

The antibacterial effect (ABE) of ceftolozane (TOL)/tazobactam (TAZ) plus amikacin (AMI) against *Pseudomonas aeruginosa* (PA) using simulated human dosing

KE Bowker, AR Noel, SG Tomaselli, MLG Attwood, AP MacGowan

BCARE, Department of Infection sciences, North Bristol NHS Trust, Bristol, UK

karen.bowker@nbt.nhs.uk

27th ECCMID Vienna April 2017

Background

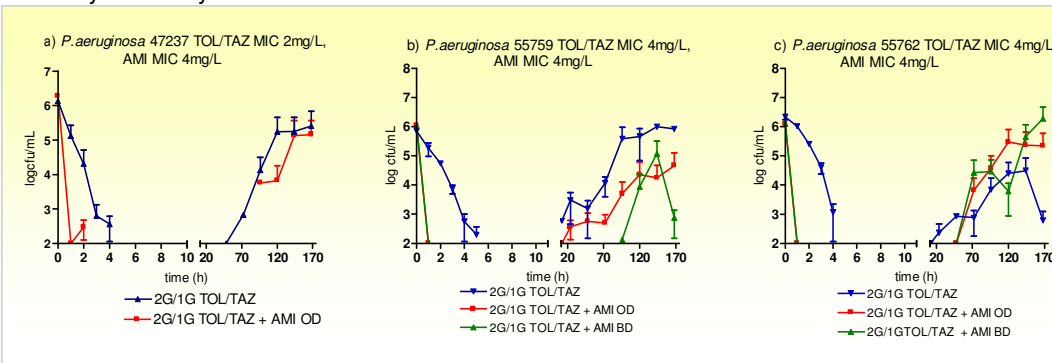
- Ceftolozane/tazobactam (TOZ/TAZ) has been approved for clinical use in Europe and is noteworthy for its potency in vitro against PA - including many multi-drug resistant strains.
- The debate of combination versus monotherapy has not been fully elucidated though combination antimicrobial chemotherapy is widely used as both empiric and definitive therapy to treat PA.
- With many anti-pseudomonal antibiotics, emergence of resistance (EoR) is a significant issue and the risk may be reduced by use of combination chemotherapy.

Objective

To determine the effect of adding AMI to TOL/TAZ in terms of bacterial killing and suppression of EoR against 3 strains of *P.aeruginosa*

Materials and methods

- A one compartment IVPKM was used to simulate free drug serum concentrations associated with TOL/TAZ 2G/1G (C_{max} 112/32mg/L; TOL t_{1/2} 2.5h, TAZ t_{1/2} 1h) alone and plus AMI 15mg/kg (OD C_{max} 50mg/L; BD C_{max} 25mg/L; t_{1/2} 2.5h).
- Dosing of TOL/TAZ was q8hly for 7 days and AMI q24hly or q12hly for 7 days. TOL and TAZ concentrations were measured using HPLC methodology, LLOQ 1.0mg/L for both compounds; amikacin concentrations were measured competitive inhibition immunoassay using Indiko Plus[®] QMS system (LLOQ 1.5mg/L)
- Three strains of PA (55759 and 55762 (AmpC) and 47237 (AmpC and OprD) were used TOL/TAZ MICs 2-4mg/L, AMI MIC 2-4mg/L. The inoculum was 10⁶ CFU/ml and simulations were performed in triplicate.
- ABE was measured by log change in viable count and area-under-the-bacterial-kill curve (AUBKC) over 7days (168h).
- EoR was assessed by changes in population analysis profiles on x2, x4 and x8 MIC plates 24hly over 7days.



Results

- The MICs of TOL/TAZ (4mg/L) were on the EUCAST clinical breakpoint for 2/3 PA strains tested (strain 3 MIC 2mg/L). For the TOL/TAZ dose simulation viable counts were reduced by >4 log by 4-6h; addition of AMI resulted in >4 log reduction in bacterial load by 2h.
- Regrowth occurred with TOL/TAZ alone by 12-72h (2-4log₁₀); however, addition of AMI OD resulted in delayed regrowth for all 3 strains; 24-96h, (2-5log₁₀). The two TOL/TAZ+AMI dosing regimens had the same ABE as measured by AUBKC.
- Comparison of AUBKC₂₄ and AUBKC₁₆₈ indicated greater ABE for TOL/TAZ+AMI compared to TOL/TAZ alone (p<0.05).

Table 1: Antibacterial effect of TOL/TAZ, AMI OD and AMI BD

		AUBKC (logcfu/mL.h) at -						
		24h	48h	72h	96h	120h	144h	168h
PA 47237	TOL/TAZ (2G/1G)	33.80 ± 8.88	295.60 ± 2.20	449.53 ± 2.05	565.50 ± 99.15	810.07 ± 34.91	1012.97 ± 64.30	1215.33 ± 95.55
PA 55759	TOL/TAZ (2G/1G)	165.50 ± 8.19	338.07 ± 15.12	518.53 ± 14.92	721.93 ± 3.04	941.73 ± 20.01	1412.67 ± 29.87	1412.67 ± 29.87
PA 55762	TOL/TAZ (2G/1G)	158.30 ± 2.72	316.20 ± 7.71	479.70 ± 13.00	622.77 ± 135.34	892.07 ± 119.78	1358.00 ± 191.94	1358.00 ± 191.94
meaned data n=9		119.20 ± 64.42	316.62 ± 20.28	482.59 ± 31.56	636.73 ± 108.34	881.29 ± 85.49	1102.51 ± 117.52	1328.67 ± 139.65
PA 47237	TOL/TAZ (2G/1G) +AMIK OD	18.54 ± 3.79	18.54 ± 3.79	158.45 ± 238.54	215.35 ± 337.10	301.45 ± 486.23	375.52 ± 557.41	777.91 ± 662.08
PA 55759	TOL/TAZ (2G/1G) +AMIK OD	7.92 ± 0.03	7.92 ± 0.03	149.82 ± 245.76	388.87 ± 329.93	496.90 ± 423.80	621.07 ± 532.98	742.30 ± 638.97
PA 55762	TOL/TAZ (2G/1G) +AMIK OD	8.13 ± 0.01	289.90 ± 0.00	454.20 ± 12.47	637.73 ± 39.95	816.63 ± 67.80	1004.47 ± 105.16	1210.33 ± 160.18
meaned data n=9		11.53 ± 5.59	105.45 ± 138.42	254.16 ± 227.79	413.99 ± 299.71	538.33 ± 394.82	667.02 ± 476.25	910.18 ± 518.64
PA 55759	TOL/TAZ (2G/1G) +AMIK BD	8.02 ± 0.00	8.02 ± 0.00	8.02 ± 0.00	197.88 ± 328.85	493.37 ± 146.19	640.33 ± 487.25	761.33 ± 1593.43
PA 55762	TOL/TAZ (2G/1G) +AMIK BD	14.45 ± 0.36	290.27 ± 0.40	460.47 ± 22.63	637.80 ± 39.94	768.73 ± 146.19	908.77 ± 266.69	1040.77 ± 380.78
meaned data n=6		11.23 ± 3.53	149.14 ± 154.59	234.24 ± 248.23	417.84 ± 319.30	631.05 ± 319.45	774.55 ± 380.33	901.25 ± 471.40

Table 2: EoR for TOL/TAZ plus AMI OD or AMI BD at T0, T24 and T72h

strain	TOL/TAZ				TOL/TAZ + AMI OD				TOL/TAZ + AMI BD			
	TOL/TAZ MIC (mg/L)	growth on x2 MIC plates		AMIK MIC (mg/L)	growth on x2 MIC plates		growth on x2 MIC plates	growth on x2 MIC plates		growth on x2 MIC plates	growth on x2 MIC plates	
		mean	stdev		mean	stdev		mean	stdev		mean	stdev
		T0			T0			T0			T0	
<i>P.aeruginosa</i> 47237	2	0/3	<2	-	4	1/3	6.55	0.81	-	-	-	-
<i>P.aeruginosa</i> 55759	4	0/3	<2	-	4	1/3	3.45	-	0/3	3.45	-	-
<i>P.aeruginosa</i> 55762	4	0/3	<2	-	4	0/3	<2	-	3/3	7.10	0.27	-
		T72			T72			T72			T72	
<i>P.aeruginosa</i> 47237	2	0/3	<2	-	4	0/3	<2	-	-	-	-	-
<i>P.aeruginosa</i> 55759	4	0/3	<2	-	4	0/3	<2	-	0/3	<2	-	-
<i>P.aeruginosa</i> 55762	4	0/3	<2	-	4	0/3	<2	-	3/3	4.35	0.99	-
		T168			T168			T168			T168	
<i>P.aeruginosa</i> 47237	2	0/3	<2	-	4	0/3	<2	-	-	-	-	-
<i>P.aeruginosa</i> 55759	4	0/3	<2	-	4	0/3	<2	-	0/3	<2	-	-
<i>P.aeruginosa</i> 55762	4	0/3	<2	-	4	2/3	3.83	-	2/3	5.76	-	-

- There was no EoR to TOL/TAZ alone (growth on MICx4 plates) with any simulation.
- Growth was noted with strain 55761 with TOL/TAZ + AMI simulations (AMI MIC x2 and MIC x4 plates (2/3 expts; 4.66logcfu/mL; TOL/TAZ and AMI MIC 4mg/L) however no changes in AMI MIC was seen. No growth was observed on x8MIC plates.

Conclusions

- TOL/TAZ plus AMI produced more rapid reduction of bacterial load compared to TOL/TAZ alone initially and delayed or reduced regrowth.
- Overall, ABE was improved by the addition of AMI.
- EoR was not a major feature with any of the dosing regimens simulated.

