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In Vitro Activity of Imipenem/Relebactam Against Various Resistance Phenotypes/Genotypes of Enterobacteriaceae and *Pseudomonas aeruginosa* Isolated from Patients across Canada: CANWARD 2016/2017

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Introduction

Relebactam (formerly known as MK-7655) is a non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor that is structurally related to avibactam, differing by the addition of a piperidine ring to the 2-position carbomyl group (1). It displays activity against Ambler class A (including extended-spectrum β-lactamases [ESBLs], *Klebsiella pneumoniae* carbapenemases [KPCs]) and class C β-lactamases (AmpC). The addition of relebactam significantly improves the activity of imipenem against most species of Enterobacteriaceae (by lowering the minimum inhibitory concentration [MIC] by 2- to 128-fold) depending on the presence or absence of β-lactamase enzymes. Against *Pseudomonas aeruginosa*, the addition of relebactam also improves the activity of imipenem (by lowering the MIC by 8-fold). Based on the data available, the addition of relebactam does not improve the activity of imipenem against *Acinetobacter baumannii*, *Strenotrophomonas maltophilia* and most anaerobes.

The pharmacokinetics of relebactam are described by a two-compartment, linear model and not altered by the co-administration of imipenem (1). Relebactam's approximate volume of distribution (V_d) and elimination half-life ($t_{½}$) of ~18 L and 1.2 to 2.1 h, respectively, are similar to imipenem. Like imipenem, relebactam is primarily renally excreted, and clearance correlates with creatinine clearance.

Phase II clinical trials have reported that imipenem/relebactam is as effective as imipenem alone for treatment of complicated intra-abdominal infections and complicated urinary tract infections, including acute pyelonephritis (1). Imipenem/relebactam is currently in Phase III of development with studies assessing imipenem/relebactam versus imipenem-resistant bacterial infections (preliminary data presented at ECCMID 2018) as well as treatment of hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). The current study assessed the *in vitro* activities of imipenem/relebactam, imipenem and comparator antimicrobial agents against various resistance phenotypes/genotypes of recent (2016/2017) clinical isolates of Enterobacteriaceae and *P. aeruginosa* submitted to the CANWARD study in 2016/2017.

Materials and Methods

Bacterial Isolates

CANWARD is an ongoing, national, Health Canada partnered study assessing antimicrobial resistance patterns of pathogens causing infections in patients receiving care in hospitals across Canada (2, 3). Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units (3). From January 2016 through October 2017, inclusive, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound and bloodstream infections. The medical centres submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media and stocked in skim milk at -80ºC until minimum inhibitory concentration (MIC) testing was carried out.

Antimicrobial Susceptibilities

Following two subcultures from frozen stock, the *in vitro* activity of imipenem, imipenem/relebactam and selected antimicrobials was determined by broth microdilution in accordance with CLSI guidelines (M7, 10th edition). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (M100, 27th edition). Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (M7-A10, 2015). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre plates (2, 3). These plates contained doubling antimicrobial dilutions in 100µL/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/mL then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

Results

Table 1. Antimicrobial activity of imipenem/relebactam, imipenem and comparators versus Enterobacteriaceae isolated from Canadian hospitals

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL)			
	MIC_{50}	MIC_{90}	Range Min	Range Max
***Citrobacter freundii* (17)**				
Amikacin	2	2	≤ 1	8
Cefepime	≤ 0.25	4	≤ 0.25	16
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	1	≤ 0.06	2
Imipenem	**0.5**	**1**	**0.25**	**2**
Imipenem/relebactam	**0.25**	**0.5**	**0.25**	**2**
Piperacillin/tazobactam	2	256	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Enterobacter aerogenes* (42)**				
Amikacin	2	4	≤ 1	32
Cefepime	≤ 0.25	0.5	≤ 0.25	0.5
Ceftriaxone	≤ 0.25	32	≤ 0.25	16
Ciprofloxacin	≤ 0.06	0.25	≤ 0.06	8
Imipenem	**1**	**2**	**0.25**	**> 32**
Imipenem/relebactam	**0.25**	**1**	**0.12**	**16**
Piperacillin/tazobactam	4	32	2	256
Trimethoprim Sulfa	≤ 0.12	0.25	≤ 0.12	0.5
***Enterobacter cloacae* (110)**				
Amikacin	2	2	≤ 1	16
Cefepime	≤ 0.25	1	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	0.25	≤ 0.06	> 16
Imipenem	**0.25**	**1**	**0.25**	**4**
Imipenem/relebactam	**0.25**	**0.5**	**0.12**	**2**
Piperacillin/tazobactam	2	32	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	1	≤ 0.12	> 8
***Escherichia coli* (424)**				
Amikacin	2	4	≤ 1	32
Cefepime	≤ 0.25	4	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06	> 16
Imipenem	**0.25**	**0.25**	**0.25**	**2**
Imipenem/relebactam	**0.25**	**0.25**	**0.12**	**1**
Piperacillin/tazobactam	2	8	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Escherichia coli* ESBL (60)**				
Amikacin	2	16	≤ 1	32
Cefepime	16	> 64	1	> 64
Ceftriaxone	> 64	> 64	4	> 64
Ciprofloxacin	> 16	> 16	≤ 0.06	> 16
Imipenem	**0.25**	**0.5**	**0.25**	**1**
Imipenem/relebactam	**0.25**	**0.25**	**0.12**	**1**
Piperacillin/tazobactam	4	64	≤ 1	512
Trimethoprim Sulfa	> 8	> 8	≤ 0.12	> 8
***Klebsiella oxytoca / Raoultella spp.* (134)**				
Amikacin	≤ 1	2	≤ 1	8
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25	16
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06	> 16
Imipenem	**0.25**	**0.5**	**0.25**	**1**
Imipenem/relebactam	**0.25**	**0.5**	**0.12**	**1**
Piperacillin/tazobactam	2	8	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	≤ 0.12	≤ 0.12	> 8
***Klebsiella pneumoniae* (200)**				
Amikacin	≤ 1	2	≤ 1	8
Cefepime	≤ 0.25	16	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	4	≤ 0.06	> 16
Imipenem	**0.25**	**0.5**	**0.25**	**2**
Imipenem/relebactam	**0.25**	**0.5**	**0.12**	**2**
Piperacillin/tazobactam	4	16	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Morganella morganii* (23)**				
Amikacin	2	4	≤ 1	4
Cefepime	≤ 0.25	1	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	2	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	16	≤ 0.06	> 16
Imipenem	**4**	**4**	**1**	**8**
Imipenem/relebactam	**2**	**4**	**1**	**4**
Piperacillin/tazobactam	≤ 1	4	≤ 1	256
Trimethoprim Sulfa	0.25	> 8	≤ 0.12	> 8
***Proteus mirabilis* (81)**				
Amikacin	4	8	≤ 1	32
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25	8
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	2
Ciprofloxacin	≤ 0.06	4	≤ 0.06	> 16
Imipenem	**2**	**4**	**0.25**	**16**
Imipenem/relebactam	**2**	**4**	**0.25**	**16**
Piperacillin/tazobactam	≤ 1	≤ 1	≤ 1	64
Trimethoprim Sulfa	0.25	> 8	≤ 0.12	> 8
***Serratia marcescens* (122)**				
Amikacin	2	4	≤ 1	16
Cefepime	≤ 0.25	0.5	≤ 0.25	16
Ceftriaxone	≤ 0.25	1	≤ 0.25	> 64
Ciprofloxacin	0.12	1	≤ 0.06	16
Imipenem	**1**	**1**	**0.25**	**4**
Imipenem/relebactam	**1**	**1**	**0.5**	**4**
Piperacillin/tazobactam	2	4	≤ 1	32
Trimethoprim Sulfa	0.5	1	≤ 0.12	> 8

ESBL = extended spectrum ß-lactamase

Table 2. MIC (µg/mL) distributions of imipenem and imipenem/relebactam versus Enterobacteriaceae isolated from Canadian hospitals

Organism	0.12	0.25	0.5	1	2	4	8	≥16	Total
Citrobacter freundii									**17**
Imipenem		7	5	4	1				
Imipenem/relebactam		13	3		1				
Enterobacter aerogenes									**42**
Imipenem		9	9	16	6			2*	
Imipenem/relebactam	7	16	12	5	1			1	
Enterobacter cloacae									**110**
Imipenem		60	28	16	5	1			
Imipenem/relebactam	4	88	15	2	1				
Escherichia coli									**424**
Imipenem		391	27	5	1				
Imipenem/relebactam	205	202	14	3					
***Escherichia coli* (ESBL)**									**60**
Imipenem		52	4	4					
Imipenem/relebactam	22	34	2	2					
Klebsiella oxytoca / Raoultella spp.									**134**
Imipenem		102	28	4					
Imipenem/relebactam	13	105	14	2					
Klebsiella pneumoniae									**200**
Imipenem		169	23	3	5				
Imipenem/relebactam	12	132	43	12	1				
Morganella morganii									**23**
Imipenem				2	5	14	2		
Imipenem/relebactam				1	12	10			
Proteus mirabilis									**81**
Imipenem		14	7	13	23	18	3	3	
Imipenem/relebactam		3	4	1	16	43	13	1	
Serratia marcescens									**122**
Imipenem	9	51	50	8	4				
Imipenem/relebactam		25	55	38	4				

ESBL, extended spectrum ß-lactamase
*2/2 isolates had a MIC ≥32 µg/mL

Table 3. Antimicrobial activity of impenem/relebactam, imipenem and comparators versus *Pseudomonas aeruginosa* isolated from Canadian hospitals

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL)			
	MIC_{50}	MIC_{90}	Range Min	Range Max
***Pseudomonas aeruginosa* (373)**				
Amikacin	4	16	≤ 1	> 64
Cefepime	2	16	≤ 0.25	> 64
Ciprofloxacin	0.12	4	≤ 0.06	> 16
Colistin	1	2	0.12	> 16
Imipenem	**2**	**16**	**0.25**	**> 32**
Imipenem/relebactam	**0.5**	**2**	**0.12**	**8**
Piperacillin/tazobactam	4	128	≤ 1	> 512
Tobramycin	≤ 0.5	2	≤ 0.5	> 64

Table 4. MIC (µg/mL) distributions of imipenem and imipenem/relebactam versus *Pseudomonas aeruginosa* isolated from Canadian hospitals

Organism	≤0.25	0.5	1	2	4	8	16	32	> 32	Total
Pseudomonas aeruginosa										**373**
Imipenem	5	15	112	140	43	16	23	16	3	
Imipenem/relebactam	60*	238	34	27	12	2				

*2/60 isolates had a MIC of 0.12 µg/mL

Imipenem/relebactam was active against two KPC-producing *E. coli* isolates tested. MICs for imipenem/relebactam were 2 to 4-fold lower than imipenem alone, with an MIC range of 0.25-1 µg/mL.

Conclusions

1. Imipenem/relebactam was highly active against commonly encountered species of Enterobacteriaceae.
2. Imipenem/relebactam was 2-fold more active than imipenem against ESBL-producing Enterobacteriaceae and retained its activity against KPC-producing Enterobacteriaceae.
3. Imipenem/relebactam was highly active against *P. aeruginosa*.
4. Imipenem/relebactam was 4-8 fold more active than imipenem against *P. aeruginosa*.

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