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Murepavadin Activity Tested against Contemporary (2016–2017) Clinical Isolates of Extensively Drug-Resistant (XDR) *Pseudomonas aeruginosa*

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Introduction

- Murepavadin (formerly POL7080) is a 14-amino-acid cyclic peptide for intravenous administration that represents the first member of a novel class of outer membrane protein targeting antibiotic (OMPTA)
- Murepavadin displays a novel mode of action as it binds to the lipopolysaccharide transport protein D (LptD) in the outer membrane of the bacterium, blocks the LPS translocation, and ultimately kills the bacterium
- Given the pathogen-specific nature of murepavadin it is unlikely to generate resistance to, or negatively impact, the patient's native bacterial flora, which are unintended sequelae of treatment with broad-spectrum antibiotics
- This novel agent is being developed for the treatment of nosocomial pneumonia suspected or caused by *Pseudomonas aeruginosa*
- *P. aeruginosa* is the second leading cause of hospital-acquired pneumonia and ventilator-associated pneumonia, and one of the major causes of healthcare-associated bloodstream infections, urinary tract infections, and skin and skin structure infections
- In this study we evaluated the *in vitro* activity of the Polyphor compound murepavadin and comparator agents against contemporary clinical isolates of extensively drug-resistant (XDR) *P. aeruginosa*

Materials and Methods

Organism collection

- Organisms tested originated from the SENTRY Antimicrobial Surveillance Program
- A total of 785 isolates (1/patient episode) were consecutively collected in 2016 (n=544) and 2017 (n=241) from 75 medical centers located in North America (n=432), and 34 medical centers in 21 European nations (n=353)
- Sites of infection from which isolates were obtained included pneumonia in hospitalized patients (63%), skin and skin structure infections (19%), bloodstream infections (10%), urinary tract infections (6%), and intra-abdominal infections (2%)

Susceptibility testing

- Isolates were tested against murepavadin and comparator agents by the reference broth microdilution method using cation-adjusted Mueller-Hinton broth
- CLSI and EUCAST interpretive criteria were used to determine susceptibility/resistance rates for comparator agents
- Quality control was tested daily and inoculum density was monitored by colony counts; the quality control strains were *P. aeruginosa* ATCC 27853 and PA3140
- *P. aeruginosa* strains were classified as XDR according to recommended guidelines (Magiorakos et al., 2012) and based on the following recommended parameters: susceptible by the CLSI criteria to 2 or fewer of the following antimicrobial classes
  - Antipseudomonal cephalosporins: ceftazidime and cefepime
  - Carbapenems: imipenem, meropenem, and doripenem
  - Broad-spectrum penicillins combined with β-lactamase inhibitor: piperacillin-tazobactam
  - Fluoroquinolones: ciprofloxacin and levofloxacin
  - Aminoglycosides: gentamicin, tobramycin, and amikacin
  - Polymyxins: colistin

Table 1 Antimicrobial activity of murepavadin, colistin, and ceftolozane-tazobactam tested against 785 XDR *P. aeruginosa* isolates from Europe and North America

Antimicrobial agent	No. of isolates at MIC (mg/L; cumulative %)											MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]		
Murepavadin	10 1.3	159 21.5	362 67.6	190 91.8	38 96.7	8 97.7	8 98.7	3 99.1				7 100.0	0.12	0.25
Colistin			6 0.8	41 6.0	242 36.8	391 86.6	55 93.6	47 99.6	0 99.6			3 100.0	1	2
Ceftolozane-tazobactam				3 0.4	41 5.6	295 43.2	144 61.5	71 70.6	34 74.9	21 77.6	31 81.5	145 100.0	2	>32

[a] Greater than the highest dilution tested.

Table 2 Activity of murepavadin and comparator antimicrobial agents when tested against XDR *P. aeruginosa* isolates

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
All isolates (785)						
Murepavadin	0.12	0.25				
Colistin	1	2	93.6	6.4	93.6	6.4
Ceftolozane-tazobactam	2	>32	70.6	25.1	70.6	29.4
Ceftazidime	32	>32	20.0	60.6	20.0	80.0
Meropenem	16	>32	5.6	84.5	5.6	65.6
Piperacillin-tazobactam	>64	>64	7.3	50.1	7.3	92.7
Levofloxacin	>4	>4	6.9	81.1	2.3	97.7
Amikacin	16	>32	61.6	26.8	45.5	38.4
Tobramycin	8	>8	47.5	48.5	47.5	52.5
North America (432)						
Murepavadin	0.12	0.5				
Colistin	1	1	95.4	4.6	95.4	4.6
Ceftolozane-tazobactam	1	8	86.8	8.1	86.8	13.2
Ceftazidime	32	>32	24.8	53.0	24.8	75.2
Meropenem	16	32	6.7	80.6	6.7	58.1
Piperacillin-tazobactam	>64	>64	9.5	50.5	9.5	90.5
Levofloxacin	>4	>4	9.3	74.8	2.1	97.9
Amikacin	8	>32	79.6	12.0	57.6	20.4
Tobramycin	2	>8	67.1	27.8	67.1	32.9
Europe (353)						
Murepavadin	0.12	0.25				
Colistin	1	2	91.5	8.5	91.5	8.5
Ceftolozane-tazobactam	4	>32	50.7	45.9	50.7	49.3
Ceftazidime	32	>32	14.2	70.0	14.2	85.8
Meropenem	32	>32	4.2	89.2	4.2	74.8
Piperacillin-tazobactam	64	>64	4.5	49.6	4.5	95.5
Levofloxacin	>4	>4	4.0	89.0	2.5	97.5
Amikacin	32	>32	39.5	44.9	30.7	60.5
Tobramycin	>8	>8	23.5	73.9	23.5	76.5

[a] Criteria as published by CLSI (2018) and EUCAST (2018).

Results

- Murepavadin ($MIC_{50/90}$, 0.12/0.25 mg/L) inhibited 96.7% of isolates at ≤0.5 mg/L and was 8-fold more potent than colistin ($MIC_{50/90}$, 1/2 mg/L) based on $MIC_{50/90}$ values (Tables 1 and 2)
- Only 7 isolates (0.9%) exhibited murepavadin MIC values >4 mg/L (Table 1); 6 isolates from the United States and 1 from Europe (Ireland)
- Among the comparator agents tested, colistin was the most active compound ($MIC_{50/90}$, 1/2 mg/L; 93.6% susceptible), followed by ceftolozane-tazobactam ($MIC_{50/90}$, 2/>32 mg/L; 70.6% susceptible), tobramycin ($MIC_{50/90}$, 8/>8 mg/L; 47.5% susceptible), and amikacin ($MIC_{50/90}$, 16/>32 mg/L; 45.5%/61.6% susceptible [EUCAST/CLSI]; Table 2)
- Susceptibility rates for meropenem, piperacillin-tazobactam, and ceftazidime were 5.6%, 7.3%, and 20.0%, respectively (Table 2)
- Murepavadin was active against isolates nonsusceptible to colistin (n=50; $MIC_{50/90}$, 0.25/0.25 mg/L; highest MIC, 0.5 mg/L) and/or ceftolozane-tazobactam (n=231; $MIC_{50/90}$, 0.12/0.25 mg/L; 97.8% inhibited at ≤1 mg/L; Table 3)
- Among tobramycin-nonsusceptible isolates (n=412), 99.3% were inhibited at ≤1 mg/L of murepavadin ($MIC_{50/90}$, 0.12/0.25 mg/L; Table 3)
- Murepavadin activity against isolates from Europe ($MIC_{50/90}$, 0.12/0.25 mg/L) were very similar to the agent's activity against isolates from North America ($MIC_{50/90}$, 0.12/0.5 mg/L; Table 2 and Figure 1)
- In contrast, susceptibility rates for ceftolozane-tazobactam and tobramycin were substantially lower among XDR *P. aeruginosa* from Europe (50.7% and 23.5%, respectively) compared to North America (86.8% and 67.1%, respectively; Table 2)

Figure 1 Murepavadin MIC distributions for XDR *P. aeruginosa* isolates from Europe and North America

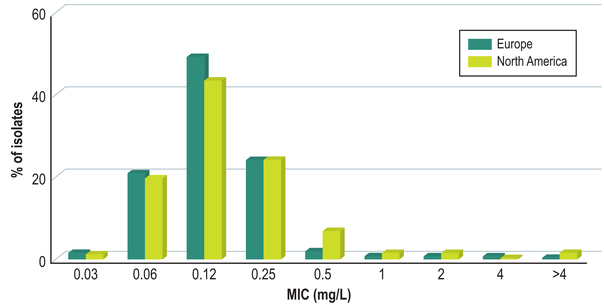

Table 3 Antimicrobial activity of murepavadin tested against XDR *P. aeruginosa* isolates nonsusceptible to colistin, ceftolozone-tazobactam, and/or tobramycin

Resistance phenotype[a]	No. of isolates at MIC (mg/L; cumulative %)									MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4		
Colistin-NS (50)		16 10.0	16 42.0	28 98.0	1 100.0					0.25	0.25
Ceftolozane-tazobactam-NS (231)	3 1.3	55 25.1	100 68.4	57 93.1	10 97.4	1 97.8	2 98.7	0 98.7	3 100.0	0.12	0.25
Tobramycin-NS (412)	6 1.5	87 22.6	204 72.1	95 95.1	13 98.3	4 99.3	0 99.3	0 99.3	3 100.0	0.12	0.25

[a] NS, nonsusceptible per EUCAST and CLSI

Conclusions

- Murepavadin was very active against a large collection of clinical XDR *P. aeruginosa* isolates from Europe and North America
- Murepavadin retained good activity against XDR *P. aeruginosa* isolates nonsusceptible to colistin, ceftolozane-tazobactam, and/or tobramycin
- The results of this study coupled with results from ongoing clinical studies will define the role of murepavadin for treating *P. aeruginosa* infections, including those caused by XDR isolates

Acknowledgements

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