Efficacy of ACHN-490 in a Murine Urinary Tract Infection Model with Escherichia coli

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Abstract

Urinary tract infections (UTIs) rank among the most prevalent of human-associated infectious diseases, with the majority of UTIs attributed to uropathogenic Escherichia coli (UPEC). UTIs are associated with significant morbidity and mortality, representing a significant economic burden. Despite recent advances in the treatment of UTIs, there remains a need for new therapeutic options, especially for resistant strains. ACHN-490 is a neoglycosylated carbohydrate antibiotic with potent in vitro activity against multidrug-resistant Gram-negative and select Gram-positive pathogens.

Methods and Materials

Female C3H/HeJ mice were placed on 5% glucose water 6 days prior to infection. Anesthetized animals were transurethrally infected with a strain of Escherichia coli (ATCC 700336) at 8.8 x 10^8 CFU. Bladders and kidney pairs were placed into 2 mL of sterile 1x PBS, homogenized, and plated for CFU counts. Bladders, and kidneys were collected from each mouse 18 hours after the final antibiotic dose. Efficacy was determined by comparing the mean CFU of treated groups to day controls. The same dose range of ACHN-490 also decreased bladder counts by 0.4 to 4.5 log (0.61 mm, o.d.) transurethrally into each mouse and injecting 0.05 mL of the inoculum (8.8 x 10^8 CFU). Bacterial infection was confirmed in all treatment groups as evidenced by stable and consistent CFU counts were achieved in the kidneys and bladder of all inoculated animals. The same dose range of ACHN-490 also decreased bladder counts by 0.4 to 4.5 log (0.61 mm, o.d.) transurethrally into each mouse and injecting 0.05 mL of the inoculum (8.8 x 10^8 CFU). Bacterial infection was confirmed in all treatment groups as evidenced by stable and consistent CFU counts were achieved in the kidneys and bladder of all inoculated animals.

Summary and Conclusions

• MIC values for ACHN-490, gentamicin, and levofloxacin indicate that the uropathogenic E. coli (UPEC) strain used, ATCC 700336, was susceptible to all antibiotics.
• The results from the daily infection control indicated that ACHN-490 and gentamicin (0.5 mg/kg) resulted in log reductions of 2.8 and 3.5, respectively in the kidneys and bladder of all inoculated animals.
• ACHN-490 administration resulted in 2.4 ± 0.6 mean CFU reduction in the bladder as compared to 1.5 ± 0.5 in the kidneys. ACHN-490 administration resulted in similar dose range, while levofloxacin at 0.5 mg/kg had mean CFU reductions of 2.1 and 0.7, respectively.
• As compared to 7-day controls, study associated dose ranges for ACHN-490, gentamicin and levofloxacin resulted in 6.6–1.1, 0.3–1.5, and 0–0.8 log reductions in the bladder and 0.2–4.9, 3.3–3 and 0.8 in the kidney, respectively.
• The results from the current study demonstrate the efficacy of ACHN-490 in a murine model of a urinary tract infection with a uropathogenic E. coli and indicate that further testing of ACHN-490 against drug-resistant UPEC could be warranted in order to provide additional non-clinical data that supports the potential use of ACHN-490 in treating UTIs caused by multidrug-resistant strains.

References


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