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

RE Mendes,[1] PR Rhomberg,[1] T Lister,[2] N Cotroneo,[2] A Rubio,[2] RK Flamm[1]

[1]JMI Laboratories, North Liberty, Iowa, USA; [2]Spero Therapeutics Inc., Cambridge, Massachusetts, USA

Contact Information:
Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: rodrigo-mendes@jmilabs.com

To obtain a PDF of this poster:
- Scan the QR code
- Or
- Visit https://www.jmilabs.com/data/posters/ECCMID2018-SPR741-beta-lactams.pdf

Charges may apply.
No personal information is stored.

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

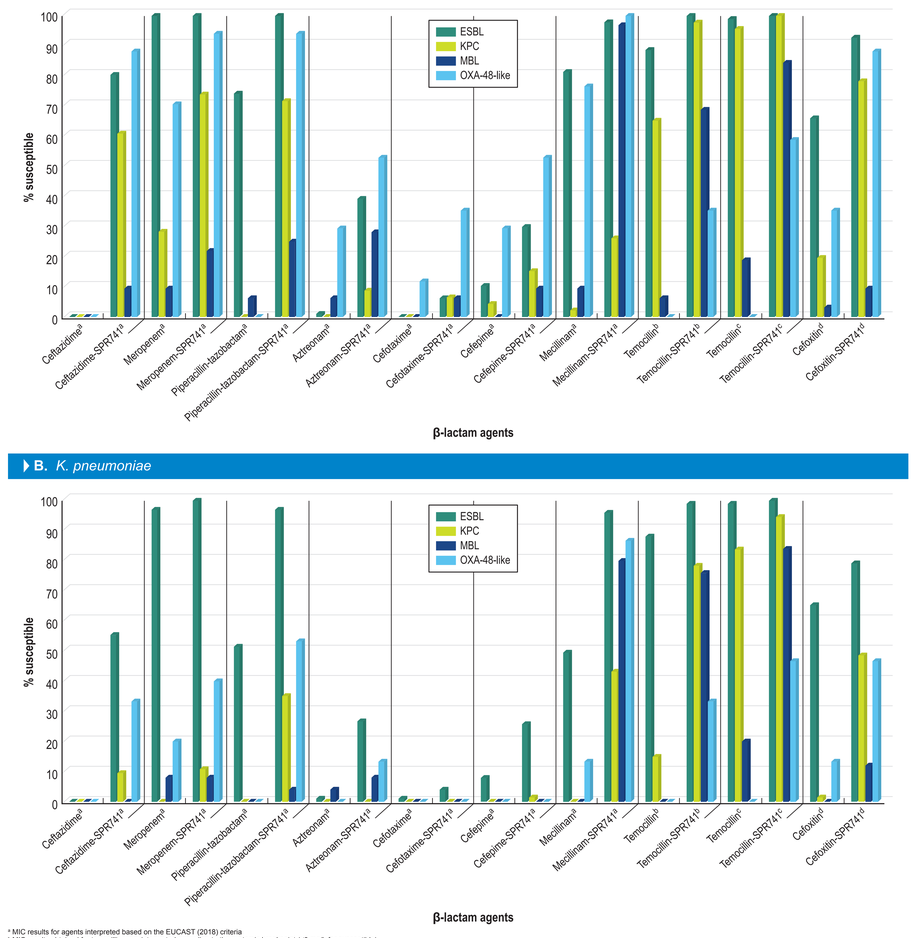
- SPR741 increased the activity of ceftazidime from 0.0% susceptible to 80.4%–88.2% susceptible when ceftazidime-SPR741 was tested against ESBL-producing *E. coli* (Table 1 and Figure 1A)
- The marginal activity to piperacillin-tazobactam against AmpC- and ESBL-producing isolates increased from 0.0%–74.2% 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[a] (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
[e] Includes 10 *E. coli* and 6 *K. pneumoniae*

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

References

Andrews JM, Jevons G, Walker R, Ashby J, Fraise AP. 2007. Temocillin susceptibility by BSAC methodology. *J Antimicrob Chemother* 60 (1):185–187.

British Society for Antimicrobial Chemotherapy (BSAC). 2014. Methods for antimicrobial susceptibility testing. Version 13. http://bsac.org.uk/wp-content/uploads/2014/06/BSAC-disc-susceptibility-testing-method-June-2014.pdf. Accessed March 2018.

British Society for Antimicrobial Chemotherapy (BSAC). 2014. Susceptibility testing methodology–current version of breakpoint tables. http://bsac.org.uk/wp-content/uploads/2012/02/BSAC-Susceptibility-testing-version-131.pdf. Accessed March 2018.

Clinical and Laboratory Standards Institute (2018). *M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement.* Wayne, PA, USA.

Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—eleventh edition*. Wayne, PA, USA.

EUCAST (2018). Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, January 2018. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf. Accessed March 2018.

EUCAST (2013). Quality control for routine antimicrobial susceptibility testing. Available at http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/EUCAST_Routine_QC_tables_3.1.pdf. Accessed March 2018.

Powered by CARB-X