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P1170 *In vitro* activity of the extended-spectrum beta-lactamase inhibitor AAI101, in combination with cefepime, against 90 molecularly characterized *Enterobacteriaceae* isolates expressing a variety of non-beta-lactam resistance mechanisms

Michael Huband*[1], Amy A. Watters[1], Jill Lindley[1], Lalitagauri M. Deshpande[1], Adam C Belley[2], Philipp Knechtle[2], Robert Flamm[1]

[1] JMI Laboratories, North Liberty, United States, [2] Allecra Therapeutics, Saint-Louis, France

Background: AAI101 is a novel extended-spectrum β-lactamase inhibitor active against a variety of β-lactamases, including ESBLs, the principal mechanism of β-lactam resistance among Enterobacteriaceae. AAI101 in combination with cefepime has recently entered phase 3 clinical trials. Here, the *in vitro* activity of cefepime-AAI101 was assessed against clinical isolates of Enterobacteriaceae expressing diverse non-β-lactam resistance mechanisms.

Materials/methods: Clinical isolates of Enterobacteriaceae resistant to gentamicin, ciprofloxacin, tetracycline and/or colistin were molecularly characterized by whole genome sequencing to identify encoded resistance genes. Ninety isolates of mainly *Escherichia coli* (48%) and *Klebsiella pneumoniae* (38%) were selected for broth microdilution susceptibility testing against cefepime-AAI101, and comparators. Isolates co-encoding class A carbapenemases and/or class B metallo-β-lactamases were excluded from analysis due to known inactivity of cefepime-AAI101. Susceptibility testing was performed using CLSI M7-A10 broth microdilution methods and CLSI interpretive criteria. Cefepime breakpoint interpretive criteria was applied to cefepime-AAI101 for comparative purposes only

Results: Sixty-nine percent of the combined 90 isolates co-expressed an ESBL, 19% an AmpC cephalosporinase, and 38% an OXA-type β-lactamase. Applying the CLSI cefepime susceptible dose-dependent (SDD) breakpoint of 8 mg/L, 50% of the combined isolates were susceptible to cefepime alone. Addition of AAI101 at a fixed concentration of 8 mg/L restored the activity of cefepime resulting in 97.8% of isolates at or below the SDD breakpoint for cefepime. Similar susceptibility rates to cefepime-AAI101 were observed against gentamicin-, ciprofloxacin-, colistin- and tetracycline-resistant isolates. Cefepime-AAI101 was at least as potent as meropenem and outperformed piperacillin-tazobactam (Table).

Conclusions: The novel extended-spectrum β-lactamase inhibitor AAI101, in combination with cefepime, was highly active *in vitro* against 90 recent, molecularly characterized clinical isolates of Enterobacteriaceae expressing a variety of non-β-lactam resistance mechanisms. Cefepime-AAI101 activity was unaffected by resistance mechanisms targeting aminoglycoside, fluoroquinolone, colistin and tetracycline classes of antibacterial agents. Cefepime-AAI101 was as potent as meropenem and overcame resistance to piperacillin-tazobactam and therefore may represent a suitable alternative for empiric therapy in settings where resistance to piperacillin-tazobactam is increasing and carbapenem-sparing strategies are employed. Further investigation is required.

Isolate (n)	MIC_{90} (mg/L) / % susceptible (CLSI)*							
	FEP-AAI101(8)	FEP	GEN	CIP	COL	TET	MEM	PIP-TAZ
All (90)	2 97.8	>64 50.0	64 58.9	>16 40.0	>16 72.2	>64 40.0	4 86.7	>512 58.9
GEN-R (34)	2 100	>64 35.3	>64 0.0	>16 8.8	>16 55.9	>64 35.3	4 82.4	>512 52.9
CIP-R (49)	2 95.9	>64 36.7	>64 38.8	>16 0.0	>16 63.3	>64 34.7	8 81.6	>512 55.1
COL-R (25)	8 92.0	>64 40.0	>64 36.0	>16 20.0	>16 0.0	>64 24.0	16 56.0	>512 48.0
TET-R (50)	2 98.0	>64 48.0	64 56.0	>16 32.0	>16 64.0	>64 0.0	2 86.0	>512 58.0

*Susceptible dose-dependent breakpoints for FEP and percentage of wild type based on ECV for COL. FEP breakpoint interpretive criteria applied to FEP-AAI101(8) for comparative purposes only. FEP cefepime; GEN gentamicin; CIP ciprofloxacin; COL colistin; TET tetracycline; MEM meropenem; PIP-TAZ piperacillin-tazobactam; -R resistant

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