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WCK 4282 [high-dose Cefepime (FEP)-Tazobactam (TAZ)]: In-vivo PK/PD studies identifying TAZ threshold concentrations (CT) against AmpC P. aeruginosa (PA)

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Background: Hyper-expression of chromosomal AmpC is the most widely prevalent resistance mechanism in PA. This resistance mechanism impacts penicillins, cephalosporins and in conjunction with efflux and porin down-regulation, impacts carbapenems. FEP-TAZ is currently under development for treating MDR Gram-negative infections and has recently completed Phase 1 studies in Europe. We have previously established that even though FEP-TAZ MICs are comparable to FEP alone, addition of TAZ improved the *in vitro* and *in vivo* FEP cidal action against AmpC PA. Here, we sought to determine the efficacy driving TAZ threshold concentrations (C_T) and its magnitude in combination with FEP for AmpC-expressing PA strains with FEP-TAZ MICs of 16 µg/mL (FEP and PIP-TAZ - resistant) employing neutropenic mouse lung infection model.

Material/methods: Mouse PK data was obtained by administering subcutaneous q2h or q3h doses of FEP-TAZ ranging from 25-200 mg/kg. Serum was collected over 24h and FEP-TAZ was assayed by LC-MS/MS method. Neutropenic mice were intranasally infected with PA S503 [MIC (µg/mL): FEP-16, FEP-TAZ -16, PIP-TAZ-64, MEM-4] or PA Q117 [MIC (µg/mL): FEP-32, FEP-TAZ-16, PIP-TAZ-64; MEM-1] or PA 2779 [MIC (µg/mL): FEP-16, FEP-TAZ -16, PIP-TAZ->128, MEM-0.5], to achieve bacterial burden of 5.91-6.52 $\log_{10}$ CFU/lung at the initiation of treatment (2h post-infection). 27h post-infection bacterial lung load was determined. To arrive at the TAZ C_T, TAZ total daily doses (TDD) of 100–900 mg/kg administered as q2h or q3h regimens in combination with otherwise *in vivo* ineffective FEP doses (50 or 75 mg/kg, q2h). PIP-TAZ (166+50 mg/kg, q2h) was employed as a negative control in PA Q117 infection model. FEP-TAZ exposure-response analysis was undertaken using nonlinear regression (Graph Pad).

Results: Standalone FEP (1-log re-growth for all strains) and PIP-TAZ (100% mortality for PA Q117) were ineffective. Against PA Q117 and PA 2779, TAZ TDD of 100-600 mg/kg (q2h) in combination with FEP (50 mg/kg, q2h; TDD: 600 mg/kg) demonstrated 1.43-3.22 log kill from base-line. Against PA S503, unlike other strains, in combination with FEP TDD 600 mg/kg q3h, it was only TAZ TDD of 600 mg/kg (q3h) that provided 1.2 log kill, while a highest TAZ TDD of 900 mg/kg (q3h) further improved the killing up to1.54 log. Owing to higher FEP-TAZ doses in providing bactericidal action, PA S503 was used to arrive at robust TAZ target based on exposure-response analysis. The best correlation coefficient was observed with 0.12 µg/mL of TAZ (R^2: 0.9949), identifying it as a threshold concentration. The exposure-response analysis also showed that TAZ *f*T >0.12 µg/mL of 39.8% and 66.2% was linked with stasis and 1-log kill.

Conclusions: *In vivo* studies provided robust WCK 4282 PK/PD target for *P. aeruginosa* that would be used to support clinical doses and PK/PD based susceptibility breakpoint.