**REVISED ABSTRACT**

**Background:** The emergence and spread of multidrug-resistant (MDR) *Pseudomonas aeruginosa* (Pa), and *Acinetobacter baumannii* (Ab) are limiting available treatment options. SPR206 is a polymyxin analogue that exhibits potent in vitro activity against key Gram-negative pathogens *Pa*, *Escherichia coli* and *Klebsiella pneumoniae*, including MDR variants. Here, we describe the efficacy of SPR206 in murine lung and thigh infection models using either Pa14 (lads mutant; hyperpyrenic) or Ab NCTC13301 (Ab13301) (OXA-23; carbapenem resistant).

**Material/methods:** Neutropenic mice were infected by inoculating into the thigh (IM) or into the lungs by intratracheal (IT) or intranasal (IN) administration. SPR206 and PMB were dosed at various concentrations by either subcutaneous (SC) or intravenous (IV) administration, every 8 hours (q8h) or every 4 hours (q4h). Mice were euthanized at either 16 h or 24 h. Lung or thigh tissues were homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

**Results:** The MIC values of SPR206 and PMB for Pa14 are 0.13 mg/L and 0.13 mg/L, respectively. SPR206 and PMB were dosed at various concentrations by either subcutaneous (SC) or intravenous (IV) administration, every 8 hours (q8h) or every 4 hours (q4h). In the lung model, administration of PMB and SPR206 at 20 mg/kg IV q4h SC reduced the burden of Pa14 by 1.5 and 4.6 log CFU/mL compared to 2 h control. Administration of PMB and SPR206 at 4 mg/kg IV q4h reduced the burden of Ab13301 by 3.4 and 4.3 log CFU/g compared to 2h control.

**Conclusions:** Our in vivo pharmacology studies described herein demonstrate that SPR206 exhibits similar or superior efficacy to PMB in both murine thigh and lung infections. These data support the continued development of SPR206 for IV administration in the hospital setting for the treatment of serious Gram-negative infections.

**METHODS**

- The minimum inhibitory concentration (MIC) was determined for SPR206 and polymyxin B (PMB) using CLSI methodology.
- Neutropenia was induced in CD-1 female or male mice by administering cyclophosphamide by intraperitoneal injection on days -4 and -1 (150 and 100 mg/kg, respectively).
- Mice were infected by inoculating into the thigh (IM) or into the lungs by intratracheal (IT) or intranasal (IN) administration.
- SPR206 and PMB were dosed at various concentrations by either subcutaneous (SC) or intravenous (IV) administration, every 8 hours (q8h) or every 4 hours (q4h).
- Mice were euthanized at either 16 h or 24 h.
- Lung or thigh tissues were homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

**RESULTS**

- The in vivo studies described herein demonstrate that SPR206 exhibits similar or superior burden reductions compared to PMB.
- These data support the continued development of SPR206 for the treatment of serious Gram-negative infections.

**REFERENCES**

1. Mikkelson H (2011) The *Pseudomonas aeruginosa* reference strain PA14 displays increased virulence due to a mutation in lasR PLoS One. 6(12):e29113
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