

Activity Profile of CXA-101 and CXA-101/Tazobactam against Target Gram-Positive and Gram-Negative Pathogens

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Abstract

Background: CXA-101 (CXA), a novel cephalosporin with potent activity against *P. aeruginosa* (PA), is under development as monotherapy and in combination with tazobactam (TAZ). This study evaluates the activity of CXA, and CXA/TAZ relative to ceftazidime (CZ) against target pathogens, including resistant isolates.

Methods: CXA, CXA/TAZ (TAZ at varied concentrations), and CZ were tested by broth microdilution (CLSI M7-A8) against 2,551 Enterobacteriaceae (EN), including extended-spectrum β -lactamase (ESBL), E. coli [EC, n=48], *K. pneumoniae* [KP, 92], and *P. mirabilis* [M]; PA (914); *Acinetobacter* spp. (AC, 238); *H. influenzae* (HI, 99); *S. pneumoniae* (SP, 276, 59 multidrug resistant (MDR)), and β -hemolytic streptococci (66).

Results: By MIC₅₀/MIC₉₀ (μ g/mL), CXA (0.5Z) was several-fold more potent than CZ (2/32) against PA, regardless of TAZ combination. Against AC, CXA MIC₅₀/MIC₉₀ was 8/32 compared to 32/128 for CZ. CXA had a low MIC₅₀/MIC₉₀ against non-ESBL EC (0.12/0.25) and KP (0.25/0.5), with an MIC₅₀/MIC₉₀ of >16/32 against ESBL isolates. CXA combined with 4 μ g/mL fixed TAZ, dropped in MIC₅₀/MIC₉₀ to 0.5/1 against ESBL EC, and 2/32 against ESBL KP. Against *Citrobacter* spp. (CS) and *E. cloacae* (EL), CXA was 4-fold more potent than CZ, and the CXA/TAZ MIC₅₀ (16 and 32, respectively) dropped 2-8 fold. CXA was potent against HI (MIC₅₀/MIC₉₀ of 0.12/0.25). CXA MIC₅₀/MIC₉₀ was 0.5/0.5 against *S. agalactiae* and 0.12/0.12 against *S. pyogenes*, comparable to CZ. Against SP, the CXA/MIC₅₀/MIC₉₀ was elevated against MDR (0.5/16) relative to non-MDR isolates (0.12/0.5). CXA activity against PA, AC, HI, β -streptococci, and SP was not affected with TAZ.

Conclusion: CXA and CZ had comparable activity against the evaluated pathogens excluding PA, EL, and CS, against which CXA was several-fold more potent than CZ. CXA when combined with TAZ was more potent than CXA alone against ESBL isolates, EL, and CS, indicating the potential benefit of combining CXA and TAZ.

Background

CXA-101 is a novel broad spectrum cephalosporin with potent activity against *Pseudomonas aeruginosa*. CXA-101 is currently under development as monotherapy and in combination with tazobactam for the treatment of serious bacterial infections in hospitalized patients. As part of its development, it is important to understand the in vitro activity profile against target pathogens collected recently and to determine the appropriate in vitro testing conditions of the combination (fixed concentration of tazobactam or a fixed ratio of tazobactam to CXA-101). This study evaluated the activity of CXA-101, CXA-101:tazobactam relative to ceftazidime, and other comparators against target pathogens, including resistant isolates.

Materials & Methods

CXA-101, CXA-101:tazobactam (tazobactam at varied concentrations), ceftazidime, and other comparators were tested by broth microdilution (CLSI M7-A8) against recent surveillance (2008-2009) clinical isolates of important Gram-positive and Gram-negative pathogens. Overall testing volumes are shown in Table 1.

Isolates were collected from all nine United States Bureau of Census regions from a total of 124 hospitals. ESBL phenotypes among *E. coli*, *K. pneumoniae*, and *P. mirabilis* were confirmed according to CLSI M100-S19 criteria. Multi-drug resistance (MDR) among *S. pneumoniae* was defined as resistance to ≥ 2 agents (macrolide, coliforme, penicillin, trimethoprim-sulfamethoxazole, and tetracycline).

Results

ACTIVITY PROFILE OF CXA-101 (Tables 1-2, Figure 1-2)

- CXA-101 was the most potent agent evaluated against *P. aeruginosa* with an MIC₅₀/MIC₉₀ (μ g/mL) of 0.5Z, several fold more potent than that of ceftazidime (2/32) (Table 1; Figure 1).
- CXA-101 maintained potency against *P. aeruginosa* that were non-susceptible to other anti-pseudomonal agents. >94% of beta-lactam non-susceptible isolates remain susceptible to CXA-101 at an equivalent cephalosporin breakpoint of 8 μ g/mL (Table 2).
- All non-susceptible *P. aeruginosa*, with the exception of amikacin non-susceptible isolates show CXA-101 MICs of ≤ 8 μ g/mL (Table 2).
- Against Enterobacteriaceae, CXA-101 was similar to ceftazidime against *E. coli* and *S. marcescens* (MIC₅₀/MIC₉₀ at or within one-doubling dilution), was more potent than ceftazidime against *S. pneumoniae*, *E. cloacae*, and *Citrobacter* spp. by MIC₅₀, and was comparatively less potent than ceftazidime against *P. mirabilis* (Table 1).
- Against *Acinetobacter* spp., CXA-101 MIC₅₀/MIC₉₀ (μ g/mL) was 8/32 compared to 32/128 for ceftazidime (Table 1).
- CXA-101 had similar potency based on MIC₅₀/MIC₉₀ (μ g/mL) relative to ceftazidime against the evaluated pneumococci ($\leq 0.12/4$), and β -hemolytic streptococci (0.12/0.12 for *S. pyogenes*, 0.5/0.5 for *S. agalactiae*) (Table 1).

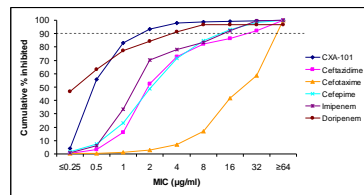
Table 1. Comparison of the activity of CXA-101 with that of other antibiotics against recent US surveillance isolates (2008-2009)

| Species | N | MIC ₅₀ /MIC ₉₀ (mg/mL) | | | | | | | | | | |
|------------------------------|-----|--|-------------|-------------|--------------|-----------|--------------|-------------|-------------|----------|------------------|------|
| | | CXA-101 | Ceftazidime | Ceftazidime | Levofloxacin | Cefepime | Imipenem | Tigecycline | Aztreonam | Ampliflu | Sulfamethoxazole | |
| Gram-negative species | | | | | | | | | | | | |
| <i>P. aeruginosa</i> | 914 | 0.5/2 | 2/32 | 32/128 | 1/1/8 | 4/16 | 2/16 | 8/16 | 4/32 | 2/32 | 2/32 | 8/32 |
| <i>Acinetobacter</i> spp. | 238 | 8/32 | 32/128 | 32/128 | >8/32 | 10/128 | 2/32 | 1/2 | ND | ND | 8/32 | |
| <i>E. coli</i> | 721 | 0.12/0.5 | 0.25/1 | 0.06/0.25 | 0.06/0.8 | 0.03/0.25 | 0.25/0.25 | 0.25/0.5 | 0.06/0.5 | 0.06/0.5 | 8/32 | |
| <i>K. pneumoniae</i> | 798 | 0.25/16 | 0.25/64 | 0.03/32 | 0.03/8 | 0.03/8 | 0.25/1 | 0.5/1 | 0.06/0.64 | 0.1/32 | 4/32 | |
| <i>E. cloacae</i> | 352 | 0.25/0.65 | 0.06/0.12 | <0.001/0.03 | 0.06/0.8 | 0.03/0.12 | 1/2 | 1/4 | 0.003/0.003 | 0.1/8 | | |
| <i>E. faecalis</i> | 206 | 0.25/32 | 0.25/128 | 0.25/128 | 0.06/4 | 0.06/4 | 0.5/1 | 0.5/1 | 0.12/64 | 32/32 | | |
| <i>Citrobacter</i> spp. | 158 | 0.5/16 | 0.5/64 | 0.12/32 | 0.06/2 | 0.03/1 | 0.5/2 | 0.25/1 | 0.12/32 | 4/32 | | |
| <i>S. marcescens</i> | 256 | 0.5/1 | 0.25/0.5 | 0.25/4 | 0.12/1 | 0.06/0.25 | 1/2 | 1/2 | 0.12/0.5 | 32/32 | | |
| <i>H. influenzae</i> | 95 | 0.12/0.25 | <0.06/0.12 | ND | 0.015/0.03 | ND | 0.5/1 | 1/1 | ND | <0.5/2 | | |
| Gram-positive species | | | | | | | | | | | | |
| <i>S. pneumoniae</i> | 277 | <0.12/4 | 0.25/8 | ND | <0.12/32 | ND | <0.015/0.5 | 0.015/0.03 | ND | ND | | |
| <i>S. pyogenes</i> | 42 | 0.12/0.12 | 0.12/0.12 | ND | 0.5/1 | ND | <0.015/0.015 | ND | ND | ND | | |
| <i>S. agalactiae</i> | 18 | 0.5/0.5 | 0.5/0.5 | ND | 0.5/1 | ND | ND | <0.008/0.03 | ND | ND | | |
| ND, Not Done | | | | | | | | | | | | |

Table 2. Cumulative CXA-101 distributions against non-susceptible *P. aeruginosa*

| Phenotype | N | Cumulative CXA-101 MIC (μ g/mL) Distribution (%) | | | | | | | | | |
|---------------------|-----|---|------|------|------|------|------|------|------|-----|--|
| | | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | >32 | |
| All isolates | 914 | 4.3 | 35.8 | 81 | 93.3 | 98 | 98.9 | 99.3 | 99.7 | 100 | |
| Ceftazidime NS | 162 | 9.9 | 29.6 | 69.8 | 90.7 | 94.4 | 96.9 | 98.1 | 100 | | |
| Imipenem NS | 199 | 2 | 25.6 | 57.8 | 80.9 | 93 | 95.5 | 97.5 | 98.5 | | |
| Cefepime NS | 140 | 2.9 | 22.9 | 65.7 | 90 | 95 | 97.9 | 98.6 | 100 | | |
| Disruptum NS | 160 | 17.5 | 50 | 76.9 | 91.9 | 94.4 | 96.9 | 98.1 | 100 | | |
| Aztreonam NS | 285 | 0.7 | 24.6 | 55.8 | 81.1 | 95.4 | 97.5 | 98.6 | 98.9 | | |
| Levofloxacin NS | 322 | 1.6 | 33.9 | 67.4 | 87.3 | 95.7 | 97.2 | 98.4 | 99.1 | | |
| Pip/Taz NS | 122 | 4.9 | 21.3 | 65.6 | 91.8 | 96.7 | 99.2 | 100 | | | |
| Amikacin NS | 16 | 6.3 | 25 | 37.5 | 62.5 | 81.3 | 87.5 | 93.8 | 100 | | |
| NS, non-susceptible | | | | | | | | | | | |

Figure 1. Cumulative susceptibility of *P. aeruginosa* to CXA-101 and comparator β -lactams



Results Continued

CXA-101 IN COMBINATION WITH TAZOBACTAM (Tables 3-4, Figure 2)

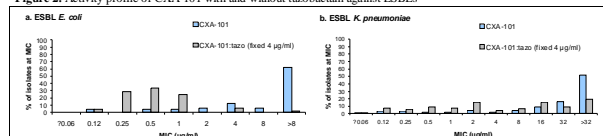
- At the various concentrations of tazobactam evaluated in combination with CXA-101, there was little impact on overall activity profile against *P. aeruginosa* and the evaluated Gram-positive organisms based on MIC distribution (Table 3).
- Against Enterobacteriaceae, there was an overall trend towards lower CXA-101 MICs when combined with tazobactam compared with CXA-101 alone based on cumulative MIC distributions (Table 3).
- The decrease in MICs observed with CXA-101:tazobactam (fixed 4 μ g/mL) relative to CXA-101 alone was particularly apparent among the ESBL-producing subpopulation of *E. coli* and *K. pneumoniae* based on MIC distribution (Figure 2).
- Based on MIC₅₀/MIC₉₀, using fixed 4 μ g/mL of tazobactam CXA-101:tazobactam was more potent than both ceftazidime:tazobactam and piperacillin:tazobactam against the evaluated pathogens (Table 4).
- In general, based on MIC distributions, the activity of CXA-101 was improved by the addition of tazobactam. The activity of CXA-101 with the addition of tazobactam at a 2:1 ratio was comparable to the fixed 4 μ g/mL concentration. At fixed 8 μ g/mL, slightly lower MICs were observed compared to the other evaluated concentrations of tazobactam (Table 3).

Table 4. Activity profile of CXA-101:tazobactam relative to comparators

| Organism | No. of Isolates | CXA-101:TAZ (fixed 4 μ g/mL) MIC ₅₀ /MIC ₉₀ | Ceftazidime:TAZ (fixed 4 μ g/mL) MIC ₅₀ /MIC ₉₀ | Piperacillin:TAZ (fixed 4 μ g/mL) MIC ₅₀ /MIC ₉₀ |
|------------------------------|-----------------|---|---|--|
| Gram-negative species | | | | |
| <i>Citrobacter</i> spp. | 168 | 0.25/4 | 0.25/32 | 2/8 |
| <i>E. cloacae</i> | 366 | 0.25/16 | 0.25/64 | 0.25/32 |
| <i>E. coli</i> | 721 | 0.25/16 | 0.12/64 | 0.12/32 |
| <i>E. coli</i> (ESBL) | 48 | 0.1/1 | 0.5/4 | 16/128 |
| <i>K. pneumoniae</i> | 798 | 0.25/2 | 0.12/4 | 4/8 |
| <i>K. pneumoniae</i> (ESBL) | 92 | 0.1/4 | 0.5/32 | 128/128 |
| <i>P. aeruginosa</i> | 914 | 0.25/16 | 0.25/64 | 0.25/32 |
| <i>S. marcescens</i> | 256 | 0.5/1 | 0.12/0.5 | 1/8 |
| <i>H. influenzae</i> | 95 | 0.12/0.25 | 0.06/0.12 | ND |
| Gram-positive species | | | | |
| <i>S. pneumoniae</i> | 277 | 0.12/8 | 0.12/16 | ND |
| <i>S. pyogenes</i> | 42 | 0.12/0.12 | 0.12/0.12 | ND |
| <i>S. agalactiae</i> | 18 | 0.5/0.5 | 0.5/0.5 | ND |

Abbreviations: ESBL = Extended-spectrum β -lactamase; ND = Not Done

Figure 2. Activity profile of CXA-101 with and without tazobactam against ESBLs



Conclusions

- CXA-101 with or without tazobactam was the most potent agent evaluated against *P. aeruginosa*, with only 1% of isolates having an MIC greater than 8 μ g/mL.
- CXA-101 was exceedingly potent against *P. aeruginosa* isolates non-susceptible to currently utilized antipseudomonal agents.
- CXA-101 was several-fold more potent than ceftazidime against *P. aeruginosa*, *E. cloacae*, and *Citrobacter* spp. and had comparable activity to ceftazidime against other evaluated pathogens.
- CXA-101 activity against *P. aeruginosa*, *H. influenzae*, beta-hemolytic streptococci, and *S. pneumoniae* was not affected when combined with tazobactam.
- CXA-101 and ceftazidime combined with tazobactam were more potent than clinically used piperacillin:tazobactam combination.
- CXA-101, when combined with tazobactam, was more potent than CXA-101 alone against ESBL isolates, *E. cloacae*, and *Citrobacter* spp., indicating the potential benefit of combining CXA-101 and tazobactam.

Table 3. Activity of CXA-101 in combination with varied tazobactam concentrations against select Gram-positive and Gram-negative pathogens

| Organism (No. of Isolates) | Drug | Cumulative (%) MIC (μ g/mL) Distribution | | | | | | | | | |
|--|------|---|------|------|------|------|------|------|-----|----|--|
| | | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | |
| <i>Citrobacter</i> spp. (N=168) | | | | | | | | | | | |
| CXA | 32.9 | 62.7 | 72.8 | 75.3 | 79.1 | 80.4 | 86.7 | 90.7 | 100 | | |
| CXA:TAZ | 49.4 | 72.2 | 79.1 | 81 | 85.4 | 91.4 | 95.6 | 98.7 | 100 | | |
| TAZ | 44.9 | 72.8 | 85.8 | 88 | 91.1 | 95.6 | 98.1 | 99.4 | 100 | | |
| CXA:TAZ:1 | 32.9 | 64.6 | 75.9 | 79.1 | 81.6 | 86.1 | 90.2 | 99.4 | 100 | | |
| <i>E. cloacae</i> (N=266) | | | | | | | | | | | |
| CXA | 12.4 | 56 | 65.9 | 69.5 | 71.6 | 74.4 | 80.8 | 90.5 | 100 | | |
| CXA:TAZ | 15.2 | 59.4 | 69.5 | 75.8 | 78.2 | 83.8 | 88 | 94.7 | 100 | | |
| TAZ | 14.7 | 60.2 | 70.7 | 77.1 | 79.3 | 83.8 | 91.7 | 97 | 100 | | |
| CXA:TAZ:1 | 12.4 | 56 | 65.9 | 69.5 | 71.6 | 74.4 | 80.8 | 90.5 | 100 | | |
| <i>E. coli</i> (N=721) | | | | | | | | | | | |
| CXA | 53.8 | 85.9 | 91.1 | 92.5 | 93.6 | 94.9 | 95.4 | 100 | — | | |
| CXA:TAZ | 62.4 | 91.7 | 92.5 | 95.8 | 97.6 | 99.4 | 100 | — | — | | |
| TAZ | 60.7 | 90.8 | 92.7 | 94.4 | 96.7 | 99.9 | — | 100 | — | | |
| CXA:TAZ:1 | 52.3 | 87.2 | 92.1 | 94.5 | 96.8 | 99.3 | 99.9 | 100 | — | | |
| <i>P. aeruginosa</i> (N=798) | | | | | | | | | | | |
| CXA | 37.3 | 71.8 | 82.7 | 85.9 | 86.8 | 87.8 | 88.6 | 90.1 | 100 | | |
| CXA:TAZ | 41.9 | 73.1 | 85.1 | 88.7 | 91 | 91.7 | 92.7 | 94.9 | 100 | | |
| TAZ | 40.1 | 72.8 | 86.3 | 91 | 92.4 | 93.1 | 94.2 | 95.6 | 100 | | |
| CXA:TAZ:1 | 39 | 71.8 | 82.8 | 86.5 | 88 | 90 | 92.4 | 95.5 | 100 | | |
| <i>P. mirabilis</i> (N=352) | | | | | | | | | | | |
| CXA | 2.3 | 55.9 | 91.8 | 96.9 | 98.3 | 98.6 | 99.7 | 100 | — | | |
| CXA:TAZ | 4.3 | 65.9 | 97.7 | 99.1 | 100 | — | — | — | — | | |
| TAZ | 4 | 69.9 | 97.2 | 99.1 | 100 | — | — | — | — | | |
| CXA:TAZ:1 | 2 | 55.7 | 98 | 98.9 | 100 | — | — | — | — | | |
| <i>S. marcescens</i> (N=256) | | | | | | | | | | | |
| CXA | 18.5 | 76.2 | 91 | 94.1 | 94.5 | 95.3 | 96.5 | 100 | — | | |
| CXA:TAZ | 0.8 | 26.2 | 81.3 | 93.8 | 97.3 | 97.7 | — | 98 | 100 | | |
| TAZ | 1.6 | 37.1 | 81.6 | 95.7 | 98 | 98.4 | 98.8 | 100 | — | | |
| CXA:TAZ:1 | 0.8 | 24.9 | 79.8 | 93 | 93.1 | 96.5 | 98 | 100 | — | | |
| <i>P. aeruginosa</i> (N=914) | | | | | | | | | | | |
| CXA | 0.1 | 4.3 | 55.8 | 87 | 93.3 | 98 | 98.9 | 99.3 | 100 | | |
| CXA:TAZ | 0.4 | 5.4 | 62.9 | 89.1 | 93.8 | 98.2 | 99.3 | 99.6 | 100 | | |
| TAZ | 0.4 | 6.1 | 60.9 | 86.3 | 95.4 | 98.5 | 99.5 | 99.6 | 100 | | |
| CXA:TAZ:1 | 0.2 | 1.6 | 58.3 | 82.4 | 93.9 | 97.9 | 99.2 | 99.3 | 100 | | |
| <i>Acinetobacter</i> spp. (N=238) | | | | | | | | | | | |
| CXA | 0.8 | 2.9 | 4.8 | 18.5 | 28.9 | 37 | 54.2 | 75.5 | 100 | | |
| CXA:TAZ | 1.8 | 21.8 | 27.7 | 33.6 | 40.8 | 46.2 | 65.5 | 76.5 | 100 | | |
| TAZ | 35.3 | 37 | 41.6 | 45.4 | 49.6 | 56.7 | 73.1 | 80.3 | 100 | | |
| CXA:TAZ:1 | 0.4 | 2.1 | 6.3 | 23 | 31.9 | 42 | 67.6 | 81. | | | |