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). The aim of the current study was to assess the in vivo activity of CXA against PA strains using a murine model of pneumonia. Methods: CXA-101 (CXA), ceftazidime (CAZ), and piperacillin-tazobactam (TZP) were administered intravenously to 11-week-old, age-matched, wild-type, female Balb/c immunocompetent mice by intratracheal inoculation of PA. Mice infected with one of these two strains were sacrificed at 48 hours, and bacterial counts in lung and spleen were determined at the end of the 72-hour treatment. Results: CXA-101 was highly efficacious in reducing the viable counts of PA in a murine infection experimental model. This new cephalosporin demonstrated comparable activity against both PA 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 against the PA1 strain, no differences were observed between the survival curves despite effective therapy. These data support further study of CXA as a potential therapeutic option for the treatment of severe P. aeruginosa infections.

INTRODUCTION

CXA-101 (Fig. 1), a novel nonsulfonamide cephalosporin with potent in vitro activity against P. aeruginosa, was selected for this study. The aim of this study was to assess the in vivo activity of CXA-101 against P. aeruginosa strains displaying significant differences in mortality rates observed 48 hours post-challenge. Methods: The doses used have been designed to simulate the drug AUC values obtained with IV formulations of the drugs in humans. The results of these strains were as follows:

- MICs for PA1/PA2 strains were 0.5/0.25 mg/L, 4/1 mg/L, and 64/64 mg/L for CXA, tazobactam (TZP), respectively. Pneumonia was induced in immunocompetent mice by intratracheal inoculation of PA.

RESULTS

- Bacterial counts in lung and spleen after 48 hours of treatment with CXA-101, ceftazidime (CAZ), and piperacillin-tazobactam (TZP) are shown in Figure 3.

- Determination of myeloperoxidase levels at 24 and 48 hours after the bacterial challenge are summarized in Figure 2.

- Bacterial counts in lung and spleen after a 2-day treatment regime 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.

- The doses used have been designed to simulate the drug AUC values obtained with IV formulations of the drugs in humans.

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 against the PA1 strain, no differences were observed between the survival curves despite effective therapy. These data support further study of CXA-101 as a potential therapeutic option for the treatment of severe P. aeruginosa infections.

REFERENCES

