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Assessment of the In Vivo Activity of CXA-101 in a Murine Model of *Pseudomonas aeruginosa* Pneumonia: Comparison with Ceftazidime and Piperacillin/Tazobactam

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ABSTRACT

Background. CXA-101 (CXA) is a novel parenteral cephalosporin with potent in vitro activity against *Pseudomonas aeruginosa* (PA), including multi-resistant strains. The aim of this work was to assess the in vivo activity of CXA against 2 PA strains using a murine model of pneumonia.
Methods. MICs for PA1/PA2 strains were 1/1 mg/L, 4/16 mg/L, and 64/64 mg/L for CXA, ceftazidime (CAZ), and piperacillin-tazobactam (TZP), respectively. Pneumonia was induced in immunocompetent mice by intratracheal inoculation of PA. Mice infected with one of these two strains were randomly assigned to: no treatment (controls), CXA (180 mg/kg q8hr), CAZ (200 mg/kg/q8hr), and TZP (400 mg/kg q8hr). The doses used have been designed to simulate the free-drug AUC values obtained with IV formulations of the drugs in humans. Treatment was injected using the subcutaneous route for 48 hours starting 2 hours after the bacterial challenge. Survival was tallied and comparative survival evaluated using a log rank test. Neutrophil accumulation was measured by determining myeloperoxidase levels in lung and bacterial counts in lung and spleen were determined at the end of the 2-days treatment.
Results. Results were as follows:

Strain	Regimen	Bacterial counts (CFU/g of tissue)		Myeloperoxidase (MPO/g of lung)	Survival (%)	
		Lung	Spleen	Lung	24h	48h
PA1	Controls	7.1 ± 0.9	5.1 ± 0.6	19.3 ± 4.3	80	25
	CXA	$3.6 \pm 0.3^{a,b}$	2.6 ± 0.5^{a}	16.3 ± 2.1	100	35
	CAZ	4.7 ± 1.0^{a}	2.7 ± 0.5^{a}	15.4 ± 3.8	90	30
	TZP	5.0 ± 0.9^{a}	2.8 ± 0.9^{a}	13.2 ± 8.3^{d}	70	27.5
PA2	Controls	6.7 ± 0.9	3.5 ± 1.0	24.5 ± 9.9	100	90
	CXA	$2.6 \pm 0.8^{a,c}$	2.3 ± 0.1^{a}	18.5 ± 5.0	100	100
	CAZ	3.4 ± 0.6^{a}	2.4 ± 0.4^{a}	14.2 ± 7.9	100	100
	TZP	4.3 ± 0.4^{a}	2.3 ± 0.2^{a}	20.0 ± 5.2	100	80

a: $P<0.001$ vs controls. *b*: $P<0.05$ vs CAZ and TZP. *c*: $P<0.001$ vs TZP. *d*: $P<0.01$ vs controls.
Conclusions. 1. CXA was highly efficacious in reducing the viable counts of PA in a murine pulmonary infection model. 2. CXA was more effective than TZP against both PA strains and more effective than CAZ against the highly-virulent PA1 strain. 3. MPO (the most abundant protein in neutrophils) activity confirmed the inflammatory status of the lung during PA pneumonia. 4. These data support further study of CXA as a potential therapeutic option for the treatment of severe PA infection.

INTRODUCTION

- CXA-101 (Fig. 1), previously designated FR264205, is a novel parenteral cephalosporin (currently under clinical development) with potent anti-*Pseudomonas aeruginosa* activity and with an antibacterial spectrum against other organisms similar to that of ceftazidime (1, 2).

- Using a *P. aeruginosa* pneumonia model in mice, the aim of this study was:
(i) to assess the in vivo activity of CXA-101 against *Pseudomonas aeruginosa* strains
(ii) to compare the activity of CXA-101 to comparators, ceftazidime, and piperacillin-tazobactam.

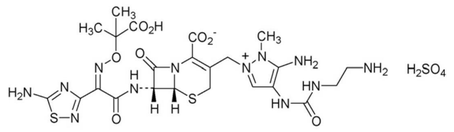
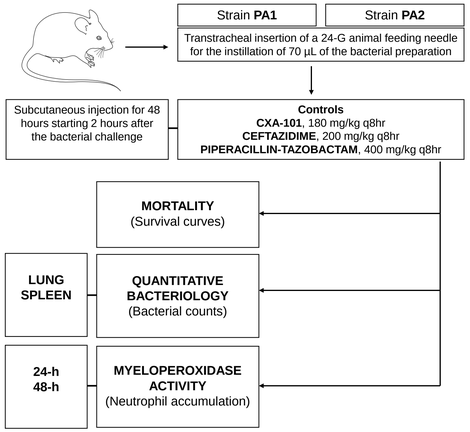


Figure 1. Structure of CXA-101

METHODS



RESULTS

• MICs of PA1 and PA2 strains are shown in Table 1 for CXA-101, ceftazidime (CAZ), and piperacillin-tazobactam (TZP).

Table 1. MICs of CXA, CAZ, and TZP for tested isolates.

STRAIN	MIC (mg/L)		
	CXA-101	CAZ	TZP
P. aeruginosa PA1	1	4	64
P. aeruginosa PA2	1	16	64

• Determination of myeloperoxidase levels 24 and 48 hours after the bacterial challenge are summarized in Figure 1.

• Bacterial counts in lung and spleen after a 2 day treatment regimen are shown in Figure 2. Survival curves for PA1- and PA2-infected mice treated by CXA-101, ceftazidime, or piperacillin-tazobactam are shown in Figure 3.

RESULTS

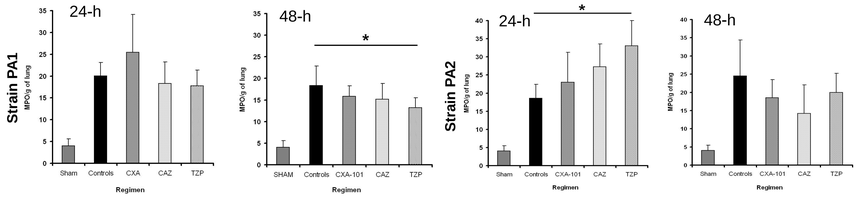


Figure 1. Myeloperoxidase levels in lung at 24- and 48-hours after the bacterial challenge for PA1 and PA2 strains. $P<0.001$ vs Sham for all treated groups (CXA-101, CAZ, and TZP).

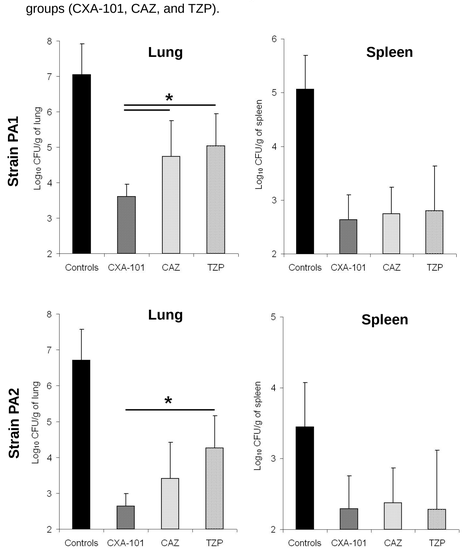


Figure 2. Bacterial counts in lung and spleen after 48 hours of treatment with CXA-101, ceftazidime (CAZ), and piperacillin/tazobactam (TZP). $P<0.01$ vs controls for all treated groups (CXA-101, CAZ, and TZP).

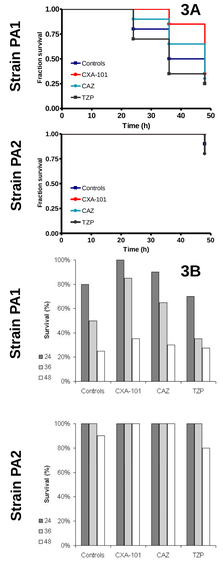


Figure 3. Survival of PA1- and PA2-infected mice. (3A) **PA1**: the survival curves are different for CXA-101 vs controls and CXA-101 vs TZP at 24- and 36 hours after the bacterial challenge; **PA2**: the survival curves are not different (3B) Survival rates expressed in percentage (%).

DISCUSSION / CONCLUSIONS

• Myeloperoxidase (the most abundant protein in neutrophils) levels at 24 and 48 hours after the bacterial challenge confirmed the inflammatory status of the lung during *P. aeruginosa* experimental pneumonia. Despite the difference in term of mortality between PA1 and PA2 strains, myeloperoxidase levels are very similar for both 24- and 48-hours timepoints. Antibacterial therapy seems to have a limited impact on the inflammatory status of the infected lung.

•All therapeutic regimens demonstrated significant activity in reducing bacterial counts in spleen (often considered as a good reflection of systemic infection).

• CXA-101 was highly efficacious in reducing the pulmonary bacterial counts in this murine infection experimental model. This new cephalosporin demonstrated comparable activity against both *P. aeruginosa* strains and was more effective than piperacillin-tazobactam. Against the highly-virulent PA1 strain, CXA-101 was more active than ceftazidime.

• Despite excellent in vivo activity of CXA-101 against the PA1 strain, no differences were observed between the survival curves (Logrank test). Nevertheless, CXA-101 seems to be able to delay the mortality by increasing the survival at 24- and 36 hours after the bacterial challenge (Figures 3A/3B). Indeed, CXA-101 significantly improves survival at 24h (P=0.0374) and 36 hours post-infection (P=0.0061) High-mortality rate observed 48 hours post-infection (i.e., 65%) is probably due to irreversible lung damage despite effective therapy.

• **These data support further study of CXA-101 as a potential therapeutic option for the treatment of severe *P. aeruginosa* infection.**

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