**ABSTRACT**

Background: Antimicrobial resistance among Gram-negative uropathogenic bacteria has increased in recent years. Tebipenem (SPR859) has potent activity against Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBLs), carbapenemase-producing Enterobacteriaceae (CRE), and carbapenem-resistant, extended-spectrum beta-lactamase-producing Pseudomonas aeruginosa. In vivo studies of SPR859 are being developed as a therapeutic for treating urinary tract infections in adults. We evaluated the bactericidal activity and post-antibiotic effect (PAE) of SPR859 against Enterobacteriaceae and other Gram-negative pathogens.

Methods: broth microdilution studies were performed against susceptible and ESBL-producing isolates of Escherichia coli (ATCC 25922 and 35218), Klebsiella pneumoniae (ATCC 700603) and Proteus mirabilis (Pm ATCC 25901) using CLSI M07-A8 and M100, respectively. The in vitro PAE of SPR859 and comparators was established against E. coli ATCC 25922 and K. pneumoniae ATCC 43816 using a method established in Antibiotics in Laboratory Medicine. Log phase cultures were treated with antimicrobial agents at 4x and/or 8x MIC for 1 h, diluted 1:1000 into fresh CAMHB, and viability was monitored for 6 h by plating on CFU/mL of the initial inoculum.

Results: SPR859 was bactericidal at 4x-8x MIC against E. coli, K. pneumoniae and Pm, with PAE of 4-8 h against E. coli and 2-3 h against K. pneumoniae.

**INTRODUCTION**

Antimicrobial resistance among Gram-negative uropathogenic bacteria has increased in recent years. Tebipenem (SPR859) has potent activity against Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBLs), carbapenemase-producing Enterobacteriaceae (CRE), and carbapenem-resistant, extended-spectrum beta-lactamase-producing Pseudomonas aeruginosa. In vivo studies of SPR859 are being developed as a therapeutic for treating urinary tract infections in adults. We evaluated the bactericidal activity and post-antibiotic effect (PAE) of SPR859 against Enterobacteriaceae and other Gram-negative pathogens.

**METHODS**

- **Broth time-kill studies**: performed against susceptible and ESBL producing isolates of Escherichia coli (ATCC 25922 and 35218), Klebsiella pneumoniae (Kp ATCC 43816 and 700603), and Proteus mirabilis (Pm ATCC 25901) using CLSI M07-A8. Log phase cultures were treated with antimicrobial agents at 4x and/or 8x MIC for 1 h, diluted 1:1000 into fresh CAMHB, and viability was monitored for 6 h by plating on CFU/mL of the initial inoculum.

- **In vitro PAE of SPR859 and comparators**: established against E. coli ATCC 25922 and K. pneumoniae ATCC 43816 using a method established in Antibiotics in Laboratory Medicine. Log phase cultures were treated with antimicrobial agents at 4x and/or 8x MIC for 1 h, diluted 1:1000 into fresh CAMHB, and viability was monitored for 6 h by plating on CFU/mL of the initial inoculum. PAE = T - C, where T and C are the time required to increase 1 log CFU/mL following 1000 dilution for the bacteria treated with and without the agents, respectively.

**RESULTS**

- **Figure 1. Time-kill studies of SPR859, MEM and LVA**
  - E. coli ATCC 25922
  - K. pneumoniae ATCC 43816

- **Figure 2. Post-antibiotic effect studies of SPR859, MEM and LVA**
  - E. coli ATCC 25922
  - K. pneumoniae ATCC 43816

- **Figure 3. Tebipenem (SPR859)**
  - CAMHB
  - SPR859 1x MIC
  - SPR859 2x MIC
  - SPR859 4x MIC
  - SPR859 8x MIC
  - MEM 4x MIC
  - LVX 4x MIC

- **Spr859** was bactericidal at 2x-8x MIC within 4 h against E. coli and Kp strains, comparable to MEM at 4x MIC.
- **Spr859** was bactericidal against susceptible Pm ATCC 25901 at 2x MIC within 9 h and at 4x-8x MIC within 4 h.
- **Spr859** was bactericidal against ESBLproducing Pm JY904 at 2x MIC within 2 h, at 4x-8x MIC within 4 h, and at 4x-8x MIC within 4 h.
- **Spr859** was comparable to MEM at all administered dosages in both time-kill and PAE studies, thus supporting the development of SPR859, for the usage of SPR859 as a potential new oral option for ESBL-producing Gram-negative uropathogens.

**CONCLUSIONS**

- **Spr859** was bactericidal at 4x-8x MIC against Kp and Pm, and at 2x MIC against E. coli and Kp strains within 4 h.
- **Spr859** was comparable to MEM at all administered dosages in both time-kill and PAE studies, thus supporting the development of SPR859, for the usage of SPR859 as a potential new oral option for ESBL-producing Gram-negative uropathogens.

**REFERENCES**

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