ECCMID 2018
Poster #P1672

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

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Introduction

- *Enterobacteriaceae* isolates account for 27% of healthcare-associated infections in the United States
  - A great proportion of these isolates produce extended-spectrum β-lactamases (ESBLs), which account for approximately 14% of *Enterobacteriaceae*
- ESBL-producing *Enterobacteriaceae* isolates have spread in the nosocomial and community settings, complicating the empiric treatment of infections caused by these organisms
- The increased frequency of ESBL-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 risen steadily in several regions worldwide
- These hard-to-treat infections have been targeted as one of the most pressing challenges in the field of infectious diseases
- SPR741 is a novel polymyxin analogue that interacts with the outer membrane of Gram-negative bacteria and compromises the integrity of the lipopolysaccharide
  - This compound has minimal direct antibacterial activity and acts by increasing cell permeability
  - When tested in combination with an antibacterial agent, SPR741 facilitates the entry of the active compound
  - This compound has been shown to display reduced nephrotoxicity
- This study screened for *in vitro* activity of a series of β-lactam agents tested in combination with SPR741 against a challenge set of *Enterobacteriaceae*

Materials and Methods

Organism collection

- A total of 423 bacterial clinical isolates (202 *Escherichia coli* and 221 *Klebsiella pneumoniae*) were selected by the presence of β-lactamases, including plasmid AmpCs (pAmpCs), ESBLs, *Klebsiella pneumoniae* carbapenemases (KPCs), metallo-β-lactamases (MBLs), and OXA-48-like enzymes
- A total of 84.9% of the 423 isolates were from 2015 to 2016, and isolates from 2002 to 2014 were added to increase counts for rare genotypes
  - Isolates were received from medical centres worldwide, including North America (n=218), Europe (n=111), Asia-Pacific (n=57), and Latin America (n=37)

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) 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 obtained for β-lactams tested against ATCC QC strains were those published in the CLSI M100 (2018)
- 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 *Escherichia coli* NCTC 10418 was 2 mg/L (expected MIC range, 1–4 mg/L), while the expected mecillinam MIC value against *E. coli* strains NCTC 10418 and ATCC 25922 was 0.12 mg/L (expected MIC range, 0.06–0.25 mg/L)
- MIC results obtained against clinical isolates were interpreted using the CLSI M100 and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2018) documents, as available
- MIC results obtained for temocillin were interpreted according to the BSAC systemic (≤8 mg/L for susceptible) and urinary tract infection (UTI; ≤32 mg/L for susceptible) breakpoints, which were also applied to the temocillin-SPR741 combination
- MIC interpretations for other combinations utilized the breakpoints available for the respective co-drugs for comparison purposes

Results

- SPR741 increased the activity of ceftazidime from 0.0% susceptible to 80.4%–88.2% susceptible when ceftazidime-SPR741 was tested against ESBL-producing *E. coli* (Table 1 and Figure 1A)
- The marginal activity to piperacillin-tazobactam against AmpC- and ESBL-producing isolates increased from 0.0%–74.2% susceptible to 93.8%–100.0% susceptible with the addition of SPR741 (Table 1)
- Adding SPR741 did not increase the activity of aztreonam, cefotaxime, or cefepime to ≥90% susceptible against selected isolates (Table 1 and Figure 1)
  - The exception was noted when aztreonam was tested in the presence of SPR741 against AmpC-producing isolates (increased from 6.2% to 93.8% susceptible)
- Mecillinam-SPR741 showed susceptibility rates of 80.0%–100.0% when tested against AmpC-, ESBL-, MBL-, or OXA-48-like-producing isolates (Table 1 and Figure 1)
  - Lower susceptibility rates (26.1%–43.2%) were obtained against KPC producers

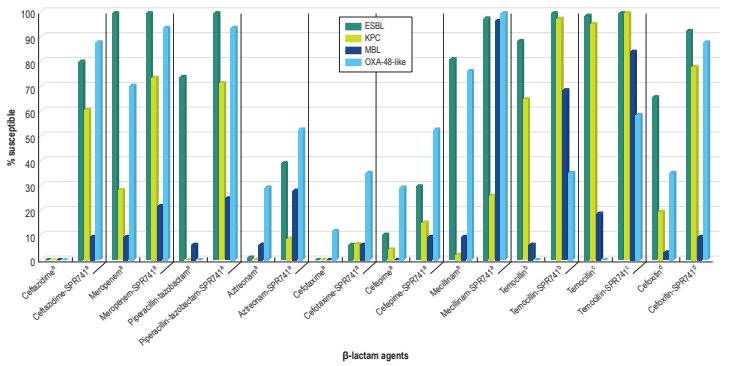
Table 1 Summary of susceptibility rates for selected β-lactam agents tested alone and in combination with SPR741

Agent	AmpC* (n=16)	*E. coli* (n=202)				*K. pneumoniae* (n=221)			
		ESBL (n=97)	KPC (n=46)	MBL (n=32)	OXA-48-like (n=17)	ESBL (n=101)	KPC (n=74)	MBL (n=25)	OXA-48-like (n=15)
Ceftazidime[a]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ceftazidime-SPR741[a]	62.5	80.4	60.9	9.4	88.2	55.4	9.5	0.0	33.3
Meropenem[a]	100.0	100.0	28.3	9.4	70.6	97.0	0.0	8.0	20.0
Meropenem-SPR741[a]	100.0	100.0	73.9	21.9	94.1	100.0	10.8	8.0	40.0
Piperacillin-tazobactam[a]	75.0	74.2	0.0	6.2	0.0	51.5	0.0	0.0	0.0
Piperacillin-tazobactam-SPR741[a]	93.8	100.0	71.7	25.0	94.1	97.0	35.1	4.0	53.3
Aztreonam[a]	6.2	1.0	0.0	6.2	29.4	1.0	0.0	4.0	0.0
Aztreonam-SPR741[a]	93.8	39.2	8.7	28.1	52.9	26.7	0.0	8.0	13.3
Cefotaxime[a]	0.0	0.0	0.0	0.0	11.8	1.0	0.0	0.0	0.0
Cefotaxime-SPR741[a]	50.0	6.2	6.5	6.2	35.3	4.0	0.0	0.0	0.0
Cefepime[a]	100.0	10.3	4.3	0.0	29.4	7.9	0.0	0.0	0.0
Cefepime-SPR741[a]	100.0	29.9	15.2	9.4	52.9	25.7	1.4	0.0	0.0
Mecillinam[a]	93.8	81.4	2.2	9.4	76.5	49.5	0.0	0.0	13.3
Mecillinam-SPR741[a]	100.0	97.9	26.1	96.9	100.0	96.0	43.2	80.0	86.7
Temocillin[b]	87.5	88.7	65.2	6.2	0.0	88.1	14.9	0.0	0.0
Temocillin-SPR741[b]	100.0	100.0	97.8	68.8	35.3	99.0	78.4	76.0	33.3
Temocillin[c]	100.0	99.0	95.7	18.8	0.0	99.0	83.8	20.0	0.0
Temocillin-SPR741[c]	100.0	100.0	100.0	84.4	58.8	100.0	94.6	84.0	46.7
Cefoxitin[d]	0.0	66.0	19.6	3.1	35.3	65.3	1.4	0.0	13.3
Cefoxitin-SPR741[d]	12.5	92.8	78.3	9.4	88.2	79.2	48.6	12.0	46.7

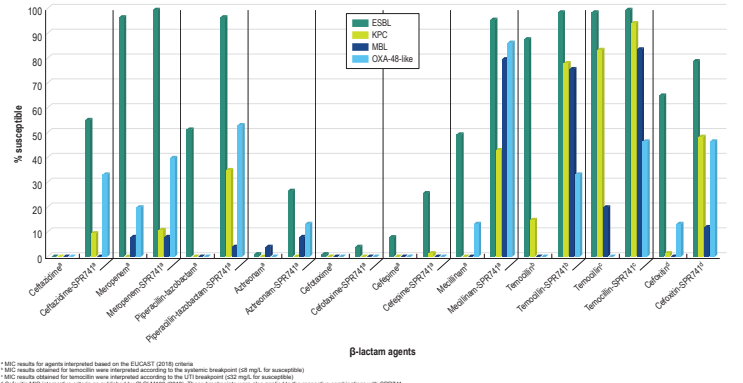
[a] MIC results for agents interpreted based on the EUCAST (2018) criteria
[b] MIC results obtained for temocillin were interpreted according to the systemic breakpoint (≤8 mg/L for susceptible)
[c] MIC results obtained for temocillin were interpreted according to the UTI breakpoint (≤32 mg/L for susceptible)
[d] Cefoxitin MIC interpretive criteria as published by CLSI M100 (2018). These breakpoints were also applied to the respective combinations with SPR741
* Includes 10 *E. coli* and 6 *K. pneumoniae*

Figure 1 Percentage of susceptibility tested agents against (a) *E. coli* and (b) *K. pneumoniae*

A. *E. coli*



B. *K. pneumoniae*



[a] MIC results for agents interpreted based on the EUCAST (2018) criteria
[b] MIC results obtained for temocillin were interpreted according to the systemic breakpoint (≤8 mg/L for susceptible)
[c] MIC results obtained for temocillin were interpreted according to the UTI breakpoint (≤32 mg/L for susceptible)
[d] Cefoxitin MIC interpretive criteria as published by CLSI M100 (2018). These breakpoints were also applied to the respective combinations with SPR741

- SPR741 increased the temocillin susceptibility rates up to 97.8% against KPC-producing *E. coli* when applying the systemic breakpoint (Table 1 and Figure 1A)
- The temocillin-SPR741 combination had susceptibility rates of 94.6%–100.0% against AmpC, ESBL, and KPC producers when applying the UTI breakpoint, regardless of species tested (Table 1)
- The activity of cefoxitin increased from 19.6%–66.0% susceptible to 78.3%–92.8% susceptible when tested against ESBL-producing isolates and *E. coli*-producing ESBL, KPC, or OXA-48-like enzymes (Table 1)

Conclusions

- In general, all β-lactam agents tested in this study showed increased *in vitro* activities in the presence of SPR741
- The activity of piperacillin-tazobactam was also potentiated in the presence of SPR741 against AmpC- and ESBL-producing isolates as well as against OXA-48-like-producing *E. coli*
- SPR741-temocillin provided high *in vitro* coverage advantages against KPC-producing *E. coli* (97.8% susceptible; systemic breakpoint), and the combination's coverage was also expanded against KPC-producing *K. pneumoniae* (94.6% susceptible) when the UTI breakpoint was applied
- Increased potencies for mecillinam when tested in combination with SPR741 provided this drug with acceptable coverage (susceptibility rate ≥90%) against ESBL-, pAmpC-, MBL-, and OXA-48-like-producing *E. coli*
- SPR741 significantly increased the mecillinam coverage against ESBL-, MBL-, and OXA-48-like-producing *K. pneumoniae* (from 0.0%–49.5% to 80.0%–96.0% susceptible)
- These *in vitro* data indicate that adding SPR741 to mecillinam, temocillin, and piperacillin-tazobactam may provide enhanced coverage against *E. coli* and *K. pneumoniae* that produce potent β-lactamase enzymes, warranting further studies

Acknowledgements

This study was supported by Spero Therapeutics. JMI Laboratories received compensation fees for services in relation to preparing this poster.

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