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Relebactam enhances Imipenem activity across the Imipenem susceptibility spectrum among *Pseudomonas aeruginosa* isolates collected in the United States - SMART 2018-2020

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Background

- Relebactam (REL) inhibits class A and C β-lactamases (BLs) and is approved in the US in the combination imipenem-cilastatin-REL (IMI/REL) for the treatment of hospital acquired bacterial pneumonia/ventilator associated bacterial pneumonia (HABP/VABP); and complicated intraabdominal abdominal infections (cIAI) & complicated urinary tract (cUTI) infections in patients with limited treatment options.
- Imipenem (IMI) nonsusceptibility in *Pseudomonas aeruginosa* is due to the combination of outer membrane porin loss (OprD) that reduces IMI permeability, along with expression of a chromosomally encoded AmpC enzyme (also known as Pseudomonas derived cephalosporinase [PDC]) that can degrade the decreased amount of IMI present in the cell[1]. REL restores IMI susceptibility by inhibiting PDC[2].
- IMI is an inducer of PDC[3] due to PBP4 inhibition[4], and REL inhibition of PDC also occurs in imipenem susceptible isolates, resulting in a reduction in IMI MICs observed in surveillance isolates[5].
- The goal of this study was to compare IMI/REL and Ceftazidime/Avibactam (CAZ/AVI) with respect to the added benefit of the cognate BLI on *P. aeruginosa* isolates from the United States that were nonsusceptible, intermediate or susceptible to their respective beta-lactam partner.

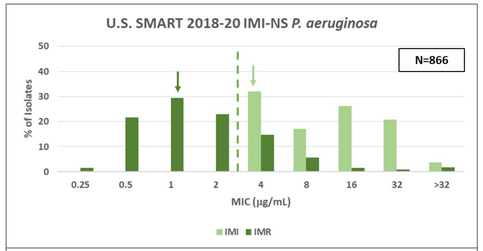
Methods

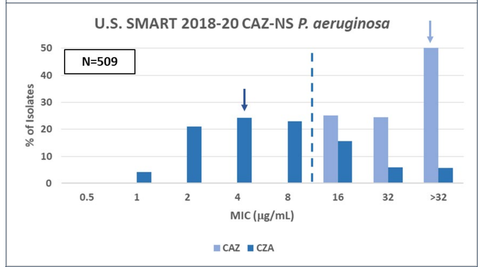
- The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a global surveillance study. In 2018-2020, 243 unique participating sites from 219 cities in 60 countries each collected up to 250 consecutive aerobic gram-negative isolates per year. The distribution of isolates in each year was 50 cUTI, 50 cIAI, 100 lower respiratory tract infections (LRTI) and 50 bloodstream infections (BSI).
- *P. aeruginosa* isolated from U.S. hospitals from 2018-20 were evaluated for IMI, Imipenem/REL (IMR), Ceftazidime (CAZ) and Ceftazidime/Avibactam (CZA) using broth microdilution and CLSI 2021 breakpoints[6].

Results

Fig. 1. Relebactam and Avibactam both restore activity towards *P. aeruginosa* isolates nonsusceptible to the partner beta-lactam

--Imipenem MIC >2 μg/mL
--Ceftazidime MIC >8 μg/mL

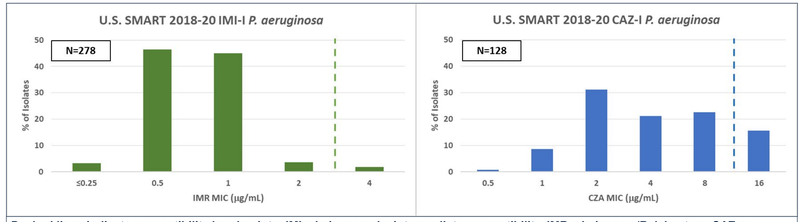




Dashed lines indicate susceptibility breakpoints; arrows indicate mode MICs; IMI = Imipenem; NS = nonsusceptible, IMR = Imipenem/Relebactam, CAZ = Ceftazidime, CZA = Ceftazidime/Avibactam

Fig. 2. Imipenem/REL has greater activity than Ceftazidime/Avibactam towards *P. aeruginosa* isolates with intermediate susceptibility to the partner Beta-Lactam

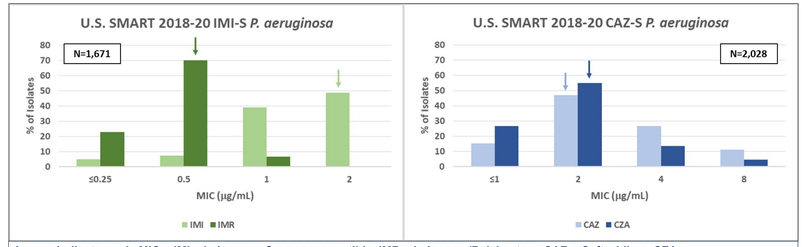
--Imipenem MIC of 4 μg/mL
--Ceftazidime MIC of 16 μg/mL



Dashed lines indicate susceptibility breakpoints; IMI = Imipenem; I = intermediate susceptibility, IMR = Imipenem/Relebactam, CAZ = Ceftazidime, CZA = Ceftazidime/Avibactam

Fig. 3. Relebactam, but not Avibactam, enhances partner beta-lactam activity towards susceptible *P. aeruginosa* isolates

--Imipenem MIC ≤2 μg/mL
--Ceftazidime MIC ≤8 μg/mL



Arrows indicate mode MICs; IMI = Imipenem; S = nonsusceptible, IMR = Imipenem/Relebactam, CAZ = Ceftazidime, CZA = Ceftazidime/Avibactam

Fig 4. Relebactam (REL) restores susceptibility to Imipenem (IMI) nonsusceptible *P. aeruginosa*

- Porin loss reduces the entry of imipenem into the periplasm; the resulting lower concentration can be hydrolyzed by PDC[1] (which is induced by imipenem[3])
- Relebactam inhibits hydrolysis of imipenem by PDC, restoring imipenem activity against IMI-NS *P. aeruginosa*[2]

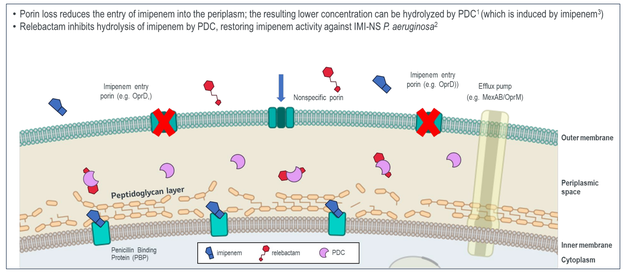


Fig. 5. Relebactam (REL) decreases Imipenem (IMI) MICs in Imipenem susceptible *P. aeruginosa*

- Imipenem enters the periplasm through the outer membrane porins OprD
- Imipenem inhibits PBP4[4] and induces expression of PDC[3], which poorly hydrolyzes IMI, thus increasing the IMI MIC but remaining in the susceptible range
- Relebactam inhibits hydrolysis of imipenem PDC, thus lowering the imipenem MIC[5]

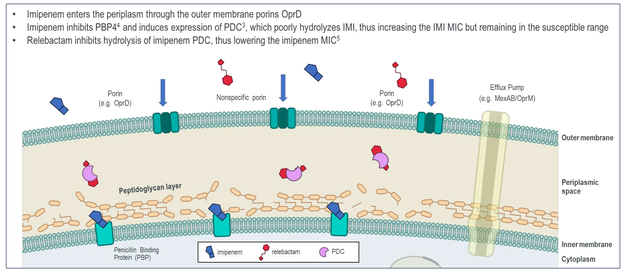
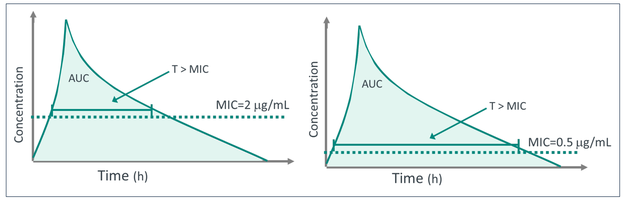


Fig. 6. Ability to reach PK/PD target (%*f*T>MIC) with IMI/REL vs IMI with the same isolates



Results Summary

- The addition of REL restores susceptibility to 75% of IMI-NS *P. aeruginosa* isolates and shifts the IMI mode MIC from 4 μg/mL to 1 μg/mL, a four-fold reduction (Figures 1 and 4). The addition of AVI restores susceptibility to 73% of CAZ-NS *P. aeruginosa* isolates (Figure 1).
- The addition of REL restored susceptibility to 98% of IMI-I *P. aeruginosa* isolates and 95% of IMI-I isolates had IMR MICs at least one dilution less than the susceptibility breakpoint (2 μg/mL) (Figure 2). The addition of AVI restored susceptibility to 84% of CAZ-I *P. aeruginosa* isolates and 62% of CAZ-I isolates had CZA MICs at least one dilution less than the susceptibility breakpoint (8 μg/mL) (Figure 2).
- The addition of REL shifted the IMI MIC of IMI-S *P. aeruginosa* isolates from 2 to 0.5 μg/mL, a four-fold reduction (Figures 3 and 5). The addition of AVI did not change the CAZ mode MIC of CAZ-S isolates (2 μg/mL) (Figure 3).

Conclusions

- Relebactam (REL) inhibits the ability of PDC to hydrolyze imipenem, further enhancing the activity of Imipenem (IMI) among *P. aeruginosa*
  - REL restores susceptibility to IMI among IMI-NS isolates
  - REL enhances the activity of IMI among IMI-S isolates
- REL is differentiated from AVI by its ability to reduce the MIC of its partner beta-lactam among both non-susceptible and susceptible *P. aeruginosa* isolates
- When lower MICs occur with IMI/REL compared with IMI among IMI-S isolates, it leads to a "pharmacodynamic boost" where % of time free drug concentration exceeds the MIC (%*f*T>MIC) for IMI is greater with IMI/REL than IMI alone.
- The ability to modify the MIC of an organism is usually not considered clinically as a strategy to optimize drug exposure. As shown in Figure 6, the ability of REL to lower the MIC of IMI among IMI-S isolates could represent a very effective strategy that has a profound effect on resultant drug exposure (e.g. a four-fold decrease in MIC from 2 μg/mL to 0.5 μg/mL would significantly increase the resultant %*f*T>MIC).
- This lowering of IMI MICs among IMI-S isolates upon addition of REL contributes to the high probability of target attainment (≥90%) observed following administration of IMI/REL 1.25g every 6 hours, further supporting the IMI/REL efficacy data observed in Phase 3 trials.

References

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