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

HS Sader[1], GE Dale[2], LR Duncan[1], PR Rhomberg[1], RK Flamm[1]

1. JMI Laboratories, North Liberty, Iowa, USA; 2. Polyphor Ltd, Hegenheimermattweg 125, CH-4123 Allschwil, Switzerland

Contact Information:
Helio S. Sader, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

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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) being developed for the treatment of nosocomial pneumonia suspected or caused by *Pseudomonas aeruginosa*
- 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
- *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 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

Materials and Methods

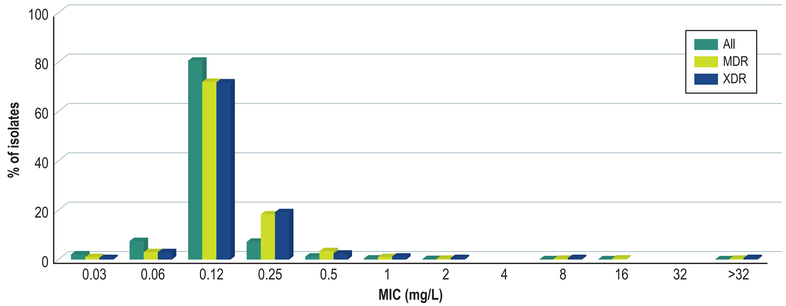
Organism collection

- Organisms tested originated from the SENTRY Antimicrobial Surveillance Program
- A total of 1,219 isolates (1/patient episode) were consecutively collected from 62 medical centers located in the United States (n=417), 40 medical centers in 22 European nations (n=491), and 10 medical centers in China (n=311)
- The isolates from the United States and Europe were collected in 2014 and the isolates from China were collected in 2012 and 2013
- 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%)

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
- Isolates were categorized as multidrug-resistant (MDR) or extensively drug-resistant (XDR) according to criteria published by Magiorakos *et al.*, which defines MDR as nonsusceptible to ≥1 agent in ≥3 antimicrobial classes, XDR as nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes, and pandrug-resistant as nonsusceptible (CLSI criteria) to all antimicrobial classes tested
- The antimicrobial classes and drug representatives used in the analysis were the following
  - 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
  - Polymyxins: colistin

Figure 1 Murepavadin MIC distributions for *P. aeruginosa* isolates and resistant subsets from the United States, Europe, and China



Results

- Murepavadin was the most potent agent (lowest MIC values) and inhibited 99.1% of isolates at ≤0.5 mg/L (Tables 1 and 2 and Figure 1)
- Murepavadin ($MIC_{50/90}$, 0.12/0.12 mg/L) was 4- to 8-fold more active than colistin ($MIC_{50/90}$, 1/1 mg/L) and polymyxin B ($MIC_{50/90}$, 0.5/1 mg/L; Table 2)
- Only 4 isolates (0.3%) exhibited murepavadin MIC values >2 mg/L; 3 isolates from the United States and 1 from Italy (Table 1)
- Murepavadin retained potent *in vitro* activity against MDR ($MIC_{50/90}$, 0.12/0.25 mg/L) and XDR ($MIC_{50/90}$, 0.12/0.25 mg/L) isolates (Tables 1 and 2 and Figure 1)
- Among the comparator agents tested, the polymyxins were the most active with polymyxin B ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible) being slightly more active than colistin ($MIC_{50/90}$, 1/1 mg/L; 98.9% susceptible; Table 2)
- Tobramycin ($MIC_{50/90}$, 0.5/>16 mg/L; 87.9% susceptible), amikacin ($MIC_{50/90}$, 4/16 mg/L; 87.4%/90.6% susceptible [EUCAST/CLSI]), and cefepime ($MIC_{50/90}$, 2/16 mg/L; 79.8% susceptible) were moderately less active against this collection of *P. aeruginosa* (Table 2)
- MDR and XDR isolates exhibited high resistance rates to all comparator agents except the polymyxins colistin and polymyxin B (Table 2)
- Murepavadin was equally active against isolates from Europe, the United States, and China ($MIC_{50/90}$, 0.12/0.12 mg/L for all 3 regions; Tables 1 and 2)
- Isolates from China exhibited slightly higher MIC values for colistin and polymyxin B compared to European and United States isolates (Table 2)
- Susceptibility rates for the aminoglycosides, β-lactams, and ciprofloxacin were slightly higher among isolates from the United States compared to Europe and China (Table 2)

Conclusions

- Murepavadin demonstrated potent activity against a large collection of clinical *P. aeruginosa* isolates from Europe, the United States, and China
- Murepavadin retained potent activity against MDR and XDR *P. aeruginosa* isolates
- The results of this study coupled with results from ongoing clinical studies will define the role of murepavadin for treating *P. aeruginosa* infections

Table 1 Murepavadin MIC distributions for *P. aeruginosa* isolates and resistant subsets from the United States, Europe, and China

Organism/subset (no. of isolates)	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	>32		
All isolates (1,219)	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	0.12	0.12
MDR isolates (300)	3 1.0	9 4.0	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
XDR isolates (167)	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
United States isolates (417)	12 2.9	35 11.3	329 90.2	27 96.6	9 98.8	1 99.0	1 99.3	0 99.3	1 99.5	1 99.8	0 99.8	1 100.0	0.12	0.12
European isolates (491)	9 1.8	37 9.4	398 90.4	37 98.0	6 99.2	2 99.6	1 99.8	0 99.8	1 100.0				0.12	0.12
Chinese isolates (311)	4 1.3	20 7.7	256 90.0	29 99.4	0 99.4	2 100.0							0.12	0.12

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

Antimicrobial agent (no.)	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
All isolates (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
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 isolates (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
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 isolates (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
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

Antimicrobial agent (no.)	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST[a]	
			%S	%R	%S	%R
United States isolates (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
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
European isolates (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
Cefepime	2	16	84.4	6.2	84.4	15.6
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
Piperacillin-tazobactam	4	128	74.1	13.4	74.1	25.9
Tobramycin	0.5	>16	86.8	12.8	86.8	13.2
Chinese isolates (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
Cefepime	2	16	79.4	9.0	79.4	20.6
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 (2018) and EUCAST (2018).

Acknowledgements

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