P1283

Activity of Imipenem-Relebactam against *Enterobacteriaceae* and *Pseudomonas aeruginosa* from Respiratory Tract Infections in Europe - SMART 2015

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Revised Abstract

Background: Relebactam (MK-7655) (REL) is a β-lactamase inhibitor of class A and class C β-lactamases that is in development in combination with imipenem. REL restores the *in vitro* activity of imipenem (IMI) against *Enterobacteriaceae,* including those producing KPCs, and *Pseudomonas aeruginosa*. In this study we evaluated the ability of REL to restore IMI susceptibility to a collection of gram-negative isolates from lower respiratory tract infections in European countries participating in the 2015 SMART surveillance program.

Material/Methods: 45 hospitals in 17 countries each collected up to 100 consecutive aerobic and facultative gram-negative pathogens from lower respiratory tract infections. MICs were determined for 1065 *P. aeruginosa* and 1949 non-Proteeae *Enterobacteriaceae* (NPE) using CLSI broth microdilution. Proteeae were excluded due to intrinsic non-susceptibility to IMI. REL was tested at a fixed concentration of 4 mg/L in combination with IMI. The percent susceptible was assessed using EUCAST breakpoints. IMI susceptible breakpoints of ≤2 mg/L (NPE) and ≤4 mg/L (*P. aeruginosa*) were applied to IMI/REL. All IMI non-susceptible isolates were tested for the presence of genes encoding β-lactamases using published multiplex PCR assays, followed by full-gene DNA sequencing.

Results: The cumulative percent of isolates at each IMI and IMI/REL MIC is shown in the table.

Organism	n	Drug	MIC (mg/L)							
			≤0.5	1	2	4	8	16	32	>32
P. aeruginosa	1065	IMI	20.8	58.3	64.1	68.9	81.4	**94.2**	97.4	100
		IMI/REL	69.9	80.9	**91.5**	93.7	96.2	96.9	97.8	100
P. aeruginosa, IMI-NS	331	IMI					40.2	81.3	**91.5**	100
		IMI/REL	9.7	40.2	72.5	79.8	87.6	**90.0**	93.1	100
NPE	1949	IMI	76.3	89.3	**94.0**	95.7	96.5	97.3	97.7	100
		IMI/REL	87.6	**95.7**	97.5	98.4	98.7	98.9	99.0	100
NPE, IMI-NS	116	IMI				27.6	41.4	55.2	61.2	**100**
		IMI/REL	38.8	45.7	58.6	73.3	78.4	81.9	83.6	**100**

Shaded area indicates susceptible by EUCAST 2015 imipenem breakpoint; MIC_{90} bolded; NPE, non-Proteeae *Enterobacteriaceae*; IMI, imipenem; REL, relebactam; NS, non-susceptible

Among 1065 *P. aeruginosa*, 68.9% (734) were susceptible to IMI; of the 331 non-susceptible isolates, 79.8% (264) were rendered susceptible by the addition of REL, for a final 93.7% susceptible. The majority of the remaining IMI/REL non-susceptible *P. aeruginosa* isolates carried metallo-β-lactamases (MBLs) or GES carbapenemases (with 13 of the 15 GES-carbapenemase-positive isolates found in one hospital). Among 1949 NPE, 94.0% (1833) were susceptible to IMI; of the 116 non-susceptible isolates, 58.6% (68) were rendered susceptible by the addition of REL, for a final 97.5% S. The majority of the NPE isolates that were rendered susceptible by REL carried KPCs, and the majority of the isolates that remained IMI/REL non-susceptible carried MBLs. Isolates carrying OXA-48 carbapenemases were found in both subsets.

Conclusions: Relebactam exhibited strong potential for restoring the *in vitro* activity of IMI against many pathogens otherwise non-susceptible to carbapenems. Further development of this compound could provide a valuable therapeutic option for treating lower respiratory tract infections caused by resistant gram-negative bacilli.

Introduction

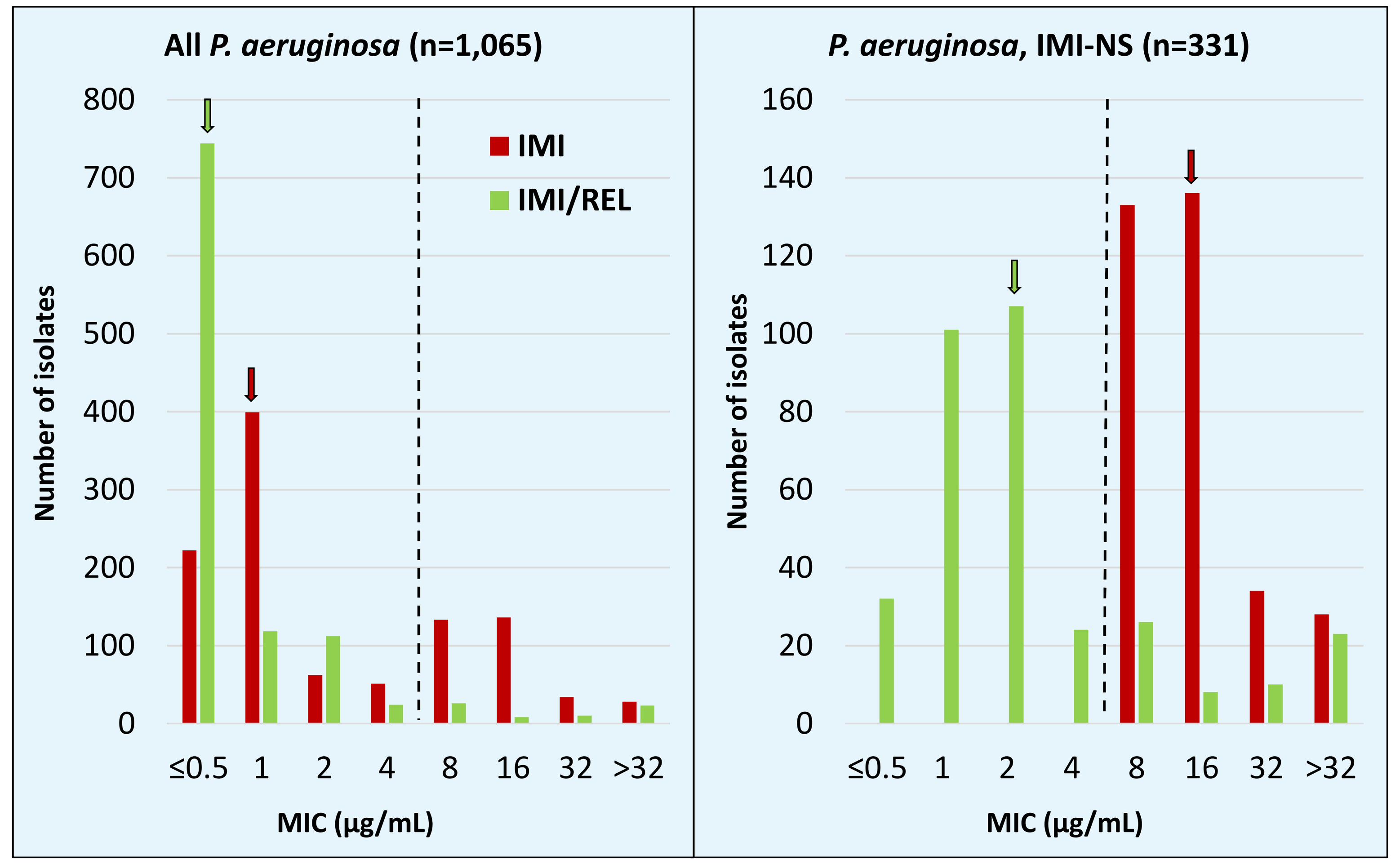
Relebactam (MK-7655) (REL) is a β-lactamase inhibitor of class A and class C β-lactamases that is in development in combination with imipenem. REL restores the *in vitro* activity of imipenem (IMI) against *Enterobacteriaceae,* including those producing KPCs, and *Pseudomonas aeruginosa*. In this study we evaluated the ability of REL to restore IMI susceptibility to a collection of gram-negative isolates from lower respiratory tract infections in European countries participating in the 2015 SMART surveillance program.

Materials & Methods

45 hospitals in 17 countries each collected up to 100 consecutive aerobic and facultative gram-negative pathogens from lower respiratory tract infections. MICs were determined for 1065 *P. aeruginosa* and 1949 non-Proteeae *Enterobacteriaceae* (NPE) using CLSI broth microdilution [1,2]. Proteeae were excluded due to intrinsic non-susceptibility to IMI. REL was tested at a fixed concentration of 4 mg/L in combination with IMI. The percent susceptible was assessed using EUCAST breakpoints [3]. IMI susceptible breakpoints of ≤2 mg/L (NPE) and ≤4 mg/L (*P. aeruginosa*) were applied to IMI/REL. All IMI non-susceptible isolates were tested for the presence of genes encoding β-lactamases using published multiplex PCR assays, followed by full-gene DNA sequencing.

Results

Figure 1. Effect of relebactam on MIC distribution of imipenem against *P. aeruginosa* isolates.



Arrows indicate the mode of the respective MIC distributions.
Dashed line represents the EUCAST susceptibility breakpoint of ≤4 µg/mL for imipenem.
IMI, imipenem; REL, relebactam.

Table 1. Susceptibility of *P. aeruginosa* to imipenem-relebactam and comparators.

Organisms (n)/Drugs	% S	% I	% R	MIC_{50}	MIC_{90}
All *P. aeruginosa* (n=1065)					
Imipenem	**68.9**	**12.5**	**18.6**	**1**	**16**
Imipenem-Relebactam[a]	**93.7**	**2.4**	**3.8**	**0.25**	**2**
Amikacin	87.1	3.9	8.9	≤4	16
Aztreonam	8.6	69.6	21.8	8	>16
Cefepime	73.1	0.0	27.0	4	32
Ceftazidime	71.4	0.0	28.6	4	>32
Colistin	99.5	0.0	0.5	≤1	≤1
Levofloxacin	54.3	0.0	45.7	1	>4
Piperacillin-Tazobactam	66.6	0.0	33.4	8	>64
***P. aeruginosa*, IMI-NS (n=331)**					
Imipenem	**0.0**	**40.2**	**59.8**	**16**	**32**
Imipenem-Relebactam[a]	**79.8**	**7.9**	**12.4**	**2**	**16**
Amikacin	66.2	10.3	23.6	≤4	>32
Aztreonam	2.7	50.8	46.5	16	>16
Cefepime	39.3	0.0	60.7	16	>32
Ceftazidime	41.1	0.0	58.9	16	>32
Colistin	99.7	0.0	0.3	≤1	≤1
Levofloxacin	22.4	0.0	77.6	>4	>4
Piperacillin-Tazobactam	33.5	0.0	66.5	64	>64

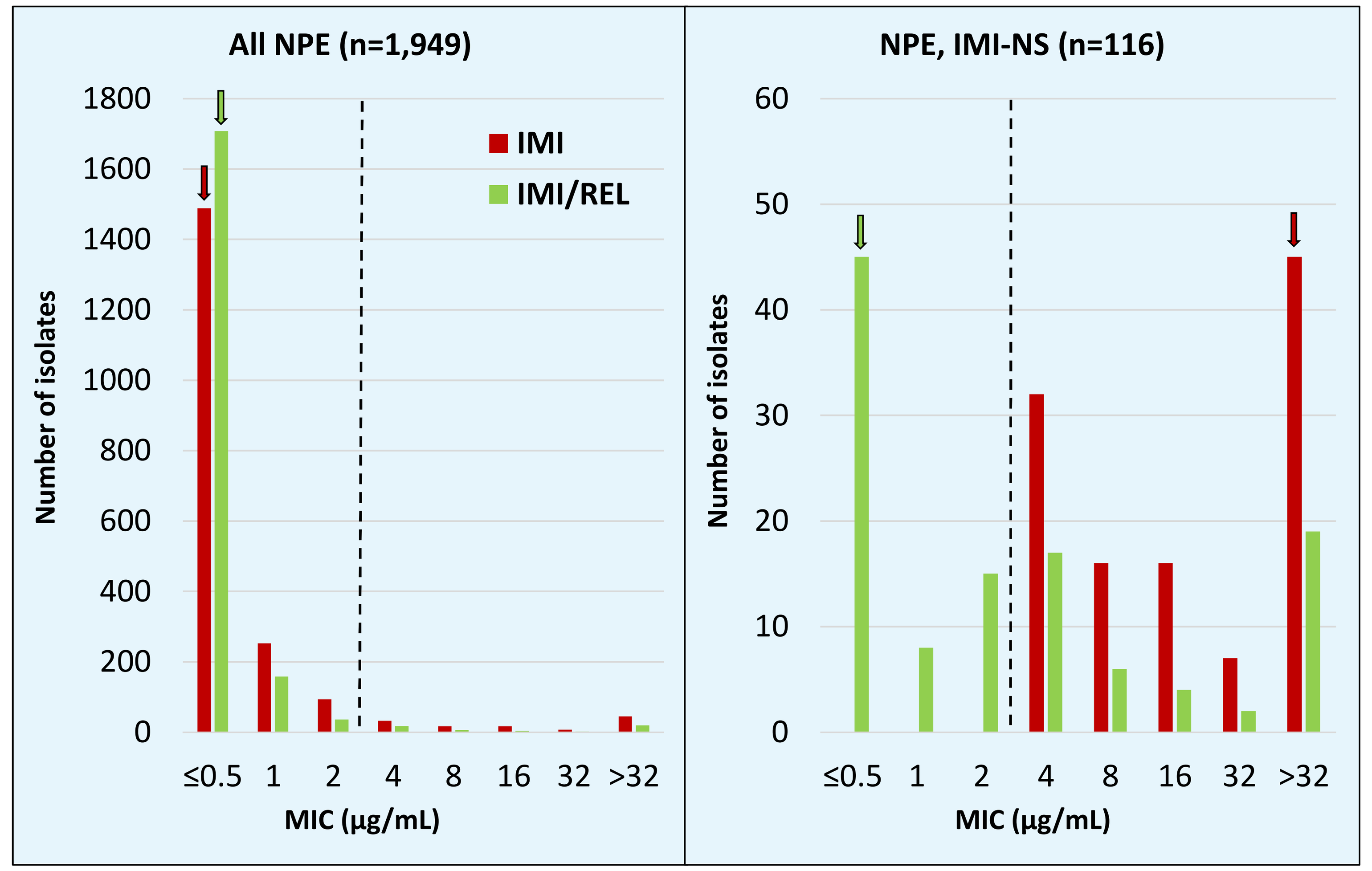
[a] In the absence of breakpoints for imipenem-relebactam, EUCAST breakpoints for imipenem were applied.
S, susceptible; I, intermediate; R, resistant; IMI-NS, imipenem non-susceptible.

Table 2. Acquired β-lactamases detected in 331 imipenem-non-susceptible *P. aeruginosa* isolates[a]

Phenotype β-lactamase content	No. of isolates (% of phenotype)
Imipenem-relebactam-susceptible[b] (n=264)	
ESBL	18 (6.8)
AmpC	4 (1.5)
No acquired β-lactamase detected	242 (91.7)
Imipenem-relebactam-non-susceptible[b] (n=67)	
NDM	2 (3.0)
VIM	31 (46.3)
IMP	3 (4.5)
GES carbapenemase[c]	15 (22.4)
ESBL	1 (1.5)
AmpC	1 (1.5)
No acquired β-lactamase detected	14 (20.9)

[a] Original spectrum β-lactamases (e.g., TEM-1) and intrinsic chromosomally-encoded AmpC β-lactamases common to *P. aeruginosa* are not shown.
[b] In the absence of breakpoints for imipenem-relebactam, EUCAST breakpoints for imipenem were applied.
[c] 13 of the15 isolates were collected in one hospital in Portugal (all GES-6).

Figure 2. Effect of relebactam on MIC distribution of imipenem against non-Proteeae *Enterobacteriaceae* (NPE) isolates.



Arrows indicate the mode of the respective MIC distributions.
Dashed line represents the EUCAST susceptibility breakpoint of ≤2 µg/mL for imipenem.
All NPE: *K. pneumoniae* (n=591), *E. coli* (n=552), *E. cloacae* (n=205), *S. marcescens* (n=200), *K. oxytoca* (n=137), *E. aerogenes* (n=85), *C. koseri* (n=50), *C. freundii* (n=41), and 17 other species (n=88).
IMI-NS NPE: *K. pneumoniae* (n=97), *S. marcescens* (n=6), *E. cloacae* (n=5), *S. liquefaciens* (n=4), and 4 other species (n=4).

Table 3. Susceptibility of NPE to imipenem-relebactam and comparators.

Organisms (n)/Drugs	% S	% I	% R	MIC_{50}	MIC_{90}
All NPE (n=1949)					
Imipenem	**94.0**	**2.5**	**3.5**	**≤0.5**	**2**
Imipenem-Relebactam[a]	**97.5**	**1.2**	**1.3**	**0.12**	**1**
Amikacin	93.5	2.2	4.3	≤4	8
Aztreonam	69.9	4.0	26.1	≤1	>16
Cefepime	75.9	5.0	19.1	≤1	>32
Ceftazidime	70.7	5.4	23.9	≤0.5	>32
Ceftriaxone	69.1	1.9	29.0	≤1	>32
Colistin	84.3	0.0	15.8	≤1	>8
Levofloxacin	72.2	4.4	23.5	≤0.5	>4
Piperacillin-Tazobactam	72.4	6.5	21.1	4	>64
NPE, IMI-NS (n=116)					
Imipenem	**0.0**	**41.4**	**58.6**	**16**	**>32**
Imipenem-Relebactam[a]	**58.6**	**19.8**	**21.6**	**2**	**>32**
Amikacin	42.2	11.2	46.6	16	>32
Aztreonam	9.5	0.0	90.5	>16	>16
Cefepime	9.5	0.9	89.7	>32	>32
Ceftazidime	9.5	0.9	89.7	>32	>32
Ceftriaxone	7.8	0.0	92.2	>32	>32
Colistin	56.0	0.0	44.0	≤1	>8
Levofloxacin	10.3	4.3	85.3	>4	>4
Piperacillin-Tazobactam	7.8	0.9	91.4	>64	>64

[a] In the absence of breakpoints for imipenem-relebactam, EUCAST breakpoints for imipenem were applied.
S, susceptible; I, intermediate; R, resistant; IMI-NS, imipenem non-susceptible.
NA, no breakpoint available.

Table 4. Acquired β-lactamases detected in 116 imipenem-non-susceptible NPE isolates[a]

Phenotype β-lactamase content	No. of isolates (% of phenotype)
Imipenem-relebactam-susceptible (n=68)	
KPC ± ESBL ± AmpC[b]	49 (72.1)
OXA-48 ± ESBL[c]	11 (16.2)
KPC + OXA-48 + ESBL[d]	1 (1.5)
ESBL[e]	1 (1.5)
No acquired β-lactamase detected[f]	6 (8.8)
Imipenem-relebactam-non-susceptible (n=48)	
OXA-48 + ESBL ± AmpC[g]	18 (37.5)
NDM + ESBL[h]	20 (41.7)
NDM + OXA-48 + ESBL[i]	4 (8.3)
VIM + ESBL[j]	1 (2.1)
VIM + OXA-48[k]	1 (2.1)
No acquired β-lactamase detected[l]	4 (8.3)

[a] Original spectrum β-lactamases (e.g., TEM-1) and intrinsic chromosomally-encoded AmpC β-lactamases common to *Enterobacter* and *Serratia* spp. are not shown.
[b] *K. pneumoniae* (n=46), *E. coli* (n=1), *E. cloacae* (n=1), and *K. oxytoca* (n=1),
[c] *K. pneumoniae* (n=9) and *E. cloacae* (n=2); IMI MIC decreased by only 1 dilution from 4 to 2 µg/ml with addition of REL.
[d] *K. pneumoniae*.
[e] *S. marcescens*.
[f] *S. marcescens* (n=4), *S. liquefaciens* (n=1), *S. ureilytica* (n=1).
[g] *K. pneumoniae* (n=17) and *R. ornithinolytica* (n=1).
[h] *K. pneumoniae* (n=19) and *E. cloacae* (n=1).
[i] *K. pneumoniae* (n=4).
[j] *K. pneumoniae.*
[k] *E. cloacae.*
[l] *S. liquefaciens* (n=3) and *S. marcescens* (n=1).

Results Summary

- Among 1,065 *P. aeruginosa*, the modal IMI MIC dropped from 1 to ≤0.5 µg/ml in the presence of REL (Figure 1), MIC_{90} dropped from 16 to 2, and % S increased from 68.9 to 93.7% (Table 1). Of the studied comparators, none exceeded 90% S, except colistin (99.5%).
- Among 331 IMI-NS *P. aeruginosa* isolates, the modal IMI MIC dropped from 16 to 2 µg/ml in the presence of REL (Figure 1), and 79.8% of isolates were rendered susceptible to IMI (Table 1).
- The majority of IMI/REL-NS *P. aeruginosa* isolates carried metallo-β-lactamases (MBL).
- Because of the relatively small proportion of IMI-NS isolates among NPE (6.0%), the IMI MIC distribution for all NPE was similar with and without REL (Figure 2).
- However, among the 116 IMI-NS NPE isolates, the modal IMI MIC dropped from >32 to ≤0.5 µg/ml in the presence of REL (Figure 2), and 58.6% of isolates were rendered susceptible.
- Of the 68 NPE isolates that were rendered IMI-S in the presence of REL, >70% carried KPC; the 11 OXA-48-positive isolates showed an IMI MIC decrease of only one dilution.
- Of the IMI/REL-NS NPE isolates, 92% carried MBL and/or OXA-48 carbapenemases.

Conclusions

Relebactam exhibited strong potential for restoring the *in vitro* activity of IMI against many pathogens otherwise non-susceptible to carbapenems. Further development of this compound could provide a valuable therapeutic option for treating lower respiratory tract infections caused by resistant gram-negative bacilli.

References and Acknowledgments:

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3. The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2017; http://www.eucast.org/clinical_breakpoints/

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