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Activity of SPR206 and Comparator Agents Against *Pseudomonas aeruginosa* and *Acinetobacter* spp. Causing Infections in Europe and Adjacent Regions

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Introduction

- Non-fermentative Gram-negative bacilli (NF-GNB) are opportunistic organisms that have emerged as important healthcare-associated pathogens, mainly in immunocompromised patients.
- These organisms are innately less susceptible to many antimicrobial classes due to the presence of intrinsic genes encoding β-lactamases and efflux pumps.
- SPR206 is a next-generation polymyxin under clinical development to treat pneumonia, bloodstream, and urinary tract infections caused by GNB multidrug-resistant (MDR) pathogens.
- The *in vitro* activity of SPR206 and comparator agents was monitored against GNB pathogens causing infection in US and European hospitals during 2021 as part of the SENTRY Antimicrobial Surveillance Program.
- This study reports the activity of SPR206 against *Acinetobacter* spp. and *Pseudomonas aeruginosa* recovered from patients hospitalized in European countries and adjacent regions.

Materials and Methods

Bacterial organisms

- This study included 437 *Acinetobacter* spp. (see Table 1 for a list of species) and 448 *P. aeruginosa* recovered from patients hospitalized in 35 medical centres in 16 European countries plus Israel and Turkey.
- Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth per CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI- and/or EUCAST-recommended quality control reference strains. MIC interpretations for comparators were performed using EUCAST breakpoints. Clinical breakpoints are not available for SPR206, so values throughout indicate the percentage of isolates inhibited by SPR206 at ≤2 mg/L for comparison purposes only.

Resistant subset definitions

- MDR was defined as any isolate resistant to ≥3 classes of antibiotics based on CLSI criteria.

Results

***Acinetobacter* spp.**

- A total of 61.6% of all *Acinetobacter* spp. included exhibited an MDR phenotype.
  - Clinical isolates originating from hospitals located in Eastern European countries plus Israel and Turkey had an MDR phenotype prevalence (77.6%) higher than those isolates from Western European hospitals (50.0%) (data not shown).
- Overall, SPR206 had $MIC_{50/90}$ values of 0.12/1 mg/L against all *Acinetobacter* spp. (Table 1), whereas colistin had $MIC_{50/90}$ results of 0.5/4 mg/L (data not shown).
- Various agents were active (95.8%–99.4% susceptible) against non-MDR *Acinetobacter* spp., including SPR206 that inhibited all but 2 strains at ≤2 mg/L (Table 2).
- SPR206 ($MIC_{50/90}$, 0.12/32 mg/L) and colistin ($MIC_{50/90}$, 0.5/>8 mg/L) MICs against the MDR subset from Eastern Europe were higher than those MICs obtained against isolates from Western Europe ($MIC_{50/90}$, 0.06/0.5 mg/L for SPR206 and $MIC_{50/90}$, 0.5/2 mg/L for colistin) (Table 2).
  - Comparator agents showed limited activities against isolates from Eastern Europe (Table 2).
  - SPR206 ($MIC_{50/90}$, 0.06/0.5 mg/L) exhibited the lowest MIC values when tested against isolates from Western Europe, followed by colistin ($MIC_{50/90}$, 0.5/2 mg/L). Other agents had limited activities (Table 2).

P. aeruginosa

- Overall, 15.6% of all *P. aeruginosa* showed an MDR phenotype (Table 1).
  - Those clinical isolates originating from hospitals located in Eastern European countries plus Israel and Turkey had an MDR phenotype prevalence (24.8%) higher than those isolates from Western European hospitals (11.7%) (data not shown).
- In general, $MIC_{50/90}$ values of 0.25/0.25 mg/L were obtained for SPR206 against all *P. aeruginosa* (Table 1), a 4-fold lower result than achieved for colistin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible) (data not shown).
- Various agents were active against non-MDR *P. aeruginosa*, although SPR206 ($MIC_{50/90}$, 0.06/0.5 mg/L) exhibited, respectively, MIC_{50} and MIC_{90} values at least 2-fold and 4-fold lower than the comparators (Table 3).
- SPR206 ($MIC_{50/90}$, 0.25/0.5 mg/L) and colistin ($MIC_{50/90}$, 1/1 mg/L) showed the lowest MIC_{50} and MIC_{90} results against the *P. aeruginosa* MDR subsets, whereas the other comparators had limited activities (Table 3).

Table 1. MIC distribution of SPR206 obtained against *Acinetobacter* spp. and *P. aeruginosa* and resistant subsets

Organism/Group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:													MIC$_{50}$	MIC$_{90}$
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
Acinetobacter spp. (437)[a]	21 (4.8)	162 (41.9)	122 (69.8)	58 (83.1)	28 (89.5)	7 (91.1)	5 (92.2)	6 (93.6)	2 (94.1)	9 (96.1)	7 (97.7)	4 (98.6)	6 (100)	0.12	1
Non-MDR (168)	11 (6.5)	46 (33.9)	60 (69.6)	32 (88.7)	12 (95.8)	3 (97.6)	2 (98.8)	1 (99.4)	1 (100.0)					0.12	0.5
E-MDR (142)	2 (1.4)	46 (33.8)	42 (63.4)	15 (73.9)	5 (77.5)	3 (79.6)	3 (81.7)	3 (83.8)	0 (83.8)	7 (88.7)	6 (93.0)	4 (95.8)	6 (100)	0.12	32
W-MDR (127)	8 (6.3)	70 (61.4)	20 (77.2)	11 (85.8)	11 (94.5)	1 (95.3)	0 (95.3)	2 (96.9)	1 (97.6)	2 (99.2)	1 (100.0)			0.06	0.5
P. aeruginosa (448)	2 (0.4)	17 (4.2)	157 (39.3)	246 (94.2)	21 (98.9)	3 (99.6)	0 (99.6)	0 (99.6)	2 (100.0)					0.25	0.25
Non-MDR (378)	2 (0.5)	11 (3.4)	143 (41.3)	210 (96.8)	8 (98.9)	2 (99.5)	0 (99.5)	0 (99.5)	2 (100.0)					0.25	0.25
E-MDR (33)		3 (9.1)	5 (24.2)	16 (72.7)	8 (97.0)	1 (100.0)								0.25	0.5
W-MDR (37)		3 (8.1)	9 (32.4)	20 (86.5)	5 (100.0)									0.25	0.5

Abbreviations: MDR, multidrug-resistant (resistant to ≥3 classes); E-MDR, Eastern Europe MDR isolates; W-MDR, Western Europe MDR isolates.
[a] Includes *A. baumannii-calcoaceticus* species complex (387), *A. berezinae* (7), *A. calcoaceticus* (2), *A. gerneri* (1), *A. gyllenbergii* (1), *A. johnsonii* (4), *A. junii* (9), *A. lwoffii* (4), *A. radioresistens* (4), *A. soli* (1), *A. ursingii* (13), *A. vivianii* (1), and *Acinetobacter* spp. (3).

Table 2. Antimicrobial activity of SPR206 and comparators against *Acinetobacter* spp. and resistant subsets

Antimicrobial agent	MIC (mg/L)			EUCAST[a]		
	50%	90%	Range	%S	%I	%R
Non-MDR (168)						
SPR206	0.12	0.5	≤0.03 to 8	98.8		
Colistin	0.5	1	0.12 to 8	97.6		2.4
Ampicillin-sulbactam	2	4	≤0.5 to 64			
Meropenem	0.25	1	≤0.015 to 16	99.4	0.0	0.6
Ceftazidime	4	8	0.25 to >32			
Ceftazidime-avibactam	4	16	≤0.015 to >32			
Piperacillin-tazobactam	≤0.06	8	≤0.06 to >128			
Amikacin	2	4	≤0.25 to >32	97.0		3.0
Tobramycin	0.5	1	≤0.12 to >16	97.6		2.4
Tigecycline	0.25	0.5	≤0.06 to 2			
Levofloxacin	0.12	0.25	≤0.015 to 16	95.8	1.8	2.4
E-MDR (142)						
SPR206	0.12	32	≤0.03 to >64	81.7		
Colistin	0.5	>8	0.12 to >8	79.6		20.4
Ampicillin-sulbactam	64	>64	4 to >64			
Meropenem	>32	>32	0.12 to >32	5.6	0.7	93.7
Ceftazidime	>32	>32	32 to >32			
Ceftazidime-avibactam	32	>32	1 to >32			
Piperacillin-tazobactam	>128	>128	32 to >128			
Amikacin	>32	>32	0.5 to >32	9.2		90.8
Tobramycin	>16	>16	≤0.12 to >16	13.4		86.6
Tigecycline	2	8	0.12 to >8			
Levofloxacin	16	>32	0.12 to >32	1.4	0.0	98.6
W-MDR (127)						
SPR206	0.06	0.5	≤0.03 to 32	95.3		
Colistin	0.5	2	0.25 to >8	90.6		9.4
Ampicillin-sulbactam	>64	>64	4 to >64			
Meropenem	>32	>32	0.5 to >32	3.1	0.0	96.9
Ceftazidime	>32	>32	4 to >32			
Ceftazidime-avibactam	>32	>32	4 to >32			
Piperacillin-tazobactam	>128	>128	16 to >128			
Amikacin	>32	>32	1 to >32	13.4		86.6
Tobramycin	>16	>16	0.25 to >16	11.8		88.2
Tigecycline	2	4	0.12 to >8			
Levofloxacin	16	>32	0.25 to >32	1.6	0.0	98.4

Abbreviations: MDR, multidrug-resistant (resistant to ≥3 classes); E-MDR, Eastern Europe MDR isolates; W-MDR, Western Europe MDR isolates.
[a] Criteria as published by EUCAST (2022). A susceptible breakpoint of ≤2 mg/L was used for SPR206 for comparison purposes.

Table 3. Antimicrobial activity of SPR206 and comparators against *P. aeruginosa* and resistant subsets

Antimicrobial agent	MIC (mg/L)			EUCAST[a]		
	50%	90%	Range	%S	%I	%R
Non-MDR (378)						
SPR206	0.25	0.25	≤0.03 to 8	99.5		
Colistin	1	1	≤0.06 to 4	100.0		0.0
Meropenem	0.5	4	≤0.015 to 32	89.7	9.0	1.3
Ceftazidime	2	8	0.25 to >32		92.9 [b]	7.1
Ceftazidime-avibactam	2	4	≤0.015 to 8	100.0		0.0
Piperacillin-tazobactam	4	16	≤0.06 to >128		92.3 [b]	7.7
Amikacin	4	8	≤0.25 to >32	98.9		1.1
Tobramycin	0.5	1	≤0.12 to >16	97.6		2.4
Levofloxacin	0.5	4	≤0.015 to >32		89.9 [b]	10.1
Ceftolozane-tazobactam	0.5	1	≤0.12 to 4	100.0		0.0
E-MDR (33)						
SPR206	0.25	0.5	0.06 to 1	100.0		
Colistin	1	1	0.25 to 2	100.0		0.0
Meropenem	16	>32	0.5 to >32	12.1	36.4	51.5
Ceftazidime	32	>32	8 to >32		3.0 [b]	97.0
Ceftazidime-avibactam	4	>32	1 to >32	69.7		30.3
Piperacillin-tazobactam	>128	>128	16 to >128		3.0 [b]	97.0
Amikacin	8	>32	1 to >32	63.6		36.4
Tobramycin	1	>16	0.25 to >16	57.6		42.4
Levofloxacin	16	>32	0.06 to >32		33.3 [b]	66.7
Ceftolozane-tazobactam	4	>16	1 to >16	60.6		39.4
W-MDR (37)						
SPR206	0.25	0.5	0.06 to 0.5	100.0		
Colistin	1	1	0.12 to 1	100.0		0.0
Meropenem	16	>32	0.06 to >32	8.1	37.8	54.1
Ceftazidime	32	>32	8 to >32		13.5 [b]	86.5
Ceftazidime-avibactam	4	32	2 to >32	73.0		27.0
Piperacillin-tazobactam	128	>128	2 to >128		5.4 [b]	94.6
Amikacin	8	>32	1 to >32	78.4		21.6
Tobramycin	1	>16	0.25 to >16	73.0		27.0
Levofloxacin	2	32	0.25 to >32		54.1 [b]	45.9
Ceftolozane-tazobactam	2	>16	1 to >16	67.6		32.4

Abbreviations: MDR, multidrug-resistant (resistant to ≥3 classes); E-EU, Eastern Europe MDR isolates; W-EU, Western European MDR isolates.
[a] Criteria as published by EUCAST (2022). Clinical breakpoints are not available for SPR206, so values indicate the percentage of isolates inhibited by SPR206 at ≤2 mg/L for comparison purposes only.
[b] Isolates can be considered as susceptible if a higher drug concentration can be achieved by increasing the dosing regimen or increased concentration is achieved in the infection site.

Conclusions

- SPR206 showed potent *in vitro* activity against these recent collections of *Acinetobacter* spp. and *P. aeruginosa* from Europe and inhibited 92.2% and 99.6% of all isolates, respectively.
  - In addition, the potency of SPR206 was consistently greater than clinically available in-class and other comparator agents.
- These SPR206 results, plus favourable safety and tolerability profiles obtained during Phase 1 studies, support the clinical development of SPR206 for difficult-to-treat infections caused by these pathogens and their resistant subsets.

References

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