Evaluation of Synergistic Effects of a Potentiator Molecule (SPR741) When Tested in Combination with a Series of β-Lactam Agents against a Challenge Set of Gram-Negative Pathogens

**Introduction**

- Enterobacteriaceae isolates account for 27% of healthcare-associated infections in the United States.
- A great proportion of these isolates produce extended spectrum β-lactamase (ESβLA), which account for approximately 14% of carbapenem-resistant isolates in the United States.
- ESβLA-producing Enterobacteriaceae isolates spread in the nosocomial and community settings, complicating the empirical treatment of infections caused by these organisms.
- The increased frequency of ESβLA-producing Enterobacteriaceae isolates may increase the use of more potent antimicrobial agents, including carbapenems although carbapenem-resistant Enterobacteriaceae (CRE) isolates are still generally uncommon in the United States and Europe, the number of facilities reporting CRE has been steady in several regions worldwide.
- These hard-to-treat infections have been targeted as one of the most pressing challenges in the field of antibiotic resistance.

SPR741 is a novel polymyxin analogue that interacts with the outer membrane of Gram-negative bacteria and compromises the integrity of the outer membrane of Gram-negative bacteria and compromises the integrity of the outer membrane.

**Materials and Methods**

**Organisms collection**

- A total of 423 bacterial clinical isolates (302 Escherichia coli and 211 Klebsiella pneumoniae) were selected by the presence of β-lactamases, including plasmid-encoded AmpC (pAmpC), ESβLA, extended-spectrum β-lactamases (ESβLs), metallo-β-lactamases (MBLs), and OXA-48-like enzymes.
- A total of 86% of the 423 isolates were from 2010 to 2016, and isolates from 2012 to 2014 were added to increase counts for some genotypes.
- Isolates were received from medical centers worldwide—excluding North America—(n=104), Europe (n=111), Asia-Pacific (n=57), and Latin America (n=221).

**Susceptibility testing**

- Isolates were tested for susceptibility by both microdilution following the Clinical and Laboratory Standards Institute (CLSI) M100-S18 document.
- β-Lactam agents were tested in combination with SPR741 at a fixed concentration of 8 mg/L.
- Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event.
- Acceptable MIC ranges defined by the CLSI were tested against ATCC QC strains.
- Target MIC quality control values expected for temocillin and mecillinam were those published by the British Society for Antimicrobial Chemotherapy (BSAC).
- The expected temocillin MIC value against Enterobacter cloacae ATCC 25086 was 8 mg/L, whereas the expected mecillinam MIC value against E. coli strain ATCC 25922 was 0.12 mg/L.
- MIC results obtained against clinical isolates were interpreted using the CLSI M100 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2016 documents, as available.
- MEC results obtained for temocillin were interpreted according to the BSAC susceptibility (c9 mg/L for susceptible) and urinary tract infection (UTI) (≤2 mg/L, for susceptibility breakpoints), which were also applied to the temocillin-SPR741 combination.
- MEC interpretations for other combinations utilized the breakpoints available for the respective drugs for comparison purposes.

**Results**

- SPR741 increased the activity of temocillin from 0% susceptible to 85.4%–98.2% susceptible when co-treatment SPR741 was tested against ESβLA-producing E. coli (Table 1 and Figure 1A).
- The marginal activity to piperacillin-tazobactam against AmpC- and ESβLA-producing isolates increased from 0.0%–74.2% susceptible to 50.0%–100.0% susceptible with the addition of SPR741 (Table 1).
- Adding SPR741 did not increase the activity of cefoxitin, carbapenems, or tigecycline against ESβLA-resistant strains (Table 1 and Figure 1A).
- The activity of SPR741 against AmpC-producing isolates increased from 6.2% to 93.8% susceptible.
- Mecillinam-SPR741 showed susceptibility rates of 83.6%–100% (in systemic breakpoint), and TEM-75-SPR741 provided this drug with acceptable coverage (susceptibility rates 97.8% susceptible).
- The activity of carbapenem-resistant isolates may increase the temocillin susceptibility rates up to 97.8% against piperacillin-tazobactam (T.
- This compound has been shown to display reduced nephrotoxicity and renal injury.

**Conclusions**

- In general, all β-lactam agents tested in this study showed increased in vitro activity in the presence of SPR741.
- The activity of piperacillin-tazobactam was also potentiated in the presence of SPR741 against AmpC- and ESβLA-producing isolates as well as against OXA-48-like-producing isolates.
- SPR741 significantly increased the coverage against ESβLs, MBLs, and OXA-48-like-producing isolates.
- The marginal activity of carbapenem-resistant isolates (Table 1 and Figure 1A)

**References**


ECCMID 2018. Evaluation of Synergistic Effects of a Potentiator Molecule (SPR741) When Tested in Combination with a Series of β-Lactam Agents against a Challenge Set of Gram-Negative Pathogens. RE Mendes, PR Rhomberg, TF Lister, NC Gonlin, A Rubio, RM Flamman. UM Laboratories, North Liberty, Iowa, USA; Spero Therapeutics Inc., Cambridge, Massachusetts, USA