ABSTRACT

Background: SPR741 is a novel agent with structural similarity to polymyxin that is capable of potentiating the activity of various classes of antibiotics. Previously published studies indicated that multidrug resistant Enterobacteriaceae (MDR) isolates have inherent susceptibility to azithromycin (AZM), the in vitro antimicrobial activity of AZM against EB was enhanced when combined with SPR741. The current study evaluated the in vivo efficacy of human-simulated infections (HSI) of AZM and SPR741 alone and in combination against multidrug resistant (MDR) EB.

Methods: We studied 30 MDR EB isolates expressing a wide spectrum of β-lactamases (ESBL, NDM, VIM and KPC) inoculated as a subset of isolates positive for genes confering macrolide resistance (ermM, eryQ, ermT and mcr). The MICs of AZM, SPR741, and the combination of AZM+SPR741 (using a fixed concentration of SPR741 = 8 mg/L) were determined in triplicate using broth microdilution. EB were rendered transiently neutropenic, and the thighs were inoculated with bacterial suspensions of 10^7/mL of HSR. MICs of AZM and SPR741 equivalent to clinical doses of 500 mg iv q24h and 400 mg iv q1 (1h infusion), respectively, as monotherapies and in combination. Treatment mice were administered the AZM, SPR741 or AZM+SPR741 EB HSR, while control mice were vehicle-dosed. Efficacy was assessed as the change in log_{10} CFU/thigh at 24 h compared with 0 h.

Results: MICs for AZM, SPR741 and AZM+SPR741 were between 0.06 and 0.53, and 0.53 and 5.62 mg/L, respectively. The average log_{10} CFU/thigh at 0 h across all isolates was 5.80 ± 0.30. At 24 h, the bacterial burden increased by an average magnitude of 2.75 ± 0.65 log_{10} CFU/thigh. The untreated control mice treated with AZM alone was associated with net growth of 3.02 ± 0.83 log_{10} CFU/thigh. SPR741 alone achieved stasis to 1 log kill relative to starting inoculum for 2/30 (6.7%) isolates with an average bacterial burden of 2.02 ± 0.73 log_{10} CFU/thigh. Among isolates with AZM MIC ≥ 16 mg/L, treatment with AZM+SPR741 was associated with a reduction in bacterial burden of -0.53 ± 0.82 log_{10} CFU/thigh and stasis to 1 log kill was observed in 9/11 isolates (81.8%). By contrast, isolates with AZM MIC 3 32 mg/L displayed an average net growth of 1.80 ± 1.41 log_{10} CFU/thigh and stasis to 1 log kill was achieved in 9/11 isolates (81.8%).

Conclusion: Combination therapy of AZM+SPR741 HSR showed promising efficacy against MDR EB for isolates with AZM MIC≥16 mg/L, including those producing a variety of β-lactamases. These data support a potential role for AZM+SPR741 for treatment of infections due to MDR EB.

CONCLUSION

Combination therapy of AZM+SPR741 HSR showed promising efficacy against MDR EB for isolates with AZM MIC≥16 mg/L, including those producing a variety of β-lactamases. These data support a potential role for AZM+SPR741 for treatment of infections due to MDR EB.

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