Poster 1200

Activity of the novel extended-spectrum β-lactamase inhibitor AAI101 in combination with cefepime towards a challenge panel of Acinetobacter baumannii

I. Morrissey[1], S. Magnet[1], S. Hawser[1], P. G. Higgins[2], H. Seifert[2], & S. Shapiro[3]

[1]IHMA Europe Sàrl, Monthey, Switzerland [2]Institute for Medical Microbiology, Immunology & Hygiene, University of Cologne, Germany [3]Allecra Therapeutics, St-Louis, France

Allecra Therapeutics SAS
rue Alexandre Freund, 10
F-68300 Saint-Louis
France
Email: info@allecra.com
www.allecra.com

REVISED ABSTRACT

Background: AAI101 is a novel extended-spectrum β-lactamase inhibitor (BLI), active against ESBLs and a broad array of other β-lactamases. AAI101 in combination with cefepime (FEP) is in Phase 2 development. Infections caused by *Acinetobacter baumannii*, a pathogen endemic to the southern United States and other global regions, are very challenging to treat, and often require combination therapy. This study examined the activity of FEP/AAI101 against a challenge panel of *A. baumannii* clinical isolates enriched with OXA carbapenemase producers.

Materials/methods: β-Lactamases in *A. baumannii* were identified by genotyping. Broth microdilution MICs and susceptibilities were obtained following CLSI methods and breakpoints (BPs), except for ceftazidime/avibactam (CAZ/AVI) where FDA *P. aeruginosa* BPs were applied. CLSI FEP BPs were used for FEP/AAI101.

Results: MIC_{90} data and percentage susceptibilities (%S) for FEP/AAI101 and comparators for all *A. baumannii* isolates examined and for different *A. baumannii* subsets are shown in the table below. FEP/AAI101 was highly active against meropenem-susceptible (MPM^S) isolates. FEP/AAI101 (AAI101 fixed at 8 μg/ml) covered 67% of OXA-51 producers and 53% of OXA-58 producers, though lower susceptibilities were obtained for strains expressing OXA-23 or OXA-24/40. All OXA-51 producers contained the ISAba1 insertion sequence upstream of bla_{OXA-51}. Colistin (COL) was the only agent with consistently high activity against all *A. baumannii* isolates.

Group		FEP	FEP/ AAI101 [4*]	FEP/ AAI101 [8*]	CAZ/ AVI [4*]	AMP/ SUL [2:1*]	PIP/ TAZ [4*]	COL
MPM^S (N = 17)	MIC_{90}	64	8	0.06	64	32	256	1
	%S	70.6	94.1	100	58.8	82.4	70.6	100
OXA-23 (N = 30)	MIC_{90}	>128	>128	>128	>128	128	>256	0.5
	%S	0	0	0	3.3	0	0	96.7
OXA-24/40 (N = 30)	MIC_{90}	>128	>128	>128	64	128	>256	4
	%S	3.3	3.3	6.7	6.7	3.3	0	86.7
OXA-51 (N = 30)	MIC_{90}	>128	>128	>128	>128	>128	>256	0.5
	%S	0	36.7	66.7	3.3	16.7	0	100
OXA-58 (N = 30)	MIC_{90}	>128	128	64	>128	64	>256	1
	%S	13.3	33.3	53.3	16.7	6.7	0	100
All (N = 137)	MIC_{90}	>128	>128	>128	>128	128	>256	1
	%S	12.4	27.7	40.1	13.9	16.1	8.8	96.4

AMP, ampicillin; SUL, sulbactam; PIP, piperacillin; TAZ, tazobactam
*BLI at fixed concentration in μg/ml or ratio as indicated

Conclusion: Infections by this difficult pathogen often require combination therapy, of which FEP/AAI101 may be a component.

INTRODUCTION

AAI101 is an new extended-spectrum β-lactamase inhibitor belonging to the penicillanic acid sulfone class (Figure 1).

In this study, the activity of cefepime/AAI101 against *Acinetobacter baumannii*, an uncommon but difficult-to-treat pathogen, was assessed using a challenge panel comprised of clinical isolates expressing predominantly one of the principal OXA β-lactamases responsible for carbapenem resistance in this species (OXA-23, OXA-24/40, OXA-51, OXA-58), plus some carbapenem-susceptible isolates.

MATERIALS & METHODS

- A collection of clinical isolates of *A. baumannii*, comprised of 120 strains characterised previously for the presence of OXA carbapenemases [1] plus 17 meropenem-susceptible (MPM^S) isolates, were tested (Table 1). The MPM^S reference strain *A. baumannii* ATCC was also included in the test panel.
  - All OXA-51-producing isolates had an IS*Aba1* insertion sequence upstream of the intrinsic chromosomal bla_{OXA-51} [2].
- MICs for cefepime/AAI101 [at fixed AAI101 concentrations of 4 or 8 μg/ml] and comparator antibiotics were determined by broth microdilution using CLSI methodology [3]. AAI101 and avibactam were provided by Allecra Therapeutics SAS, and other antibacterials were purchased from commercial sources.
- Susceptibility was determined according to CLSI breakpoints [4] except for:
  - ceftazidime/avibactam, for which FDA breakpoints for *Pseudomonas aeruginosa* were used [5];
  - cefoperazone, for which FDA breakpoints were used [6]; and
  - tigecycline, for which FDA breakpoints (for *Enterobacteriaceae*) were used [7].
- For comparative purposes, susceptibility of AAI101 combinations with cefepime was determined using CLSI breakpoints for cefepime alone [4], whereas cefoperazone/sulbactam susceptibility was determined using FDA breakpoints for cefoperazone alone [6].

RESULTS

Figure 1. Chemical structure of AAI101

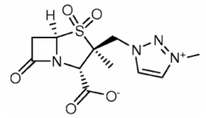

Table 1. Source of clinical isolates investigated

Country of origin	Meropenem-resistant isolates: OXA-51	OXA-23	OXA-24/40	OXA-58	Meropenem-susceptible isolates	Total
Africa		3		3	1	7
Asia	4	3		3	2	12
Europe		17	23	13	9	62
Latin America	8	3		11	3	25
Middle East		2				2
North America	18	1	7		2	28
South Pacific		1				1
Total	30	30	30	30	17	136

Table 2. Activity of AAI101, cefepime, and AAI101 combined with cefepime against the *A. baumannii* panel

Antimicrobial (breakpoints used: S|I|R)	Genotype	Percentage S	I	R	MIC (μg/ml)* MIC_{50}	MIC_{90}
AAI101 (--| -- | --)	All (n = 137)	-	-	-	64	>128
	MPM^S (n = 17)	-	-	-	4	8
	OXA-23 (n = 30)	-	-	-	64	>128
	OXA-24/40 (n = 30)	-	-	-	128	>128
	OXA-51 (n = 30)	-	-	-	16	64
	OXA-58 (n = 30)	-	-	-	32	64
Cefepime (≤8 | 16 | ≥32)	All (n = 137)	12.4	9.5	78.1	64	>128
	MPM^S (n = 17)	70.6	17.6	11.8	4	64
	OXA-23 (n = 30)	0	0	100	>128	>128
	OXA-24/40 (n = 30)	3.3	13.3	83.3	64	>128
	OXA-51 (n = 30)	0	6.7	93.3	32	>128
	OXA-58 (n = 30)	13.3	13.3	73.3	32	>128
Cefepime/AAI101 [4 μg/ml] (≤8 | 16 | ≥32)	All (n = 137)	27.7	15.3	56.9	32	>128
	MPM^S (n = 17)	94.1	5.9	0	0.125	8
	OXA-23 (n = 30)	0	3.3	96.7	128	>128
	OXA-24/40 (n = 30)	3.3	20	76.7	64	>128
	OXA-51 (n = 30)	36.7	26.7	36.7	16	>128
	OXA-58 (n = 30)	33.3	16.7	50	16	128
Cefepime/AAI101 [8 μg/ml] (≤8 | 16 | ≥32)	All (n = 137)	40.1	11.7	48.2	16	>128
	MPM^S (n = 17)	100	0	0	≤0.03	0.06
	OXA-23 (n = 30)	0	10	90	128	>128
	OXA-24/40 (n = 30)	6.7	20	73.3	64	>128
	OXA-51 (n = 30)	66.7	6.7	26.7	4	>128
	OXA-58 (n = 30)	53.3	16.7	30	8	64

*For cefepime/AAI101 combinations, MIC values refer to the cefepime component.

Figure 2. Cumulative MIC distribution for β-lactam/β-lactamase inhibitor combinations towards *A. baumannii* (n = 137)

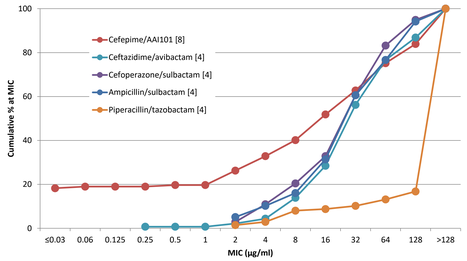

Table 3. Activity of other β-lactam/β-lactamase inhibitor combinations against *A. baumannii*

Antimicrobial (breakpoints used: S|I|R)	Genotype	Percentage S	I	R	MIC (μg/ml)* MIC_{50}	MIC_{90}
Ampicillin/sulbactam [4 μg/ml] (≤8 | 16 | ≥32)	All (n = 137)	16.1	15.3	68.6	32	128
	MPM^S (n = 17)	82.4	5.9	11.8	4	32
	OXA-23 (n = 30)	0	10	90	64	128
	OXA-24/40 (n = 30)	3.3	10	86.7	32	128
	OXA-51 (n = 30)	16.7	23.3	60	32	>128
	OXA-58 (n = 30)	6.7	23.3	70	32	64
Cefoperazone (≤8 | -- | ≥16)	All (n = 137)	0	0	100	>128	>128
	MPM^S (n = 17)	0	0	100	64	>128
	OXA-23 (n = 30)	0	0	100	>128	>128
	OXA-24/40 (n = 30)	0	0	100	>128	>128
	OXA-51 (n = 30)	0	0	100	>128	>128
	OXA-58 (n = 30)	0	0	100	>128	>128
Cefoperazone/sulbactam [4 μg/ml] (≤8 | -- | ≥16)	All (n = 137)	20.4	-	79.6	32	128
	MPM^S (n = 17)	88.2	-	11.8	4	32
	OXA-23 (n = 30)	0	-	100	64	128
	OXA-24 (n = 30)	6.7	-	93.3	32	128
	OXA-51 (n = 30)	23.3	-	76.7	32	128
	OXA-58 (n = 30)	13.3	-	86.7	32	64
Ceftazidime (≤8 | 16 | ≥32)	All (n = 137)	16.1	5.1	78.8	128	>128
	MPM^S (n = 17)	82.4	5.9	11.8	8	128
	OXA-23 (n = 30)	10	0	90	>128	>128
	OXA-24 (n = 30)	6.7	10	83.3	64	>128
	OXA-51 (n = 30)	0	3.3	96.7	128	>128
	OXA-58 (n = 30)	10	6.7	83.3	>128	>128
Ceftazidime/avibactam [4 μg/ml] (≤8 | -- | ≥16)	All (n = 137)	13.9	-	86.1	32	>128
	MPM^S (n = 17)	58.8	-	41.2	8	64
	OXA-23 (n = 30)	3.3	-	96.7	64	>128
	OXA-24 (n = 30)	6.7	-	93.3	32	64
	OXA-51 (n = 30)	3.3	-	96.7	32	>128
	OXA-58 (n = 30)	16.7	-	83.3	32	>128
Meropenem (≤2 | 4 | ≥8)	All (n = 137)	13.1	2.9	83.9	32	>128
	MPM^S (n = 17)	100	0	0	0.5	2
	OXA-23 (n = 30)	0	0	100	64	128
	OXA-24 (n = 30)	0	0	100	128	>128
	OXA-51 (n = 30)	3.3	0	96.7	32	64
	OXA-58 (n = 30)	0	13.3	86.7	16	32
Piperacillin/tazobactam [4 μg/ml] (≤16 | 32-64 | ≥128)	All (n = 137)	8.8	4.4	86.9	>256	>256
	MPM^S (n = 17)	70.6	11.8	17.6	8	256
	OXA-23 (n = 30)	0	0	100	>256	>256
	OXA-24 (n = 30)	0	3.3	96.7	>256	>256
	OXA-51 (n = 30)	0	10	90	256	>256
	OXA-58 (n = 30)	0	0	100	>256	>256

*For β-lactam/β-lactamase inhibitor combinations, MIC values refer to the β-lactam component.

Table 4. Activity of non-β-lactams against *A. baumannii*

Antimicrobial (breakpoints used: S|I|R)	Genotype	Percentage S	I	R	MIC (μg/ml) MIC_{50}	MIC_{90}
Ciprofloxacin (≤1 | 2 | ≥4)	All (n=137)	9.5	2.9	87.6	>16	>16
	MPM^S (n=17)	70.6	5.9	23.5	0.25	>16
	OXA-23 (n=30)	0	0	100	>16	>16
	OXA-24/40 (n-30)	0	0	100	>16	>16
	OXA-51 (n=30)	0	0	100	>16	>16
	OXA-58 (n=30)	3.3	10	86.7	>16	>16
Colistin (≤2 | -- | ≥4)	All (n=137)	96.4	-	3.6	0.5	1
	MPM^S (n=17)	100	-	0	0.5	1
	OXA-23 (n=30)	96.7	-	3.3	0.5	0.5
	OXA-24/40 (n-30)	86.7	-	13.3	0.5	4
	OXA-51 (n=30)	100	-	0	0.5	0.5
	OXA-58 (n=30)	100	-	0	0.5	1
Gentamicin (≤4 | 8 | ≥16)	All (n=137)	29.9	3.6	66.4	>32	>32
	MPMS (n=17)	82.4	0	17.6	0.5	16
	OXA-23 (n=30)	30	0	70	>32	>32
	OXA-24/40 (n-30)	30	10	60	>32	>32
	OXA-51 (n=30)	3.3	3.3	93.3	>32	>32
	OXA-58 (n=30)	26.7	3.3	70	16	>32
Minocycline (≤4 | 8 | ≥16)	All (n=137)	75.9	10.9	13.1	1	16
	MPM^S (n=17)	88.2	11.8	0	0.125	8
	OXA-23 (n=30)	50	13.3	36.7	4	16
	OXA-24/40 (n-30)	86.7	10	3.3	1	8
	OXA-51 (n=30)	83.3	3.3	13.3	1	16
	OXA-58 (n=30)	76.7	16.7	6.7	0.5	8
Tigecycline (≤2 | 4 | ≥8)	All (n=137)	59.9	30.7	9.5	2	4
	MPM^S (n=17)	100	0	0	0.5	2
	OXA-23 (n=30)	50	43.3	6.7	2	4
	OXA-24/40 (n-30)	36.7	43.3	20	4	8
	OXA-51 (n=30)	53.3	43.3	3.3	2	4
	OXA-58 (n=30)	76.7	10	13.3	2	8

RESULTS

- The whole panel of 137 *A. baumannii* clinical isolates was highly resistant to the antibacterial agents tested, except colistin (96.4% susceptibility) and minocycline (75.9% susceptibility).
- Cefepime alone had moderate activity against MPM^S isolates (70.6% susceptibility), but poor activity against meropenem-resistant OXA producers (<15% suscepti-bility; Table 2).
- Combinations of cefepime with AAI101 had very good activity towards MPM^S isolates of *A. baumannii*, and broadened coverage of OXA-51 and OXA-58 producers, though coverage of OXA-23 and OXA-24/40 producers remained inadequate.
- AAI101 alone had some activity against MPM^S isolates (MIC_{90} = 8 μg/ml), but poor activity towards OXA producers (MIC_{90} ≥64 μg/ml).
- All β-lactams (cefepime, cefoperazone, ceftazidime, meropenem) and β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, cefoperazone/sulbactam, piperacillin/ tazobactam, ceftazidime/avibactam) examined were inactive towards OXA-23 and OXA-24/40 producers (Table 3).
- There was a dosage effect for AAI101 in combination with cefepime, lower MICs being achieved with 8 μg/ml of AAI101 than with 4 μg/ml of AAI101.
  - Cefepime/AAI101 (fixed AAI101 concentration of 8 μg/ml), susceptibilities were 100%, 66.7%, and 53.3% susceptibility for MPM^S isolates, OXA-51 producers, and OXA-58 producers, respectively.
- OXA-23 producers proved most resistant to antibacterial agents, with only colistin, minocycline, and tigecycline having ≥50% susceptibility (Table 4).
- OXA-24/40 producers also were highly resistant to most antibacterial agents, with colistin the most active agent, though colistin susceptibility was reduced compared to OXA-23 producers. OXA-24/40-producing isolates were more susceptible to minocycline and less susceptible to tigecycline than OXA-23-producing isolates.

SUMMARY

- Meropenem-susceptible *A. baumannii* isolates have good *in vitro* susceptibilities (≥80%) towards diverse antibacterial classes (β-lactam/β-lactamase inhibitor combinations, aminoglycosides, tetracyclines), with ceftazidime/avibactam (58.8% susceptibility), and piperacillin/tazobactam (70.6% susceptibility) being notable exceptions.
- Against *A. baumannii* isolates producing OXA carbapenemases, only colistin (polymyxin class) showed nearly complete coverage (95.6% susceptibility).
- Most (≥93.3%) OXA-23 and OXA-24/40 producers were resistant to all β-lactam/β-lactamase inhibitor combinations, including cefepime/AAI101.
- Cefepime combined with a fixed concentration of 8 μg/ml of AAI101 was active against all clinical isolates of meropenem-susceptible *A. baumannii* surveyed, with an MIC_{90} of 0.06 μg/ml.
  - For meropenem-susceptible *A. baumannii* the MIC_{90} of cefepime in the presence of 8 μg/ml of AAI101 is 4 log_2 dilution steps lower than the corresponding MIC for colistin.
- AAI101 showed intrinsic dose-dependent activity against meropenem-susceptible *A. baumannii* strains.
  - Penicillanic acid sulfones, particularly sulbactam, are known to have intrinsic anti-*Acinetobacter* activity [8].
  - AAI101 is devoid of intrinsic activity against Enterobacteriaceae or *P. aeruginosa* [9].

CONCLUSIONS

- **AAI101 alone had some activity against MPM^S isolates of A. baumannii (MIC_{90} = 8 μg/ml), but poor activity towards OXA producers (MIC_{90} ≥64 μg/ml).**
- **Combinations of cefepime with AAI101 had low MICs towards MPM^S isolates of A. baumannii (MIC_{90} for cefepime + 8 μg/mL AAI101 = 0.06 μg/mL)**
- **Addition of AAI101 to cefepime broadened coverage of OXA-51 and OXA-58 producers, though coverage of OXA-23 and OXA-24/40 producers remained inadequate.**

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