Repurposing of the tamoxifen metabolites in combination with tigecycline against Gram-negative bacteria

Arbeloa Gómez, Laura; Vila Domínguez, Andrea; Jiménez Mejías, Manuel Enrique; Smani, Younes*.

Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventina. Hopital Universitario Virgen del Rocío. Instituto de Biomedicina de Sevilla. • Avda. Manuel Siurot, s/n • 41013 Sevilla

INTRODUCTION AND PURPOSE

Emerging of multidrug-resistant (MDR) bacteria represent a matter of grave urgency and a problem for public health. Due to the emergence of resistance new strategic antimicrobial therapeutic approaches are proposed, such as drug repurposing. Tamoxifen was previously reported to present efficacy against MDR *Acinetobacter baumannii* and *Escherichia coli* [1]. The objective of this study was to evaluate *in vitro* the activity of the three major metabolites of tamoxifen (MET): N-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen, in combination with tigecycline against colistin-susceptible (COL-S) and colistin-resistant (COL-R*) A. baumannii* and *E. coli*.

METHODS

A collection of Gram-negative bacteria [8 COL-R and 1 COL-S *A. baumannii*, 17 COL-R and 1 COL-S *E. coli*] was used [2]. All strains were grown in Mueller-Hinton Broth (MHB) at 37°C.

- **Microdilution and checkerboard assays:** Minimal Inhibitory Concentration (MIC) was determined for all strains by using microdilution assay. In order to determine the synergy between a mix of the three MET (MIX) and tigecycline (TIGE) checkerboard assay was performed.
- **Macrodilution assays:** Time-kill curve assays were performed at 1xMIC TIGE, 1xMIC MIX and 1xMIC TIGE+MIX with starting inoculum of 1x10^6 colony-forming units (cfu)/mL.

RESULTS

1. Microdilution and checkerboard assays

Table 1. MIC determination of MET and tigecycline alone or in combination against Col-S and Col-R *A. baumannii* and *E. coli*.

Strain	MIC (mg/L)			FICI	Fold change in TIGE MIC
	TIGE	MIX	TIGE in the presence of MIX		
Col-S					
ATCC 17978	0.25	32	0.015	0.56	16.7
ATCC 25922	0.5	16	0.25	0.3625	3.33
Col-R					
A. baumannii #1	8	32	4	0.75	2
A. baumannii #10	8	32	8	1.25	1
A. baumannii #14	8	32	1	0.375	8
A. baumannii #16	4	32	2	0.625	2
A. baumannii #17	4	16	2	1	2
A. baumannii #19	4	32	2	0.75	2
A. baumannii #99	8	16	2	0.75	4
A. baumannii CR17	4	16	1	0.75	4
E. coli CRA 3	1	16	0.25	0.5	4
E. coli CRA 5	1	8	0.25	0.75	4
E. coli CRA 7	1	16	0.5	1	2
E. coli CRA 8	0.5	16	0.25	1.5	2
E. coli CRA 17	1	8	0.25	1.25	4
E. coli CRA 20	1	32	0.5	0.75	2
E. coli CRA 32	0.5	8	0.25	0.75	2
E. coli CRA 57	0.5	8	0.06	0.37	8.3
E. coli CRA 59	1	8	0.25	0.5	4
E. coli CRA 62	1	8	0.25	0.75	4
E. coli CRA 63	1	4	0.5	1	2
E. coli CRA 69	1	8	0.125	0.625	8
E. coli CRA 71	0.25	8	0.015	0.56	16.7
E. coli CRA 72	0.125	8	0.125	1.5	1
E. coli CRA 75	1	8	0.125	0.625	8
E. coli CRA 76	1	32	0.125	0.25	8
E. coli MCR-1 +	0.5	32	0.125	0.75	4

2. Time-kill curve assays

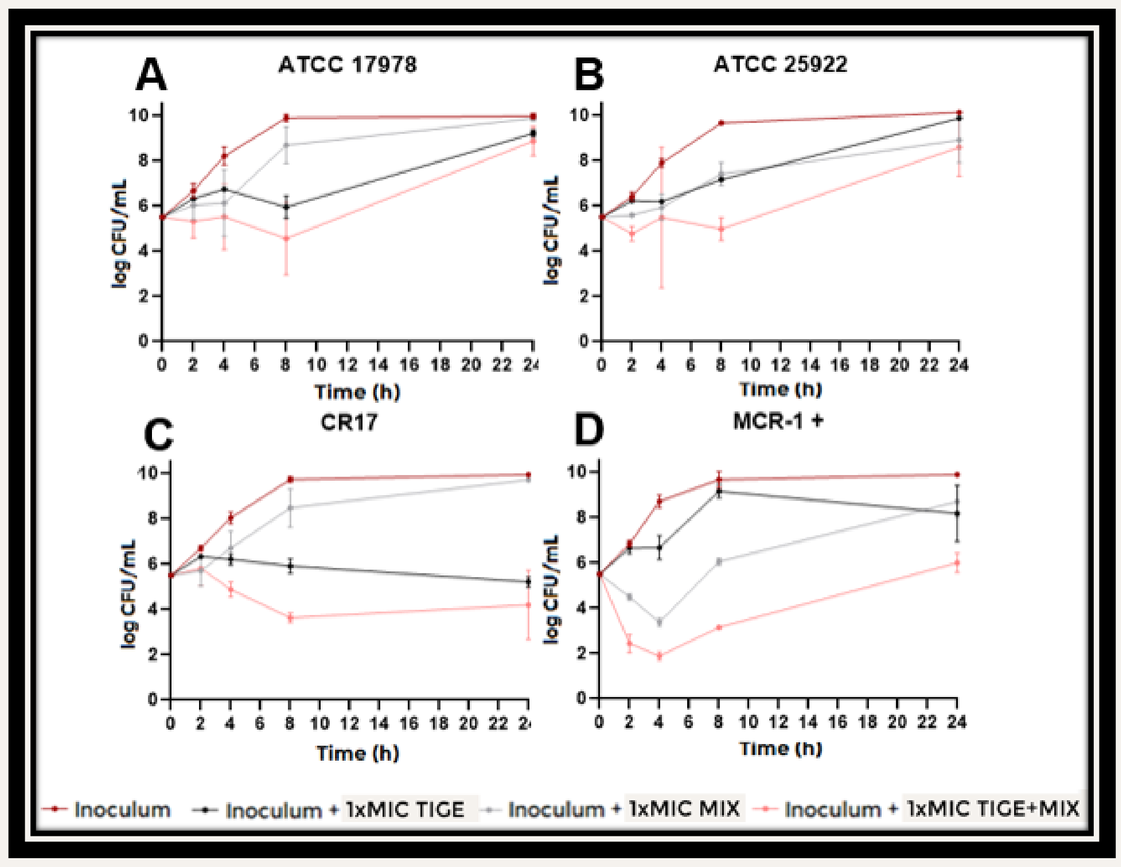

Figure 1. Time-kill curves of COL-S (ATCC 17978 [A], ATCC 25922 [B]) and COL-R (CR17 [C], MCR-1 + [D]) *A. baumannii* and *E. coli* strains in absence and presence of MET and tigecycline alone and in combination during 24 h.

CONCLUSIONS

Tamoxifen metabolites in combination with tigecycline showed *in vitro* synergetic effect against COL-R *A. baumannii* and *E. coli* strains, representing a potential new alternative for treatment of infections caused by MDR *A. baumannii* and *E. coli*.

REFERENCES

[1] Miró Canturri, A., Ayerbe-Algaba, R., Toro, R. D., Pachón, J., & Smani, Y. (2020). Tamoxifen repurposing to combat infections by multidrug-resistant Gram-negativa bacilli. bioRxiv 2020.03.30.017475

[2] Molina-Panadero, I. (2021). Uso de fármacos anticancerígenos como estrategia antimicrobiana frente a las bacterias gramnegativas. Trabajo Fin de Máster. Universidad Pablo de Olavide, Sevilla.