBL (original-spectrum β-lactamase)-TEMs and/or OSBL-SHVs (not shown).
- MIC_{90}s for cefepime and ertapenem were in the resistant category for all subsets of isolates tested (**Table 1**).
- Against ESBL-only-producing clinical isolates of *K. pneumoniae*, AAI101 at a fixed concentration of of 4 mg/L or 8 mg/L restored the MIC_{90} for cefepime to the susceptible category. Similarly, the imipenem MIC_{90} was in the susceptible category while the cefepime/tazobactam MIC_{90} was in the resistant category (**Table 1 and Figure 3**)
- Cefepime/AAI101 was at least as potent as imipenem, and more potent than cefepime/tazobactam against ESBL-only-producing isolates (**Figure 4**).
- Against isolates co-producing an ESBL and an AmpC or OXA-48, AAI101 at a fixed concentration of 4 mg/L or 8 mg/L restored the MIC_{90} for cefepime to the susceptible-dose-dependent category, whereas imipenem and cefepime/tazobactam MIC_{90}s were in the resistant category (**Table 1 and Figure 5**)
- Cefepime/AAI101 was more potent than imipenem and much more potent than cefepime/tazobactam against isolates co-producing an ESBL and an AmpC or OXA-48 (**Figure 6**).
- The combined MIC distributions of all 120 isolates are shown in **Figures 7 and 8**.

CONCLUSIONS

- **AAI101 restores the activity of cefepime against clinical isolates of *K.* pneumoniae expressing ESBLs with or without the OXA-48 carbapenemase or a plasmid-encoded AmpC cephalosporinase.**
- **Combined with cefepime, AAI101 proved more potent than tazobactam against ESBL-producing clinical isolates of *K. pneumoniae*.**
- **Cefepime/AAI101 is as potent as imipenem, and more potent than ertapenem, against ESBL-producing clinical isolates of *K. pneumoniae*.**
- **Cefepime/AAI101 may be useful for treatment of infections by ESBL-producing *K. pneumoniae*, including isolates co-producing OXA-48 or a plasmid-encoded AmpC.**

REFERENCES & ACKNOWLEDGMENT

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