Activity of Imipenem-Relebactam against Multidrug-Resistant *P. aeruginosa* from Europe – SMART 2015-2017

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INTRODUCTION

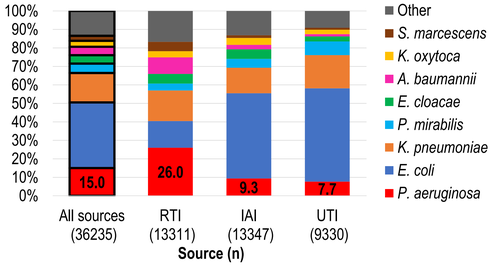
Relebactam (REL), formerly MK-7655, is an inhibitor of class A and C β-lactamases that is in development in combination with imipenem (IMI). In this study, we evaluated the activity of IMI/REL against multidrug-resistant (MDR) *Pseudomonas aeruginosa* collected in Europe as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program.

METHODS

In 2015-2017, 67 hospitals in 22 countries in Europe were requested to collect up to 250 consecutive aerobic or facultatively anaerobic gram-negative bacilli per year (100 isolates from lower respiratory tract infections per year; 100 isolates from intra-abdominal infections in 2015-2016 and 75 in 2017; 50 isolates from urinary tract infections in 2015-2016 and 75 in 2017). Only one isolate per patient per species was allowed. MICs were determined for 5,447 *P. aeruginosa* isolates using CLSI broth microdilution and interpreted with CLSI break-points; for comparison purposes, the IMI susceptible breakpoint of 2 µg/ml was applied to IMI/REL [1, 2]. REL was tested at a fixed concentration of 4 µg/ml in combination with IMI. MDR isolates were defined as non-susceptible (intermediate or resistant) to any 3 or more of the following 8 sentinel drugs: amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, colistin, IMI, and piperacillin-tazobactam.

RESULTS

Figure 1. Proportion of *P. aeruginosa* among all collected gram-negative bacilli



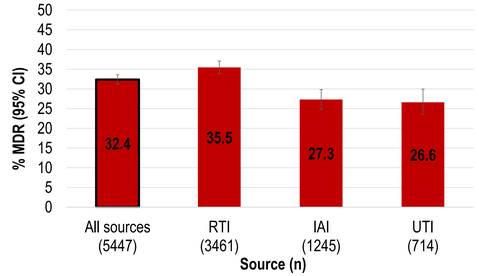
RTI, respiratory tract infection; IAI, intra-abdominal infection; UTI, urinary tract infection

Table 1. Activity of IMI/REL and comparators against all *P. aeruginosa* isolates (n=5,447)

Drug	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
Imipenem-relebactam[a]	**0.5**	**4**	**≤0.03 - >32**	**89.6**	**2.7**	**7.7**
Imipenem	1	16	≤0.5 - >32	65.0	4.4	30.6
Cefepime	4	32	≤1 - >32	72.5	11.8	15.7
Ceftazidime	4	>32	≤0.5 - >32	71.5	5.9	22.7
Aztreonam	8	>16	≤1 - >16	65.5	13.0	21.6
Piperacillin-tazobactam	8	>64	≤2 - >64	66.6	15.5	17.9
Ciprofloxacin	≤0.25	>2	≤0.25 - >2	70.8	4.2	24.9
Amikacin	≤4	32	≤4 - >32	89.8	3.2	7.0
Colistin	≤1	≤1	≤1 - >8	99.4	--	0.6

[a] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem were applied
S, susceptible; I, intermediate; R, resistant

Figure 2. MDR rate among *P. aeruginosa* isolates



RTI, respiratory tract infection; IAI, intra-abdominal infection; UTI, urinary tract infection

Table 2. Activity of IMI/REL and comparators against MDR *P. aeruginosa* isolates

Source/Drug	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
All sources (n=1763)						
Imipenem-relebactam[a]	**2**	**>32**	**≤0.03 - >32**	**68.7**	**7.7**	**23.7**
Imipenem	8	>32	≤0.5 - >32	25.2	4.7	70.2
Cefepime	16	>32	≤1 - >32	17.6	34.1	48.3
Ceftazidime	32	>32	≤1 - >32	16.2	14.2	69.6
Aztreonam	>16	>16	≤1 - >16	11.8	25.9	62.3
Piperacillin-tazobactam	>64	>64	≤2 - >64	7.5	37.7	54.8
Ciprofloxacin	>2	>2	≤0.25 - >2	31.2	5.7	63.1
Amikacin	8	>32	≤4 - >32	69.8	9.1	21.1
Colistin	≤1	≤1	≤1 - >8	98.5	--	1.5
RTI (n=1227)						
Imipenem-relebactam[a]	**2**	**>32**	**≤0.03 - >32**	**67.6**	**8.3**	**24.0**
Imipenem	8	>32	≤0.5 - >32	23.7	5.0	71.3
Cefepime	16	>32	≤1 - >32	17.3	33.6	49.1
Ceftazidime	32	>32	≤1 - >32	16.0	13.8	70.3
Aztreonam	>16	>16	≤1 - >16	11.9	26.2	61.9
Piperacillin-tazobactam	>64	>64	≤2 - >64	7.3	38.3	54.4
Ciprofloxacin	>2	>2	≤0.25 - >2	31.4	6.4	62.3
Amikacin	8	>32	≤4 - >32	68.5	9.1	22.4
Colistin	≤1	≤1	≤1 - >8	98.1	--	1.9
IAI (n=340)						
Imipenem-relebactam[a]	**1**	**>32**	**0.12 - >32**	**74.4**	**5.0**	**20.6**
Imipenem	8	>32	≤0.5 - >32	29.4	3.5	67.1
Cefepime	16	>32	4 - >32	17.7	37.9	44.4
Ceftazidime	32	>32	1 - >32	13.5	15.9	70.6
Aztreonam	>16	>16	≤1 - >16	9.4	25.6	65.0
Piperacillin-tazobactam	>64	>64	≤2 - >64	5.3	35.0	59.7
Ciprofloxacin	>2	>2	≤0.25 - >2	37.1	4.4	58.5
Amikacin	≤4	>32	≤4 - >32	77.1	5.9	17.1
Colistin	≤1	≤1	≤1 - >4	99.1	--	0.9
UTI (n=190)						
Imipenem-relebactam[a]	**2**	**>32**	**0.12 - >32**	**64.7**	**7.9**	**27.4**
Imipenem	8	>32	≤0.5 - >32	27.4	4.7	67.9
Cefepime	32	>32	4 - >32	19.5	30.0	50.5
Ceftazidime	32	>32	2 - >32	22.6	14.2	63.2
Aztreonam	>16	>16	4 - >16	15.8	24.7	59.5
Piperacillin-tazobactam	64	>64	4 - >64	12.1	40.0	47.9
Ciprofloxacin	>2	>2	≤0.25 - >2	19.5	3.2	77.4
Amikacin	8	>32	≤4 - >32	65.3	14.7	20.0
Colistin	≤1	≤1	≤1 - 2	100	--	0.0

[a] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem were applied
S, susceptible; I, intermediate; R, resistant

Table 3. Susceptibility to IMI/REL and comparators of isolates at different MDR levels

			% Susceptible				
MDR level	n	% among all MDR	IMI/REL[a]	IMI	FEP	CAZ	P/T
3-drug resistant	246	14.0	**93.9**	45.9	77.2	61.8	34.6
4-drug resistant	341	19.3	**89.4**	63.3	27.0	24.6	6.2
5-drug resistant	311	17.6	**80.7**	28.6	8.7	12.5	2.3
6-drug resistant	516	29.3	**59.3**	5.0	0.2	2.1	3.7
≥7-drug resistant	349	19.8	**33.8**	0.0	0.0	0.0	0.0
All MDR	1763		**68.7**	25.2	17.6	16.2	7.5

[a] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem were applied
IMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam

Table 4. Susceptibility to IMI/REL of the 10 most common MDR phenotypes[a]

MDR phenotype	n	% among all MDR	% Susceptible
1. ATM, CAZ, FEP, IMI, P/T, CIP	400	22.7	**64.3**
2. ATM, CAZ, FEP, IMI, P/T, CIP, AMK	337	19.1	**33.5**
3. ATM, CAZ, FEP, P/T	179	10.2	**100**
4. ATM, CAZ, FEP, IMI, P/T	141	8.0	**85.1**
5. ATM, CAZ, FEP, P/T, CIP	76	4.3	**100**
6. ATM, CAZ, P/T	57	3.2	**100**
7. ATM, IMI, P/T	47	2.7	**85.1**
8. CAZ, FEP, IMI, P/T, CIP, AMK	46	2.6	**4.3**
9. ATM, CAZ, IMI, P/T	30	1.7	**93.3**
10. ATM, IMI, CIP	28	1.6	**92.9**
All MDR	1763		**68.7**

[a] Sentinel drugs used for the definition of MDR included aztreonam (ATM), ceftazidime (CAZ), cefepime (FEP), imipenem (IMI), piperacillin-tazobactam (P/T), ciprofloxacin (CIP), amikacin (AMK), and colistin. Agents shown in the table tested as non-susceptible; sentinel agents not shown tested as susceptible. Agents tested but not included in the list of sentinel agents may have tested as susceptible or non-susceptible.
In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem were applied

RESULTS SUMMARY

- Among all gram-negative bacilli collected in Europe, the proportion of *P. aeruginosa* was 15.0%, with a proportion about three times higher among RTI than IAI and UTI isolates (Figure 1)
- Overall susceptibility of *P. aeruginosa* to IMI/REL was 89.6%, whereas susceptibility to the β-lactam comparators was <73% (Table 1)
- Overall, the MDR rate among *P. aeruginosa* was 32.4%, with higher rates in RTI than IAI or UTI isolates (Figure 2)
- Activity of IMI/REL against MDR *P. aeruginosa* was 68.7%, similar to the susceptibility to amikacin and only exceeded by colistin, whereas susceptibility to imipenem was 25.2% and to the other β-lactam comparators <18%. Antimicrobial activity was similar across specimen sources (Table 2)
- IMI/REL was active against >80% of isolates at the 3-, 4-, and 5-drug resistant MDR levels, with susceptibility generally ~20-80 percentage points higher than the β-lactam comparators (Table 3)
- The ten most common MDR phenotypes are shown in Table 4; IMI/REL was active against 64% of isolates of the most common phenotype and against 85-100% of isolates of another 7 phenotypes

CONCLUSIONS

IMI/REL was active against 68.7% of MDR *P. aeruginosa* isolates from Europe, 44 percentage points higher than imipenem and between 51 and 61 percentage points higher than the other β-lactam comparators. Continued clinical development of IMI/REL appears warranted given its potential as a therapeutic option for treating patients with infections caused by multidrug-resistant *P. aeruginosa*, especially considering the substantially reduced susceptibilities to other commonly used β-lactams.

REFERENCES & ACKNOWLEDGMENTS

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