Activity of the Novel Cephalosporin CXA-101 Tested in Combination with Tazobactam against Cephalosporin-resistant Enterobacteriaceae, *P. aeruginosa* and *B. fragilis*

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Revised Abstract*

Background: CXA-101 (CXA), a novel oxyimino-aminothiazolyl cephalosporin, has shown greater anti-pseudomonal and similar anti-Enterobacteriaceae (ENT) activity when compared to ceftazidime (CAZ).

Methods: CXA, various CXA/tazobactam (CXA/TAZ) combinations, and comparators were tested by CLSI broth microdilution against 1,330 well characterized clinical strains, which included 690 CAZ-resistant (R) ENT, 68 ESBL-producing *P. mirabilis*, 53 KPC-producing *K. pneumoniae* (KPN), 449 *P. aeruginosa** (PSA) and 41 *B. fragilis* (BF) strains collected worldwide in 2006-2008. CXA was combined with TAZ at a fixed concentration of 4 (CXA/TAZ4) or 2 µg/ml and at 2:1 (CXA/TAZ2:1), 4:1 and 8:1 ratios.

Results: Highest enhanced effect of CXA activity was noted with CXA/TAZ4 and CXA/TAZ2:1. CXA/TAZ4 was ≥16fold and 2- to 8-fold more active than cefepime (CPM) and piperacillin/TAZ (P/TAZ) when tested against CAZ-R *E. coli* and KPN, respectively (Table). Against other CAZ-R ENT, CXA/TAZ4 was 2- to 8-fold more active than P/TAZ but less active than CPM. All drugs tested showed poor activity vs KPC-producing KPN. CXA was very active against PSA; the addition of TAZ did not enhance CXA anti-PSA activity. CXA and CXA/TAZ4 were 8- to >32-fold more potent than CAZ, CPM and P/TAZ against PSA. CXA/TAZ4 showed activity against BF (MIC$_{50}$, 1 µg/ml), but 22% of strains had CXA/TAZ4 MIC >16 µg/ml.

Organism (no. tested)	MIC$_{50}$/MIC$_{90}$ (µg/ml)					
	CXA	CXA/TAZ4	CXA/TAZ2:1	CAZ	CPM	P/TAZ
CAZ-R *E. coli* (224)	>32/>32	1/16	4/16	64/>64	>16/>16	16/>64
CAZ-R *K. pneumoniae* (186)	>32/>32	4/>16	8/>16	>64/>64	8/>16	32/>64
CAZ-R Indol+ Proteae (82)	32/>32	2/>16	8/>16	64/>64	0.5/16	4/64
CAZ-R *Enterobacter* spp. (90)	32/>32	16/>16	8/>16	>64/>64	2/>16	64/>64
CAZ-R *Citrobacter* spp.	32/>32	16/>16	16/16	>64/>64	1/16	64/>64
ESBL+ *P. mirabilis* (68)	8/>32	1/8	2/8	≤4/>64	4/>16	1/8
P. aeruginosa (81)	1/2	1/2	1/2	≤4/32	4/16	8/>64
B. fragilis (41)	>32/>32	1/>32	4/>32	4/>64	-	-

Conclusions: CXA demonstrated higher anti-PSA activity than currently available anti-PSA cephalosporins and P/TAZ. Combination with TAZ improved CXA activity against CAZ-R ENT, especially ESBL-producing strains.

* The collection of *P. aeruginosa* was expanded after the submission of the abstract and the results incorporated in the poster.

Introduction

Multidrug resistant bacteria, especially those nosocomially-acquired, are often difficult to treat and have been reported to increase morbidity, mortality and healthcare costs. Of special concern are clinical infections due to *Pseudomonas aeruginosa* - a leading cause of nosocomial pneumonia and bacteremia. *P. aeruginosa* is intrinsically resistant to many antimicrobials and easily acquires additional resistance determinants, thus becoming difficult to eradicate. Another major concern is the treatment of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, since these organisms are usually resistant to multiple antimicrobial agents.

To address drug resistant infections, the development of new antimicrobial agents is necessary. CXA-101 (formerly FR264205), a novel oxyimino-aminothiazolyl cephalosporin, has shown greater activity, as compared to ceftazidime, against Gram-negative organisms, including many types of ESBL-producing *Escherichia coli*, wild type multidrug-resistant *P. aeruginosa* and *Burkholderia cepacia* complex isolates.

In the present study, we evaluated the potency and spectrum of activity of CXA-101 designed for combination therapy with tazobactam, an established β-lactamase inhibitor. CXA-101, CXA-101/tazobactam combinations and comparator drugs were tested against a contemporary set of clinically-derived Enterobacteriaceae and *P. aeruginosa* strains with various patterns of antimicrobial resistance, and *Bacteriodes fragilis.*

Materials & Methods

Organism collection: The organisms were collected from patients in USA, Europe, Latin America and Asia, 2006-2008 and selected based on antimicrobial susceptibility patterns. Sources of recovered isolates included skin and soft tissue, respiratory tract and bloodstream infections. Enterobacteriaceae isolates were chosen based on resistance to ceftazidime (MIC, ≥32 µg/ml), except for *Proteus mirabilis,* which were selected based on ESBL production. Multidrug-resistant (MDR) *P. aeruginosa* was defined as acquired resistance to at least three of the following antimicrobial classes: cephalosporins, carbapenems, aminoglycosides and fluoroquinolones; while carbapenem-non-susceptible *P. aeruginosa* included isolates with MIC results of ≥8 µg/ml for both imipenem and meropenem, but not MDR *P. aeruginosa*.

Susceptibility testing: MIC values for aerobic pathogens were determined using the reference CLSI broth microdilution method (M07-A8, 2009). Quality control (QC) ranges and interpretive criteria for comparator compounds used the CLSI M100-S19 (2009) guidelines. QC strains included *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853. For *B. fragilis*, MIC values were determined using the reference CLSI broth microdilution method (M11-A7, 2007). Quality control (QC) ranges and interpretive criteria for comparator compounds were those published in CLSI M11-A7 [2007]; tested QC strains included *B. fragilis* ATCC 25285.

Antimicrobial agents: CXA-101 (Calixa Therapeutics, San Diego, CA) was tested alone (0.25 - 32 µg/ml) and in combination with tazobactam at 2 or 4 µg/ml fixed concentrations and 2:1, 4:1 and 8:1 ratios. Comparator drugs included: ceftazidime, ceftriaxone, cefepime, imipenem, meropenem, piperacillin/tazobactam, doripenem, amikacin and levofloxacin.

Results

- Against ceftazidime-resistant Enterobacteriaceae and ESBL-producing *P. mirabilis*, the highest enhanced effect with CXA-101 was obtained when this compound was combined with tazobactam at a fixed concentration of 4 µg/ml (CXA/TAZ4; MIC$_{50}$, 4 µg/ml; Table 1).
- Baseline CXA/TAZ4 MIC$_{50}$ values were consistent (1-2 µg/ml) across most Enterobacteriaceae and *B. fragilis*, except for ceftazidime-resistant strains of *Enterobacter* spp. (MIC$_{50}$, 16 µg/ml) and *Citrobacter* spp. (MIC$_{50}$, 32 µg/ml; Table 2).
- Ceftriaxone (MIC$_{50}$, 64->64 µg/ml) and piperacillin/tazobactam (MIC$_{50}$, 16 µg/ml [CLSI breakpoint]) exhibited limited activity against ceftazidime-resistant *Enterobacteriaceae* and ESBL-producing *P. mirabilis* (Table 1). Cefepime showed some activity (MIC$_{50}$, 8 µg/ml) against strains from the USA but was less active against strains from Europe (MIC$_{50}$ >16 µg/ml) or from Latin America/Asia (MIC$_{50}$, 16 µg/ml; data not shown). Meropenem (MIC$_{90}$, 0.12 µg/ml) and imipenem (MIC$_{90}$, 0.5 µg/ml) were very active against *Enterobacteriaceae* (Table 1).
- Overall, CXA/TAZ4 was two- to >32-fold more potent than CXA-101 alone for all Enterobacteriaceae organisms and *B. fragilis* (Tables 2 and 3).
- CXA/TAZ4 demonstrated greater potency against organisms when compared to other cephalosporins and piperacillin/tazobactam, but was less active than cefepime against ceftazidime-resistant strains of *Enterobacter* spp. and *Citrobacter* spp. (Table 2).
- Although CXA-101 showed limited activity against *B. fragilis* (MIC$_{50}$, >32 µg/ml), CXA/TAZ4 exhibit good activity against this organism (MIC$_{50}$, 1 µg/ml; Table 3).
- CXA-101 alone was highly active in vitro against *P. aeruginosa* and the addition of tazobactam did not produce significant enhancement in activity. MIC distributions for CXA-101 tested with and without tazobactam were very similar for the three subsets of *P. aeruginosa* strains tested (Table 4).
- CXA-101 and the CXA/TAZ4 (MIC$_{50}$ and MIC$_{90}$, 0.5 µg/ml) were four- to eight-fold more active than ceftazidime (MIC$_{50}$, 2 µg/ml and MIC$_{90}$, 4 µg/ml) and as active as doripenem (MIC$_{50}$, 0.25 µg/ml and MIC$_{90}$, 1 µg/ml) against wild type *P. aeruginosa* (Table 4).
- CXA-101 and CXA/TAZ4 (MIC mode 0.5 µg/ml, MIC$_{50}$, 1 µg/ml and MIC$_{90}$, 4 µg/ml) were eight- to 32-fold more active than ceftazidime (MIC mode and MIC$_{50}$, 8 µg/ml; MIC$_{90}$, 128 µg/ml) and four- to eight-fold more active than doripenem (MIC mode and MIC$_{50}$, 8 µg/ml and MIC$_{90}$, 16 µg/ml) against carbapenem-non-susceptible (not MDR) *P. aeruginosa* strains (Table 4).
- CXA-101 and CXA/TAZ4 (MIC mode and MIC$_{50}$, 2 µg/ml; MIC$_{90}$, 16-32 µg/ml) were generally more active than doripenem (MIC$_{50}$ and MIC mode, 8 µg/ml; MIC$_{90}$, 32 µg/ml) when tested against MDR *P. aeruginosa* (Table 4). Only 18.5% of strains were inhibited at ≤2 µg/ml of doripenem, which is the current susceptible breakpoint established by the United States Food and Drug Administration and CLSI. In contrast, 53.7 and 60.5% of strains were inhibited at the same concentration (≤2 µg/ml) of CXA-101 (Table 4).

Table 1. MIC distribution for CXA-101 ± tazobactam (TAZ) and various comparator agents tested against 881 ceftazidime-resistant Enterobacteriaceae strains[a].

Antimicrobial agent[b]	Number of isolates (cumulative %) inhibited at CXA-101[b]										
	≤0.12	0.25	0.5	1	2	4	8	16	32/>16	64/>32	>64
CXA-101		2(0.3)	6(1.0)	5(1.6)	11(3.0)	35(7.3)	78(16.9)	109(30.33)	136(47.10)	429(100.0)[b]	-[c]
CXA/TAZ4[d]	4(0.5)	36(4.9)	102(17.5)	143(35.1)	83(45.4)	95(57.1)	63(64.9)	95(76.6)	190(23.4)	-	-
CXA/TAZ(2)[d]	0(0.0)	24(3.0)	60(10.4)	107(23.6)	76(32.9)	71(41.7)	65(49.7)	128(65.5)	280(100.0)	-	-
CXA/TAZ(2:1)[d]	0(0.0)	2(0.3)	13(1.9)	21(4.4)	91(15.7)	209(41.4)	190(64.9)	163(85.0)	122(100.0)	-	-
CXA/TAZ(4:1)[d]	0(0.0)	2(0. 3)	8(1.2)	19(3.6)	43(8.9)	118(23.4)	225(51.2)	209(76.9)	187(100.0)	-	-
CXA/TAZ(8:1)[d]	0(0.0)	1(0.1)	8(1.1)	13(2.7)	24(5.7)	68(14.1)	159(33.7)	247(64.1)	291(100.0)	-	-
Ceftazidime	-	-	-	-	-	39(4.8)	7(5.7)	4(6.2)	66(14.3)	204(39.5)	491(100.0)
Ceftriaxone	-	11(1.4)	4(1.9)	6(2.6)	17(4.7)	33(8.8)	53(15.3)	102(27.9)	128(43.7)	457(100.0)	-
Cefepime	44(5.4)	40(10.4)	81(20.6)	98(32.4)	91(43.7)	51(49.9)	46(55.6)	58(62.8)	302(100.0)	-	-
Imipenem	-	-	548(67.6)	104(80.4)	74(89.5)	24(92.5)	13(94.1)	48(100.0)	-	-	-
Meropenem	685(79.4)	38(89.3)	14(91.0)	5(91.6)	7(92.5)	7(93.3)	10(94.6)	44(100.0)	-	-	-
Piperacillin/tazobactam	-	-	-	78(9.6)	51(15.9)	78(25.5)	74(34.7)	110(48.2)	93(59.7)	95(71.4)	232(100.0)

a. Isolates were composed of *E. coli* (224), *K. pneumoniae* (239), indole-positive *Proteae* (82), *Enterobacter* spp. (90), *Citrobacter* spp. (108), and *P. mirabilis* (68).
b. Underlined value represents the MIC$_{50}$
c. - = concentration not tested.
d. Abbreviations: CXA/TAZ4 = CXA-101/tazobactam at fixed concentration of 4 µg/ml; CXA/TAZ(2) = CXA-101/tazobactam at fixed concentration of 2 µg/ml; CXA/TAZ(2:1) = CXA-101/tazobactam at 2:1 ratio; CXA/TAZ(4:1) = CXA-101/tazobactam at 4:1 ratio; and CXA/TAZ(8:1) = CXA-101/tazobactam at 8:1 ratio.

Table 2. Antimicrobial activity of CXA-101, CXA-101 combined with tazobactam at a fixed concentration of 4 µg/ml (CXA/TAZ4) and various comparator agents.

Organism (no. tested)/ Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	Range	% susceptible[a]	% resistant[a]
E. coli, ceftazidime-resistant (224)					
CXA-101	>32	>32	1->32	-	-
CXA/TAZ4[b]	1	16	≤0.12->16	-	-
Ceftazidime	64	>64	32->64	0.0	100.0
Ceftriaxone	>32	>32	1->32	7.6	73.7
Cefepime	>16	>16	0.25->16	33.5	59.4
Imipenem	≤0.5	≤0.5	≤0.5->8	99.6	0.4
Meropenem	≤0.12	≤0.12	0.015-8	99.6	0.0
Pip/tazo	16	>64	1->64	59.4	17.4
K. pneumoniae, ceftazidime-resistant (239)					
CXA-101	>32	>32	4->32	-	-
CXA/TAZ4	1	16	≤0.12->16	-	-
Ceftazidime	>64	>64	32->64	0.0	100.0
Ceftriaxone	>32	>32	0.5->32	8.4	61.1
Cefepime	8	>16	0.25->16	43.9	46.4
Imipenem	≤0.5	≤0.5	≤0.5->8	77.0	18.8
Meropenem	≤012	≤0.12	≤0.12->8	78.2	18.4
Pip/tazo	32	>64	1->64	35.1	48.5
B. fragilis (41)					
CXA-101	>32	>32	1->32	-	-
CXA/TAZ4	1	>16	≤0.12->64	-	-
Ceftazidime	32	>64	8->64	-	-

Organism (no. tested)/ Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	Range	% susceptible[a]	% resistant[a]
Indole (+) Proteus, ceftazidime-resistant (82)					
CXA-101	>32	>32	4->32	-	-
CXA/TAZ4	2	>16	0.25->16	-	-
Ceftazidime	64	>64	32->64	0.0	100.0
Ceftriaxone	8	>32	≤0.25->32	54.9	14.6
Cefepime	0.5	16	≤0.12->16	86.6	8.5
Imipenem	2	4	≤0.5->8	96.3	1.2
Meropenem	≤0.12	0.25	≤0.12-2	100.0	0.0
Pip/tazo	4	64	≤0.25->64	70.7	8.5
Enterobacter spp., ceftazidime-resistant (90)					
CXA-101	>32	>32	4->32	-	-
CXA/TAZ4	16	>16	0.25->16	-	-
Ceftazidime	>64	>64	32->64	0.0	100.0
Ceftriaxone	>32	>32	8->32	4.4	64.4
Cefepime	2	>16	0.25->16	71.1	20.0
Imipenem	≤0.5	1	≤0.5->8	98.9	1.1
Meropenem	≤0.12	0.25	≤0.12-4	100.0	0.0
Pip/tazo	64	>64	2->64	16.7	38.9

Organism (no. tested)/ Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	Range	% susceptible[a]	% resistant[a]
Citrobacter spp., ceftazidime-resistant (108)					
CXA-101	32	>32	1->32	-	-
CXA/TAZ4	16	>16	0.25->16	-	-
Ceftazidime	>64	>64	32->64	0.0	100.0
Ceftriaxone	32	>32	4->32	3.7	44.4
Cefepime	1	16	≤0.12->16	88.9	7.4
Imipenem	≤0.5	1	≤0.5-8	99.1	0.0
Meropenem	≤0.12	<0.12	≤0.12-4	100	0.0
Pip/tazo	64	>64	1->64	32.4	32.4
P. mirabilis, ESBL-phenotype (68)					
CXA-101	8	>32	≤0.25->32	-	-
CXA/TAZ4	1	8	0.25->16	-	-
Ceftazidime	≤4	>64	≤4->64	67.6	26.5
Ceftriaxone	8	>32	≤0.25->32	50.0	41.2
Cefepime	4	>16	≤0.12->16	58.8	36.8
Imipenem	2	4	≤0.5-4	100.0	0.0
Meropenem	≤0.12	≤0.12	≤0.12-8	98.5	0.0
Pip/tazo	1	8	≤0.5-32	97.1	0.0

a. According to CLSI breakpoints.
b. CXA/TAZ4 = CXA-101 combined with tazobactam at fixed concentration of 4 µg/ml.

Table 3. MIC distributions of CXA-101/tazobactam (fixed 4 µg/ml) tested against ceftazidime-resistant Enterobacteriaceae, ESBL-producing *P. mirabilis* and *B. fragilis*.

Organism (no.tested)	No. of isolates (cumulative %) inhibited at CXA-101/tazobactam (fixed 4 µg/ml) MIC of:								
	≤0.12	0.25	0.5	1	2	4	8	16	>16
E. coli, ceftazidime-resistant (224)	2(0.9)	5(3.1)	42(21.9)	72(54.0)	35(69.6)	18(77.7)	18(85.7)	14(92.0)	18(100.0)
K. pneumoniae, ceftazidime-resistant (239)	2(1.0)	6(4.3)	20(15.0)	33(32.8)	18(42.5)	22(54.3)	10(59.7)	16(68.3)	59(100.0)
Indode (+) *Proteus*, ceftazidime-resistant (82)	0(0.0)	12(14.6)	8(24.4)	10(36.6)	15(54.9)	12(69.5)	7(78.0)	5(84.1)	13(100.0)
Enterobacter spp., ceftazidime-resistant (90)	0(0.0)	6(6.7)	2(8.9)	6(15.6)	3(18.9)	16(36.7)	11(48.9)	25(76.7)	21(100.0)
Citrobacter spp. , ceftazidime-resistant (108)	0(0.0)	2(1.9)	2(3.7)	7(10.2)	5(14.8)	22(35.2)	13(47.2)	31(75.9)	26(100.0)
P. mirabilis, ESBL-phenotype (68)	0(0.0)	5(7.3)	28(48.5)	15(70.6)	7(80.9)	5(88.2)	4(94.1)	2(97.1)	2(100.0)
B. fragilis (41)	1(7.4)	4(12.2)	5(24.4)	15(61.0)	4(70.7)	0(70.7)	2(75.6)	2(80.5)	8(100.0)

Table 4. MIC distributions of CXA-101, CXA-101/tazobactam (fixed 4 µg/ml; CXA/TAZ4), ceftazidime and doripenem tested against *P. aeruginosa* strains having various patterns of antimicrobial resistance.

Organism/compound (no. tested)	No. isolates (cumulative %) inhibited at MIC (µg/ml) of:											
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>=[a]
Wildtype (53)													
CXA-101	-	-	6(11.3)	45(96.2)	2(100.0)	-	-	-	-	-	-	-	-
CXA/TAZ (fixed 4)[c]	-	-	5(9.4)	46(96.2)	2(100.0)	-	-	-	-	-	-	-	-
Ceftazidime	-	-	-	-	3(5.7)	33(66.9)	15(96.3)	2(100.0)[d]	-	-	-	-	-
Doripenem	1(1.9)	15(30.2)	17(62.3)	12(84.9)	8(100.0)	-[e]	-	-	-	-	-	-	-
Carbapenem-non-susceptible[f] (191)													
CXA-101	-	-	2(1.1)	70(37.7)	61(69.6)[b]	24(82.2)	20(92.7)	11(98.4)	2(99.5)	0(99.5)	1(100.0)	-	-
CXA/TAZ (fixed 4)[c]	-	-	1(0.5)	73(38.7)	59(69.6)	25(82.7)	19(92.7)	12(99.0)	1(99.5)	0(99.5)	1(100.0)	-	-
Ceftazidime	-	-	-	-	-	7(3.7)	35(22.0)	68(57.6)[d]	28(72.3)	9(77.0)	16(85.3)	22(96.9)	6(100.0)
Doripenem	-	-	-	-	-	4(2.1)[e]	77(42.4)	80(84.3)	22(95.8)	8(100.0)	-	-	-
MDR[g] (205)													
CXA-101	-	-	1(0.5)	11(5.9)	45(27.8)	53(53.7)	45(75.6)	18(84.4)	7(87.8)	3(89.3)	3(90.7)	11(96.1)	8(100.0)
CXA/TAZ (fixed 4)[c]	-	-	1(0.5)	12(6.3)	52(31.7)	59(60.5)	38(79.0)	13(85.4)	70(88.8)	4(90.7)	7(94.2)	4(96.1)	8(100.0)
Ceftazidime	-	-	-	-	-	2(1.0)	16(8.8)	16(16.6)[d]	16(24.4)	33(40.5)	58(68.8)	35(85.9)	29(100.0)
Doripenem	-	-	5(2.4)	7(5.9)	10(10.7)	16(18.5)[e]	40(38.1)	74(74.2)	28(87.8)	16(95.6)	NT[h]	NT[h]	9(100.0)

a. Greater than the highest concentration tested.
b. Underline values represents MIC$_{50}$
c. CXA-101 combined with tazobactam at fixed concentration of 4 µg/ml.
d. Current CLSI susceptible breakpoints (≤8 µg/ml).
e. Current USA-FDA susceptible breakpoint (≤2 µg/ml).
f. MIC, ≥8 µg/ml for both imipenem and meropenem.
g. Acquired resistance to at least 3 of the following antimicrobial classes: cephalosporins, carbapenems, aminoglycosides and fluoroquinolones.
h. NT = not tested.

Conclusions

- An important enhanced effect in the CXA-101 activity was obtained with tazobactam (highest at a fixed concentration of 4 µg/ml) when testing ceftazidime-resistant Enterobacteriaceae, ESBL-producing *P. mirabilis* and *B. fragilis*.
- CXA-101 and CXA/TAZ4 potencies were four- to eight-fold greater than that of ceftazidime and similar to that of doripenem when tested against wildtype strains of *P. aeruginosa*. Furthermore, CXA-101 and CXA/TAZ4 appeared more active than doripenem against the carbapenem-non-susceptible and the MDR *P. aeruginosa* isolates tested in the present study. The addition of tazobactam produced a limited effect on the in vitro activities of CXA-101 against *P. aeruginosa.*
- The results of this study suggest that CXA/TAZ4 has great potential as a new therapeutic agent for infections caused by Enterobacteriaceae and *P. aeruginosa*, including MDR strains.

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