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Antimicrobial Activity of Murepavadin Tested against Clinical Isolates of *Pseudomonas aeruginosa* from the United States, Europe, and China

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ABSTRACT Murepavadin (formerly POL7080), a 14-amino-acid cyclic peptide, and comparators were tested by the broth microdilution method against 1,219 *Pseudomonas aeruginosa* isolates from 112 medical centers. Murepavadin ($MIC_{50/90}$, 0.12/0.12 mg/liter) was 4- to 8-fold more active than colistin ($MIC_{50/90}$, 1/1 mg/liter) and polymyxin B ($MIC_{50/90}$, 0.5/1 mg/liter) and inhibited 99.1% of isolates at ≤0.5 mg/liter. Only 4 isolates (0.3%) exhibited murepavadin MICs of >2 mg/liter. Murepavadin was equally active against isolates from Europe, the United States, and China.

KEYWORDS murepavadin, Polyphor, POL7080, cyclopeptide, *Pseudomonas aeruginosa*, antimicrobial resistance, China, cyclic peptide

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 antibiotics (OMPTAs) being developed for the treatment of serious infections caused by *Pseudomonas aeruginosa* (1–3). Murepavadin targets the lipopolysaccharide transport protein D (LptD). Through binding to LptD in the outer membrane of the bacterium, murepavadin causes lipopolysaccharide alterations and ultimately kills the bacterium (4–6). Murepavadin is under development for hospital-acquired pneumonia and ventilator-associated pneumonia caused by *P. aeruginosa* (https://clinicaltrials.gov/ct2/results?term=POL7080).

P. aeruginosa is the second leading cause of hospital-acquired pneumonia and ventilator-associated pneumonia and one of the major causes of health care-associated bloodstream infections, urinary tract infections, and skin and skin structure infections (7–9). This organism is intrinsically resistant to a wide range of antimicrobials and has an extraordinary capacity for developing resistance to commonly used antimicrobials through the selection of mutations in chromosomal genes or by horizontal acquisition of resistant determinants (10, 11). In the United States, approximately 15% of health care-associated *P. aeruginosa* infections are caused by multidrug-resistant (MDR) organisms (9, 12); whereas in Europe, the MDR phenotype is reported in >10% of clinical *P. aeruginosa* isolates in many countries, including Portugal (11.8%), France (12.0%), Spain (14.2%), Italy (20.0%), Greece (28.4%), and various eastern European countries (13).

The increasing prevalence of MDR strains is a cause for concern because it compromises the selection of appropriate empirical and definitive antimicrobial treatments (14). In the present study, we evaluated the activity of murepavadin and many comparator agents against a large collection of clinical isolates of *P. aeruginosa* from the United States, Europe, and China.

Organisms tested originated from the SENTRY Antimicrobial Surveillance Program. Bacterial isolates were consecutively collected from medical centers according to the site of infection. Only 1 isolate per patient episode was included in the study. Isolate

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identity was confirmed at the species level by the monitoring reference laboratory (JMI Laboratories, North Liberty, IA, USA). The isolates were collected from 62 medical centers in the United States ($n = 417$), 40 medical centers in 22 European nations ($n = 491$), and 10 medical centers in China ($n = 311$). Sites of infection from which isolates were obtained included pneumonia in hospitalized patients (48%), skin and skin structure infections (29%), bloodstream infections (10%), urinary tract infections (6%), and others (7%). The isolates from the United States and Europe were collected in 2014, and the isolates from China were collected in 2012 and 2013.

Isolates were categorized as MDR or extremely drug resistant (XDR) according to criteria published by Magiorakos et al. (15), who define MDR as nonsusceptible to ≥1 agent in ≥3 antimicrobial classes, XDR as nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes, and pan-drug-resistant as nonsusceptible (CLSI criteria) to all antimicrobial classes tested. The antimicrobial classes and drug representatives used in the analysis were antipseudomonal cephalosporins (ceftazidime and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillins combined with a β-lactamase inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), and the polymyxins (colistin and polymyxin B).

Isolates were tested against murepavadin and comparator agents by the reference broth microdilution method (16) using cation-adjusted Mueller-Hinton broth. CLSI (17) and EUCAST (18) 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.

Among all isolates, murepavadin ($MIC_{50/90}$, 0.12/0.12 mg/liter) was the most active agent and inhibited 99.1% of isolates at ≤0.5 mg/liter (Table 1). Only 4 isolates exhibited murepavadin MIC values of >2 mg/liter, including 3 isolates from the United States with MIC values of >32 mg/liter (Gilbert, AZ), 16 mg/liter (Los Angeles, CA), and 8 mg/liter (Jacksonville Beach, FL) and 1 isolate with an MIC value of 8 mg/liter from Milan, Italy. Importantly, murepavadin retained potent *in vitro* activity against MDR ($MIC_{50/90}$, 0.12/0.25 mg/liter) and XDR ($MIC_{50/90}$, 0.12/0.0.25 mg/liter) isolates (Table 1).

Among the comparators, the polymyxins colistin ($MIC_{50/90}$, 1/1 mg/liter) and polymyxin B ($MIC_{50/90}$, 0.5/1 mg/liter) were roughly 4- to 8-fold less active than murepavadin. Polymyxin B (100.0% susceptible) was slightly more active than colistin (98.9% susceptible) (Tables 1 and 2).

Among other comparators, amikacin ($MIC_{50/90}$, 4/16 mg/liter; 90.6/87.4% susceptible by CLSI/EUCAST criteria) was the most active agent, followed by tobramycin ($MIC_{50/90}$, 0.5/>16 mg/liter; 87.9% susceptible by both criteria), cefepime ($MIC_{50/90}$, 2/16 mg/liter; 79.8% susceptible by both criteria), ceftazidime ($MIC_{50/90}$, 2/>32 mg/liter; 79.1% susceptible by both criteria), ciprofloxacin ($MIC_{50/90}$, 0.12/>8 mg/liter; 77.4/73.0% susceptible by CLSI/EUCAST criteria), meropenem ($MIC_{50/90}$, 0.5/16 mg/liter; 74.7% susceptible by both criteria), and piperacillin-tazobactam ($MIC_{50/90}$, 4/128 mg/liter; 73.9% susceptible by both criteria) (Table 2).

MDR and XDR isolates exhibited high resistance rates to all comparator agents except the polymyxins (colistin and polymyxin B). Amikacin and tobramycin were active (CLSI criteria) against 66.0% and 56.0% of MDR *P. aeruginosa* isolates, respectively, and against only 48.5% and 35.3% of XDR *P. aeruginosa* isolates, respectively; whereas cefepime was active against 32.3% of MDR and 12.6% of XDR isolates (Table 2).

Murepavadin was equally active against isolates from the United States, Europe, and China ($MIC_{50/90}$, 0.12/0.12 mg/liter for all 3 geographic regions). Isolates from China exhibited slightly higher MIC values for colistin ($MIC_{50/90}$, 1/2 mg/liter) and polymyxin B ($MIC_{50/90}$, 1/1 mg/liter) than the United States and Europe ($MIC_{50/90}$ of 1/1 mg/liter for colistin and 0.5/1 mg/liter for polymyxin B, respectively) (Table 2). Additionally, susceptibility rates for the aminoglycosides, β-lactams, and ciprofloxacin were slightly higher among isolates from the United States than among those from Europe and China (Table 2).

TABLE 1 Antimicrobial activity of murepavadin and comparator polymyxin agents tested against *P. aeruginosa* isolates from the United States, Europe, and China

Organism and subset (no. of isolates)	No. (cumulative %) of isolates at MIC (mg/liter) of:														
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Pseudomonas aeruginosa															
Murepavadin (1,219)	0 (0.0)	25 (2.1)	92 (9.6)	983 (90.2)	93 (97.9)	15 (99.1)	5 (99.5)	2 (99.7)	0 (99.7)	2 (99.8)	1 (99.9)	0 (99.9)	1 (100.)	0.12	0.12
Colistin (1,219)			0 (0.0)	1 (0.1)	22 (1.9)	170 (15.8)	927 (91.9)	86 (98.9)	13 (100.0)					1	1
Polymyxin B (1,219)			0 (0.0)	1 (0.1)	26 (2.2)	643 (55.0)	541 (99.3)	8 (100.0)						0.5	1
MDR *P. aeruginosa*															
Murepavadin (300)	0 (0.0)	3 (1.0)	9	216 (76.0)	55 (94.3)	10 (97.7)	3 (98.7)	1 (99.0)	0 (99.0)	1 (99.3)	1 (99.7)	0 (99.7)	1 (100.0)	0.12	0.25
Colistin (300)				0 (0.0)	8 (2.7)	42 (16.7)	232 (94.0)	1599.0	3 (100.0)					1	1
Polymyxin B (300)				0 (0.0)	8 (2.7)	142 (50.0)	148 (99.3)	2 (100.0)						0.5	1
XDR *P. aeruginosa*															
Murepavadin (167)	0 (0.0)	1 (0.6)	5 (3.6)	120 (75.4)	32 (94.6)	4 (97.0)	2 (98.2)	1 (98.8)	0 (98.8)	1 (99.4)	0 (99.4)	0 (99.4)	1 (100.0)	0.12	0.25
Colistin (167)				0 (0.0)	4 (2.4)	19 (13.8)	139 (97.0)	4 (99.4)	1 (100.0)					1	1
Polymyxin B (167)				0 (0.0)	3 (1.8)	77 (47.9)	85 (98.8)	2 (100.0)						1	1

TABLE 2 Activity of murepavadin and comparator antimicrobial agents tested against *P. aeruginosa*

Antimicrobial agent (no. of isolates)	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
All (1,219)						
Murepavadin	0.12	0.12				
Colistin	1	1	98.9	1.1	98.9	1.1
Polymyxin B	0.5	1	100.0	0.0		
Amikacin	4	16	90.6	6.1	87.4	9.4
Aztreonam	8	32	69.1	15.2	4.2	15.2
Cefepime	2	16	79.8	8.8	79.8	20.2
Ceftazidime	2	>32	79.1	16.9	79.1	20.9
Ciprofloxacin	0.12	>8	77.4	18.1	73.0	27.0
Meropenem	0.5	16	74.7	18.2	74.7	11.6
Piperacillin-tazobactam	4	128	73.9	13.3	73.9	26.1
Tobramycin	0.5	>16	87.9	11.3	87.9	12.1
MDR (300)						
Murepavadin	0.12	0.25				
Colistin	1	1	99.0	1.0	99.0	1.0
Polymyxin B	0.5	1	100.0	0.0		
Amikacin	8	>64	66.0	22.3	59.0	34.0
Aztreonam	16	64	24.0	45.0	2.7	45.0
Cefepime	16	>32	32.3	34.0	32.3	67.7
Ceftazidime	32	>32	32.7	55.0	32.7	67.3
Ciprofloxacin	8	>8	25.3	64.3	21.3	78.7
Meropenem	8	>16	16.3	68.3	16.3	45.3
Piperacillin-tazobactam	64	>128	21.3	45.3	21.3	78.7
Tobramycin	2	>16	56.0	42.0	56.0	44.0
XDR (167)						
Murepavadin	0.12	0.25				
Colistin	1	1	99.4	0.6	99.4	0.6
Polymyxin B	1	1	100.0	0.0		
Amikacin	32	>64	48.5	34.1	43.7	51.5
Aztreonam	32	>64	14.4	51.5	0.6	51.5
Cefepime	16	>32	12.6	49.1	12.6	87.4
Ceftazidime	>32	>32	13.8	73.1	13.8	86.2
Ciprofloxacin	>8	>8	9.0	85.0	5.4	94.6
Meropenem	16	>16	1.8	86.8	1.8	67.7
Piperacillin-tazobactam	128	>128	5.4	57.5	5.4	94.6
Tobramycin	>16	>16	35.3	62.9	35.3	64.7
United States (417)						
Murepavadin	0.12	0.12				
Colistin	1	1	99.3	0.7	99.3	0.7
Polymyxin B	0.5	1	100.0	0.0		
Amikacin	4	8	95.7	2.4	91.6	4.3
Aztreonam	8	32	71.5	13.7	5.3	13.7
Cefepime	2	16	84.4	6.2	84.4	15.6
Ceftazidime	2	32	84.2	10.8	84.2	15.8
Ciprofloxacin	0.12	8	81.1	14.4	77.7	22.3
Meropenem	0.5	8	80.6	13.9	80.6	6.5
Piperacillin-tazobactam	4	64	79.4	8.6	79.4	20.6
Tobramycin	0.5	2	92.6	7.0	92.6	7.4
Europe (491)						
Murepavadin	0.12	0.12				
Colistin	1	1	99.0	1.0	99.0	1.0
Polymyxin B	0.5	1	100.0	0.0		
Amikacin	4	32	86.8	7.3	84.3	13.2
Aztreonam	4	32	69.7	12.0	3.5	12.0
Cefepime	2	16	79.4	9.0	79.4	20.6
Ceftazidime	2	>32	77.8	18.3	77.8	22.2
Ciprofloxacin	0.12	>8	75.8	21.2	70.7	29.3
Meropenem	0.5	16	72.9	19.3	72.9	14.5

(Continued on next page)

TABLE 2 (Continued)

Antimicrobial agent (no. of isolates)	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
Piperacillin-tazobactam	4	128	74.1	13.4	74.1	25.9
Tobramycin	0.5	>16	86.8	12.8	86.8	13.2
China (311)						
Murepavadin	0.12	0.12				
Colistin	1	2	98.4	1.6	98.4	1.6
Polymyxin B	1	1	100.0	0.0		
Amikacin	4	16	90.0	9.0	86.5	10.0
Aztreonam	8	32	65.0	22.2	3.9	22.2
Cefepime	4	32	74.3	11.9	74.3	25.7
Ceftazidime	4	>32	74.3	22.8	74.3	25.7
Ciprofloxacin	0.25	8	74.9	18.3	70.4	29.6
Meropenem	1	16	69.8	22.2	69.8	13.8
Piperacillin-tazobactam	8	>128	66.2	19.3	66.2	33.8
Tobramycin	0.5	>16	83.6	14.8	83.6	16.4

[a]Criteria as published by CLSI and EUCAST (17, 18). S, susceptible; R, resistant.

P. aeruginosa represents a serious therapeutic challenge, and selecting the appropriate antimicrobial agent to initiate therapy is essential to optimize the clinical outcome (19). However, treatment decisions are difficult due to the high rates of resistance exhibited by this organism and its ability to develop resistance to multiple classes of antimicrobial agents, even during the course of treating an infection (11, 19). Among the antimicrobial agents evaluated in this investigation, murepavadin was the most active compound, followed by the polymyxins colistin and polymyxin B, and the aminoglycosides amikacin and tobramycin. All other comparator agents exhibited limited activity (<80% susceptibility) against this collection of clinical *P. aeruginosa* isolates. Furthermore, only murepavadin and the polymyxins exhibited good activity against MDR and XDR isolates.

Commonly used broad-spectrum antimicrobial agents can cause major collateral damage to the human microbiome, with complications ranging from antibiotic-associated colitis to the spread of antimicrobial resistance through horizontal gene transfer (20). Thus, the concept of applying narrow-spectrum or pathogen-specific antibiotics has been developed with the aim of minimizing collateral damage to the microbiome, and murepavadin development is based on this concept of antimicrobial usage. Murepavadin is highly active against *P. aeruginosa* and largely inactive against other Gram-negative and Gram-positive species (4, 5).

The data from the present investigation document the *in vitro* activity of murepavadin against *P. aeruginosa* isolates from the United States, Europe, and China. In addition to demonstrating potent activity against a large collection of organisms, murepavadin retained activity against MDR and XDR isolates. Furthermore, no cross-resistance was observed with current standard-of-care antimicrobial agents. The results of this study and the good safety profile observed in the phase 1 study (21), combined with results from ongoing clinical studies, support continued clinical development of murepavadin for treating serious *P. aeruginosa* infections.

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We have no speakers' bureaus or stock options to declare.

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