27th ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID

Session: P060 News on relebactam and vaborbactam

Category: 3b. Resistance surveillance & epidemiology: Gram-negatives

24 April 2017, 12:30 - 13:30
P1283

Activity of imipenem-relebactam against Enterobacteriaceae and Pseudomonas aeruginosa from respiratory tract infections in Europe, SMART 2015

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Background: Relebactam (MK-7655) (REL) is a β-lactamase inhibitor of class A and class C beta-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 S 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**	95.6	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				26.7	40.5	55.2	61.2	**100**
		IMI/REL	39.7	46.6	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.