P1836 Activity of Murepavadin Against Colistin-resistant *Pseudomonas aeruginosa* Clinical Isolates

Hans H. Locher[1], Petra Chiquet[1], Stéphanie Brun[1], **Francesca Bernardini[1]**, Ian Morrissey[2], Stephen Hawser[2] , Glenn E. Dale[1] and D. Obrecht[1]
[1]Polyphor Ltd., Hegenheimermattweg 125, CH-4123 Allschwil, Switzerland; [2]IHMA Europe Sàrl, Route de l'Ile-au-bois 1A, 1870 Monthey/VS, Switzerland

Background

The increasing prevalence of multi-drug resistant Gram-negative bacteria, especially those resistant to carbapenems, has led to the increased use of polymyxins as a last resort treatment. This has resulted in the evolution and spread of colistin-resistant isolates [Olaitan 2014, Bialvaei 2015, Poirel 2017].

The most prevalent polymyxin-resistance mechanism in *Pseudomonas* (*P.*) *aeruginosa* and other Gram-negative bacteria is associated with the addition of 4-amino-L-arabinose (L-Ara4N) or phosphoethanolamine (pEtN) to the lipid A region of the lipopolysaccharides (LPS). The resulting reduced net negative charge decreases the affinity to polymyxins and leads to reduced susceptibility. Mutations in regulatory two-component systems such as PhoP-PhoQ and PmrA-PmrB have been shown to be involved in acquired colistin-resistance [Poirel 2017, Olaitan 2014, Bialevi 2015].

Murepavadin has potent and specific activity against *P. aeruginosa* and acts by blocking the translocation of lipopolysaccharides from the periplasm to the outer membrane by interacting with the outer membrane β-barrel transporter LptD [Srinivas et al. 2010]. A recent study showed potent activity of murepavadin against MDR and XDR *P. aeruginosa* isolates, most of them susceptible to colistin [Sader 2018]. The present study investigated the activity of murepavadin against a collection of colistin-resistant *P. aeruginosa* clinical isolates. Relevant anti-*Pseudomonas* reference antibiotics of different classes were included for comparison.

Material & Methods

495 clinical isolates of *P. aeruginosa* were obtained from the IHMA collection (IHMA Europe Sarl, Monthey, Switzerland). Isolates were collected world-wide (Europe 224, North America 132 Asia 104, Africa 35) between 2013 and 2017 and selected based on colistin-susceptibility or resistance. MICs of murepavadin, colistin and anti-*Pseudomonas* reference antibiotics were determined by the CLSI broth microdilution method (M07-A10) at Polyphor Ltd. Strains were confirmed as *P. aeruginosa* by growth on cetrimide agar (Sigma 22470) and API 20 NE V.80 test strips (BioMérieux 20050). Colistin-resistance was defined as >2 mg/L, according to EUCAST [EUCAST 2018] and CLSI guidelines [CLSI 2017]. *P. aeruginosa* ATCC 27853 and *E. coli* NCTC 13846 (DSMZ 105182 (mcr-1 positive, for colistin testing) were used as QC organisms.

For murepavadin provisional QC ranges of 0.06-0.25 mg/L was applied for the strain *P. aeruginosa* ATCC 27853 (based on a CLSI M23 Tier 2 study (PH7080-X0030).

Results

Table 1. MICs (mg/L) of murepavadin and comparators against *P. aeruginosa* isolates (n=495, all strains)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI			EUCAST		
				%S	%I	%R	%S	%I	%R
Murepavadin	0.06	0.25	0.03–>8	n.a.			n.a.		
Colistin	2	16	0.25->64	63.8		36.2	63.8		36.2
Polymyxin B	1	4	≤0.06–64	87.9		12.1	n.a.		
Amikacin	4	32	0.5–>64	84.2	5.9	9.9	74.8	9.4	15.8
Aztreonam	16	>64	0.5–>64	42.6	19.6	37.8	62.2		37.8
Cefepime	4	32	0.25–>64	75.4	9.4	15.2	75.4		24.6
Ceftazidime	4	64	0.5–>64	70.9	5.9	23.2	70.9		29.1
Ceftazidime-avibactam	2	16	0.25->64	87.7	5.7	6.6	87.7		12.3
Ciprofloxacin	0.25	>8	0.03–>8	76.2	3.4	20.4	70.5		29.5
Doripenem	1	16	≤0.06–64	72.5	8.1	19.4	60.4	12.1	27.5
Gentamicin	2	>64	≤0.06–>64	70.1	10.3	19.6	70.1		29.1
Levofloxacin	1	>8	0.125–>8	71.3	5.9	22.8	61.6		38.4
Piperacillin-tazobactam	8	>64	0.125–>64	68.9	14.1	17.0	68.9		31.1
Ticarcillin-clavulanic acid	64	>64	0.125–>64	7.3	53.7	39	7.3		92.7
Tobramycin	0.5	64	≤0.06–>64	85.1	1.7	48.5	85.1		14.9

n.a., not availble

Table 2. MICs (mg/L) of murepavadin and comparators against 179 colistin-resistant (MIC >2 µg/mL) *P. aeruginosa* isolates

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI			EUCAST		
				%S	%I	%R	%S	%I	%R
Murepavadin	0.125	0.5	0.03–>8	n.a.			n.a.		
Colistin	8	64	4->64	0.0		100	0		100
Polymyxin B	1	16	≤0.06–64	n.a.			68.7		31.3
Amikacin	8	>64	1–>64	71.0	11.7	17.3	58.7	12.3	29.0
Aztreonam	16	>64	0.5–>64	38.0	21.8	40.2	59.8		40.2
Cefepime	8	>64	0.5–>64	67.0	9.5	23.5	67.0		33.0
Ceftazidime	4	>64	0.5–>64	68.2	7.3	24.5	68.2		31.8
Ceftazidime-avibactam	2	16	0.25->64	86.0	6.2	7.8	86.0.		14.0
Ciprofloxacin	0.5	>8	0.03–>8	67.6	3.9	28.5	60.9		29.1
Doripenem	2	32	≤0.06–64	62.6	11.2	26.2	49.2	13.4	37.4
Gentamicin	4	>64	0.5–>64	54.2	12.9	32.9	54.2		45.8
Levofloxacin	0.5	>8	0.125–>8	62.6	6.7	30.7	52.5		47.5
Piperacillin-tazobactam	8	>64	0.125–>64	66.5	15.1	18.4	66.5		33.5
Ticarcillin-clavulanic acid	64	>64	0.125–>64	8.4	45.3	46.3	8.4		91.6
Tobramycin	0.5	>64	0.125–>64	77.6	2.8	48.5	77.6		22.4

n.a., not availble

Table 3. MICs (mg/L) of murepavadin and comparators against colistin-susceptible (MIC ≤2 µg/mL) *P. aeruginosa* isolates (n=316)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI			EUCAST		
				%S	%I	%R	%S	%I	%R
Murepavadin	0.06	0.125	0.03–2	n.a.			n.a.		
Colistin	2	2	0.25-2	100		0	100		0
Polymyxin B	0.5	1	0.125–4	98.7		1.3	n.a.		
Amikacin	4	16	0.5–>64	91.8	2.5	5.7	83.9	7.9	8.2
Aztreonam	16	>64	0.5–>64	63.6	18.4	36.4	63.6		36.4
Cefepime	4	32	0.25–>64	80.1	9.2	10.7	80.1		19.9
Ceftazidime	4	64	0.5–>64	72.5	5.1	22.4	72.5		27.5
Ceftazidime-avibactam	2	16	0.25->64	88.6	5.4	6.0	88.6		11.4
Ciprofloxacin	0.125	>8	0.03–>8	81.0	3.2	16.8	76.0		24
Doripenem	1	8	≤0.06–64	78.2	6.3	15.5	66.8	11.4	21.8
Gentamicin	2	32	≤0.06–>64	79.1	8.9	12.0	79.1		21.9
Levofloxacin	0.5	>8	0.125–>8	76.3	5.4	18.3	66.8		33.2
Piperacillin-tazobactam	8	>64	0.25–>64	70.3	13.6	16.1	70.3		29.7
Ticarcillin-clavulanic acid	64	>64	0.125–>64	6.7	58.6	34.7	6.7		93.3
Tobramycin	0.5	8	≤0.06–>64	89.2	0.9	10.8	89.2		10.8

n.a., not availble

Figure 1. Cumulative MIC distribution of murepavadin and comparators against 495 *P. aeruginosa* isolates (top=all strains; bottom= sub-set of 179 colistin-resistant isolates (MIC >2 mg/L)

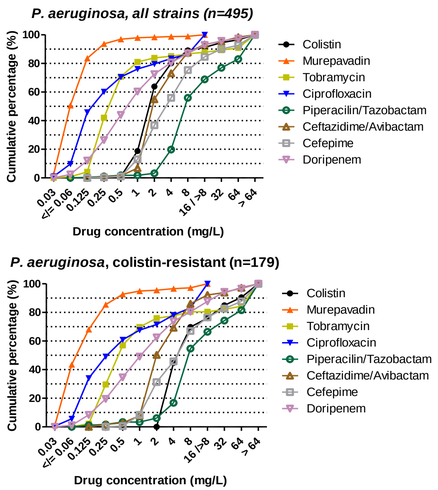
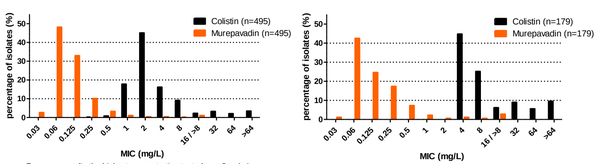
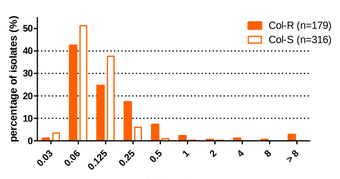


Figure 2 . MIC distribution of murepavadin and colistin for all strains (left) and for the sub-set of colistin-resistant (MIC >2 mg/L) *P. aeruginosa* (right)



For murepavadin the highest concentration tested was 8 µg/mL

Figure 3. Comparison of MIC distribution of murepavadin in colistin-susceptible (CST-S) and colistin-resistant (CST-R) *P. aeruginosa*



- MICs of colistin obtained for the 495 isolates ranged from 0.25 to > 64 mg/L. 179 of the 495 *P. aeruginosa* isolates were confirmed as colistin-resistant (MIC >2 mg/L) and 316 as colistin-susceptible (MIC ≤ 2 µg/mL) by applying EUCAST criteria.
- MIC_{50} and MIC_{90} of murepavadin were 0.06 and 0.25 mg/L, respectively, when tested against all 495 isolates, and 0.125 and 0.5 mg/L, respectively, when tested against the confirmed 179 colistin-resistant strains. The overall MIC range was 0.03->8 mg/L (**Tables 1-3**).
- Murepavadin MIC distributions for colistin-resistant and colistin-susceptible stains were similar, indicating no cross-resistance (**Figures 1-3)**).
- Murepavadin was more active than all standard of care anti-*Pseudomonas* antibiotics tested (**Tables 1-3 and Figure 1**).
- Susceptibility rates of reference antibiotics were lower for the colistin-resistant subset when compared to the colistin-susceptible subset (**Tables 2 and 3**). The highest susceptibilities were observed for ceftazidime-avibactam (86%) and tobramycin (77.6%), while susceptibilities for the other agents, notably for carbapenems (doripenem), fluoroquinolones (ciprofloxacin, levofloxacin) and piperacillin-tazobactam were less than 70%.

Conclusions

- The present study data indicate potent activity of murepavadin against colistin-resistant clinical isolates of *P. aeruginosa*.
- MICs against such strains are comparable to those against colistin-susceptible strains and are in agreement with results obtained from a large collection of MDR and XDR *P. aeruginosa* isolates [Sader 2018].
- Murepavadin was more active than all currently approved anti-*Pseudomonas* agents tested.
- The promising results presented here coupled with results from ongoing clinical studies will define the role of murepavadin for treating *P. aeruginosa* infections, including those caused by colistin-resistant isolates.

References

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