1230

Clinical and Microbiologic Outcomes by Causative Pathogen in Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia Treated With Imipenem/Cilastatin/Relebactam vs Piperacillin/Tazobactam

Maria C. Losada; Alok Maniar; Jiejun Du; Michelle L. Brown; Katherine Young; David W. Hilbert; Robert Tipping; C. Andrew DeRyke; Joan R. Butterton; Amanda Paschke; Luke F. Chen

Merck & Co., Inc., Kenilworth, NJ, USA

Background

- The small-molecule β-lactamase inhibitor relebactam (REL) inhibits class A carbapenemases (eg, KPC) and class C cephalosporinases (eg, AmpC), which commonly contribute to carbapenem nonsusceptibility[1]
- The combination of imipenem/cilastatin (IMI) and REL (IMI/REL) has broad antibacterial activity, including many strains of carbapenem-resistant Enterobacterales (CRE) and carbapenem-nonsusceptible *Pseudomonas aeruginosa*,[2,3] and has good intrapulmonary penetration[4]
- In the recently completed RESTORE-IMI 2 trial, IMI/REL was noninferior to piperacillin/tazobactam (PIP/TAZ) for empiric therapy of hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) in both primary and key secondary endpoints. IMI/REL was recently approved for this indication by the United States Food & Drug Administration[5]
- Here we present data on key per-pathogen outcomes from RESTORE-IMI 2

Methods

- RESTORE-IMI 2 was a randomized, controlled, double-blind, multinational phase 3 noninferiority trial in adult patients with HABP/VABP[5]
- Participants were randomized 1:1 to IMI/REL 500 mg/500 mg/250 mg or PIP/TAZ 4 g/500 mg every 6 hr for 7-14 days; a 14-day treatment duration was required for baseline *P aeruginosa*
- Lower respiratory tract (LRT) samples for Gram stain, microbiologic culture, and susceptibility testing were obtained ≤48 hours prior to screening, at end of therapy (EOT), and at early follow-up (EFU; 7-14 days after EOT)
  - Intermediate-susceptible pathogens were classified as nonsusceptible (NS)
  - Pathogen identification and susceptibility were confirmed at a central laboratory using broth dilution and current Clinical and Laboratory Standards Institute breakpoints[6,7]
  - All baseline IMI-NS non-*Morganellaceae* Enterobacterales and *Pseudomonas* spp. isolates (and baseline susceptible isolates from participants with only IMI-NS isolates at later visits), from the IMI/REL arm only, were screened for KPC genes
- The microbiologic MITT (mMITT) population comprised all randomized participants with ≥1 dose of study drug, with ≥1 baseline LRT pathogen species against which IMI/REL is known to have in vitro activity, and who did not have only gram-positive cocci on baseline Gram stain
- We evaluated the following outcomes by causative pathogen: microbiologic response at EOT (secondary endpoint), clinical response at EFU (key secondary endpoint), and Day 28 all-cause mortality (primary endpoint)
- These outcomes were prospectively evaluated in the protocol-defined mMITT population and retrospectively in these mMITT subgroups:
  - ≥1 confirmed KPC-positive baseline LRT pathogen
  - ≥1 extended-spectrum β-lactamase (ESBL)-positive baseline LRT pathogen
- In a sensitivity analysis, these outcomes were also retrospectively evaluated in patients with ≥1 gram-negative baseline LRT pathogen confirmed susceptible to both study drugs

Results

- The most common pathogens were *Klebsiella* spp., *P aeruginosa*, *Acinetobacter calcoaceticus-baumannii* complex, and *Escherichia coli* (Table 1), consistent with other recent HABP/VABP clinical trials and surveillance data[2,3,8-10]
- In the IMI/REL arm, 8 participants had a KPC-positive baseline LRT pathogen (*Klebsiella pneumoniae* n=7, *Klebsiella aerogenes* n=1); all isolates were IMI/REL susceptible (MIC range: 0.12-1 µg/mL)
- Causative pathogens were similar in patients with ≥1 gram-negative baseline LRT pathogen susceptible to both study drugs (sensitivity analysis):
  - Most common were *Klebsiella* spp. (32.2% IMI/REL, 28.7% PIP/TAZ), *P aeruginosa* (20.0% IMI/REL, 24.5% PIP/TAZ), *E coli* (20.8% IMI/REL, 23.1% PIP/TAZ), and *H influenzae* (10.0% IMI/REL, 8.4% PIP/TAZ)
  - *A calcoaceticus-baumannii* complex was less frequent (3.8% IMI/REL, 7.0% PIP/TAZ)

Table 1. Most Frequent Baseline Gram-Negative LRT Pathogens in the mMITT Population[a]

Pathogen, n (%)	IMI/REL (N=215)	PIP/TAZ (N=218)
Enterobacterales	132 (61.4%)	129 (59.2%)
Klebsiella spp.	65 (30.2%)[b]	59 (27.1%)[c]
Escherichia coli	30 (14.0%)	37 (17.0%)
Serratia marcescens	13 (6.0%)	4 (1.8%)
Enterobacter cloacae	8 (3.7%)	19 (8.7%)
Pseudomonas aeruginosa	34 (15.8%)	48 (22.0%)
***Acinetobacter calcoaceticus-baumannii* complex**	32 (14.9%)	36 (16.5%)
Haemophilus influenzae	13 (6.0%)	12 (5.5%)

[a]Shown are only those gram-negative pathogens with ≥10 baseline LRT isolates in either treatment arm; patients could have had multiple baseline pathogens. [b]*Klebsiella pneumoniae* (n=58), *Klebsiella aerogenes* (n=5), *Klebsiella oxytoca* (n=2). [c]*Klebsiella pneumoniae* (n=53), *Klebsiella aerogenes* (n=4), *Klebsiella oxytoca* (n=2).

N, number of participants in treatment arm; n, number of participants with ≥1 baseline LRT isolate of corresponding pathogen.

- Per-pathogen outcomes in these analyses need to be interpreted with caution, because denominators for individual pathogens were small, there were some imbalances between treatment arms, and numbers of outcome events were low
- Outcomes by pathogen were generally comparable between IMI/REL and PIP/TAZ in the mMITT population (Table 2) and in the sensitivity analysis of patients with ≥1 gram-negative baseline LRT pathogen susceptible to both study drugs (Table 3)
- Outcomes differed numerically between treatment arms, but the 95% confidence interval for the difference excluded 0 only for microbiologic response at EOT against *E coli,* favoring IMI/REL (data not shown)
- In the mMITT population, the numerical difference in most outcomes favored IMI/REL, except for clinical response in *Serratia marcescens* (very small sample size) and clinical response and Day 28 all-cause mortality in *P aeruginosa* (Table 2)
- In the sensitivity analysis of patients with ≥1 gram-negative baseline LRT pathogen susceptible to both study drugs, numerical differences for microbiologic response in all pathogens favored IMI/REL; for per-pathogen clinical response favored IMI/REL except in *Klebsiella* spp. and *S marcescens;* and for per-pathogen Day 28 all-cause mortality favored IMI/REL except in *P aeruginosa* (Table 3)
- For *P aeruginosa*, microbiologic eradication at EOT was high (65.4%-70.6% with IMI/REL, 62.9%-64.6% with PIP/TAZ) and numerically favored IMI/REL, while clinical and mortality outcomes showed a slightly different pattern (Table 2, Table 3)
  - This observation was unrelated to lack of susceptibility of *P aeruginosa* to randomized study drug, which was 88.6% (31/35 isolates) with IMI/REL and 68.0% (34/50 isolates) with PIP/TAZ
  - This may have been due to small sample size, low number of deaths (≤11 in either arm), uneven distribution of *P aeruginosa* between treatment arms (fewer with IMI/REL), and differences in host and disease characteristics between treatment arms
- For *A calcoaceticus-baumannii* complex, microbiologic response, clinical response, and mortality all numerically favored IMI/REL (Table 2, Table 3)

Table 2. Per-Pathogen Outcomes in mMITT Patients (ie, ≥1 Baseline LRT Pathogen Species Against Which IMI/REL is Known to Have In Vitro Activity)

LRT Pathogen, n (%)	Microbiologic Response at EOT		Clinical Response at EFU		Day 28 All-Cause Mortality	
	IMI/REL	PIP/TAZ	IMI/REL	PIP/TAZ	IMI/REL	PIP/TAZ
Enterobacterales	104/132 (78.8%)	88/129 (68.2%)	82/132 (62.1%)	76/129 (58.9%)	22/132 (16.7%)	29/129 (22.5%)
Klebsiella spp.	48/65 (73.8%)	38/59 (64.4%)	39/65 (60.0%)	36/59 (61.0%)	13/65 (20.0%)	13/59 (22.0%)
Escherichia coli	28/30 (93.3%)	26/37 (70.3%)	18/30 (60.0%)	21/37 (56.8%)	6/30 (20.0%)	10/37 (27.0%)
Serratia marcescens	10/13 (76.9%)	1/4 (25.0%)	9/13 (69.2%)	3/4 (75.0%)	2/13 (15.4%)	1/4 (25.0%)
Enterobacter cloacae	7/8 (87.5%)	15/19 (78.9%)	6/8 (75.0%)	13/19 (68.4%)	1/8 (12.5%)	3/19 (15.8%)
Pseudomonas aeruginosa	24/34 (70.6%)	31/48 (64.6%)	14/34 (41.2%)	29/48 (60.4%)	11/34 (32.4%)	7/48 (14.6%)
***Acinetobacter calcoaceticus-baumannii* complex**	21/32 (65.6%)	22/36 (61.1%)	19/32 (59.4%)	21/36 (58.3%)	5/32 (15.6%)	8/36 (22.2%)
Haemophilus influenzae	12/13 (92.3%)	9/12 (75.0%)	9/13 (69.2%)	8/12 (66.7%)	2/13 (15.4%)	3/12 (25.0%)
KPC-positive	6/8 (75.0%)	—	4/8 (50.0%)	—	2/8 (25.0%)	—
ESBL-positive Enterobacterales	37/45 (82.2%)	24/35 (68.6%)	29/45 (64.4%)	21/35 (60.0%)	9/45 (20.0%)	8/35 (22.9%)

The 95% CI for the difference excluded 0 only for microbiologic response with *E coli*, favoring IMI/REL. n/N, number of participants achieving specified outcome/number of participants with corresponding pathogen.

Table 3. Per-Pathogen Outcomes in Patients With ≥1 Baseline LRT Pathogen Confirmed as Susceptible to Both Study Drugs (Sensitivity Analysis)

LRT Pathogen, n (%)	Microbiologic Response at EOT		Clinical Response at EFU		Day 28 All-Cause Mortality	
	IMI/REL	PIP/TAZ	IMI/REL	PIP/TAZ	IMI/REL	PIP/TAZ
Enterobacterales	78/97 (80.4%)	72/100 (72.0%)	62/97 (63.9%)	62/100 (62.0%)	13/97 (13.4%)	22/100 (22.0%)
Klebsiella spp.	32/42 (76.2%)	30/41 (73.2%)	25/42 (59.5%)	28/41 (68.3%)	6/42 (14.3%)	8/41 (19.5%)
Escherichia coli	25/27 (92.6%)	23/33 (69.7%)	16/27 (59.3%)	19/33 (57.6%)	5/27 (18.5%)	8/33 (24.2%)
Serratia marcescens	8/10 (80.0%)	1/4 (25.0%)	7/10 (70.0%)	3/4 (75.0%)	2/10 (20.0%)	1/4 (25.0%)
Enterobacter cloacae	6/7 (85.7%)	13/16 (81.3%)	6/7 (85.7%)	12/16 (75.0%)	1/7 (14.3%)	3/16 (18.8%)
Pseudomonas aeruginosa	17/26 (65.4%)	22/35 (62.9%)	12/26 (46.2%)	20/35 (57.1%)	7/26 (26.9%)	5/35 (14.3%)
***Acinetobacter calcoaceticus-baumannii* complex**	4/5 (80.0%)	4/10 (40.0%)	4/5 (80.0%)	6/10 (60.0%)	0/5 (0.0%)	1/10 (10.0%)
Haemophilus influenzae	12/13 (92.3%)	9/12 (75.0%)	9/13 (69.2%)	8/12 (66.7%)	2/13 (15.4%)	3/12 (25.0%)

The 95% CI for the difference excluded 0 only for microbiologic response with *E coli*, favoring IMI/REL. n/N, number of participants achieving specified outcome/number of participants with corresponding pathogen.

Conclusions

- IMI/REL is an efficacious treatment option for HABP/VABP, regardless of causative pathogen
- Outcomes in a retrospective sensitivity analysis, which accounted for differences in susceptibility to assigned study drug, were comparable to those in the protocol-defined mMITT population
- The denominator for most of the per-pathogen outcomes analyses was small, along with low numbers of outcome events, and the results should be interpreted with caution
- *P aeruginosa* as a causative pathogen of HABP/VABP was an independent predictor of lower clinical response rates, regardless of treatment arm (see Poster 1574 at this meeting)

References

1. Livermore DM, et al. *J Antimicrob Chemother.* 2013;68(10):2286-2290.
2. Karlowsky JA, et al. *J Antimicrob Chemother.* 2018;73(7):1872-1879.
3. Karlowsky JA, et al. *J Glob Antimicrob Resist.* 2018;15:140-147.
4. Rizk ML, et al. *Antimicrob Agents Chemother.* 2018;62(3):e01411-e01417.
5. Titov I, et al. *Clin Infect Dis.* 2020;ciaa803.
6. CLSI. M100. 30th edition. 2020.
7. CLSI. January 2020 BWG Report – Part 1. 2020.
8. Karlowsky JA, et al. *Int J Antimicrob Agents.* 2020;55(1):105841.
9. Kollef MH, et al. *Lancet Infect Dis.* 2019;19(12):1299-1311.
10. Torres A, et al. *Lancet Infect Dis.* 2018;18(3):285-295.

Disclosures

- Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).
- Medical writing assistance was provided by Dominik Wolf, MSc, and editorial assistance by Michele McColgan, BA, both employees of MSD.

Acknowledgments

- The authors thank the patients and their families and all investigators and site personnel.

Presented at IDWeek 2020; Virtual meeting; October 21-25, 2020.