Stability of imipenem/relebactam against *Pseudomonas aeruginosa* β-lactam (including recently introduced combinations) resistance mechanisms

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BACKGROUND

In this work we analyzed the stability of the novel β-lactam/β-lactamase inhibitor combination imipenem/relebactam against *Pseudomonas aeruginosa* β-lactam mutation-driven resistance mechanisms, including those involving the recently introduced combinations ceftolozane/tazobactam (C/T) and ceftazidime/avibactam.

MATERIALS AND METHODS

Imipenem and Imipenem+ 4 mg/L relebactam MICs were determined in 3 different sets of strains:

- ✓ A panel of 16 PAO1 isogenic mutants showing combinations of the most relevant resistance mutations, including AmpC hyperproduction, porin (OprD) inactivation and efflux pumps overexpression.
- ✓ 7 pairs of isogenic XDR clinical isolates that had developed resistance to ceftolozane/tazobactam during treatment.
- ✓ A panel of derivatives from a PAO1 OprD$^-$ ΔAmpC mutant expressing 5 different AmpC variants conferring ceftolozane/tazobactam and ceftazidime/avibactam resistance, previously cloned from these clinical isolates.

RESULTS

STRAIN	MIC (mg/l)	
	IMIPENEM	IMIPENEM/ RELEBACTAM (4 mg/L)
PAO1 Δ*dacB*	1	0.125
PAO1 Δ*dacC*	0.5	0.125
PAO1 Δ*dacB*Δ*dacC*	1	0.125
PAO1 Δ*dacB*Δ*dacC*Δ*pbpG*	0.125	0.125
PAO1 ΔAmpD	0.5	0.125
PAO1 ΔAmpDΔAmpDh2ΔAmpDh3	0.5	0.0625
PAO1 Δ*dacB*ΔAmpD	1	0.125
PAOD1 (OprD$^-$)	8	0.25
PAO1 ΔMexR	0.5	0.125
PAO1 ΔNfxB	0.5	0.125
PAO1 ΔMexZ	1	0.125
PAO1 ΔAmpDΔMexR	0.5	0.125
PAOD1 ΔAmpD	8	0.5
PAOD1 Δ*dacB*	8	0.5
PAOD1 ΔMexR	8	0.5
PAOD1 ΔMexZ	16	1

Table 1. PAO1 isogenic mutants showing combinations of the most relevant resistance mutations.

PATIENT ID (ST)	RESISTANT MECHANISMS		MIC (mg/l)			
	C/T SUSCEPTIBLE ISOLATE	C/T RESISTANT ISOLATE	IMIPENEM		IMIPENEM/ RELEBACTAM (4 mg/L)	
			C/T S	C/T R	C/T S	C/T R
1 (ST179)	OXA-10	OXA-14, OprD$^-$	1	8	0.5	2
2 (ST175)	OprD$^-$, AmpC↑	+AmpCT96I	8	1	1	0.5
3 (ST175)	OprD$^-$, AmpC↑	+AmpCT96I	16	1	0.5	0.5
4 (ST175)	OprD$^-$, AmpC↑	+AmpCE247K	8	1	1	1
5 (ST175)	OprD$^-$, AmpC↑	+AmpCΔG229-E247	16	1	1	0.5
6 (ST175)	OprD$^-$, AmpC↑	+AmpCF147L	16	2	1	0.5
7 (ST175)	OprD$^-$, AmpC↑	+AmpCE247G	8	2	1	0.5

Table 2. Isogenic XDR clinical isolates that had developed resistance to ceftolozane/tazobactam.

STRAIN	MIC (mg/l)	
	IMIPENEM	IMIPENEM/ RELEBACTAM (4 mg/L)
PAO1	0.5	0.125
PAOD1 (OprD$^-$)	8	0.25
PAOD1 ΔAmpC	0.5	0.5
PAOD1 ΔAmpC +pUCPAmpC $_{WT}$ (PDC-1)	4	0.5
PAOD1 ΔAmpC +pUCPAmpC $_{T96I}$ (PDC-222)	0.5	0.5
PAOD1 ΔAmpC +pUCPAmpC $_{E247K}$ (PDC-221)	0.5	0.5
PAOD1 ΔAmpC +pUCPAmpC $_{ΔG299-E247K}$ (PDC-223)	0.5	0.5
PAOD1 ΔAmpC +pUCPAmpC $_{F147L}$ (PDC-316)	0.5	0.5
PAOD1 ΔAmpC +pUCPAmpC $_{E247G}$ (PDC-80)	1	0.5

Table 3. PAO1 OprD$^-$ ΔAmpC mutants expressing AmpC variants conferring ceftolozane/tazobactam and ceftazidime/avibactam resistance.

CONCLUSION

Imipenem/relebactam adds valuable potential to our antipseudomonal arsenal, overcoming the most relevant mutation-driven resistance mechanisms, including those leading to ceftolozane/tazobactam and ceftazidime/avibactam resistance development.

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