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

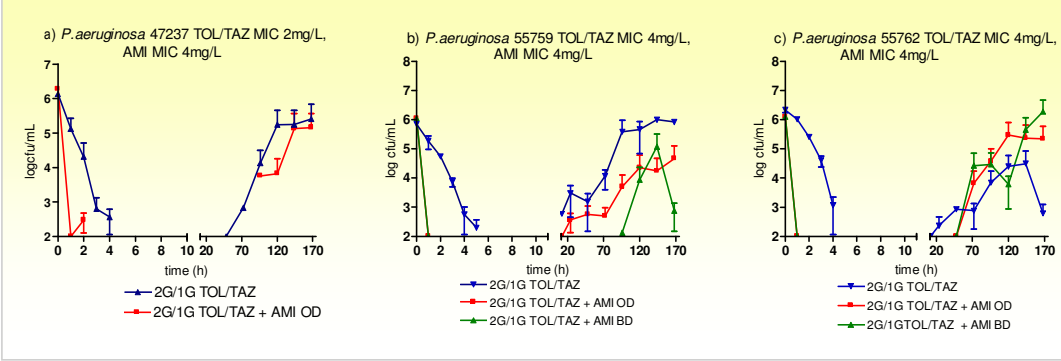
- Ceftolozane/tazobactam (TOZ/TAZ) has been approved for clinical use in Europe and is noteworthy for its potency in vitro against PA - including many multi-drug resistant strains.
- The debate of combination versus monotherapy has not been fully elucidated though combination antimicrobial chemotherapy 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 (Cmax 112/32mg/L; TOL t½ 2.5h, TAZ t½ 1h) alone and plus AMI 15mg/kg (OD Cmax 50mg/L; BD Cmax 25mg/L; t½ 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 10^6 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 $AUBKC_{24}$ and $AUBKC_{168}$ 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

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

Bristol Centre for Antimicrobial Research and Evaluation

North Bristol NHS Trust