

P0296

Poster Session I

New therapeutic alternatives

ACTIVITY OF BAL30072 ALONE AND IN COMBINATION WITH CARBAPENEMS AGAINST GRAM-NEGATIVE BACTERIA

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**Objectives:** BAL30072 is a novel siderophore sulfactam, currently in early clinical development, that has previously been shown to have good *in vitro* activity against multi-resistant Gram-negative bacteria. This study investigated the effect of combining BAL30072 with carbapenems.

**Methods:** The minimum inhibitory concentration (MIC) for BAL30072 alone and in combination with doripenem, meropenem or imipenem at 1:1, 2:1 and 4:1 (carbapenem: BAL30072) ratio was determined by CLSI broth microdilution methodology [CLSI M07-A9] against 320 recent clinical isolates of *Enterobacteriaceae* (125), *Pseudomonas aeruginosa* (100) and *Acinetobacter baumannii* (95) enriched for carbapenem resistance (~80% resistant). The *Enterobacteriaceae* included *Citrobacter amalonaticus* (1), *C. farmeri* (1), *C. freundii* (1), *Enterobacter aerogenes* (18), *E. cloacae* (30), *Escherichia coli* (8), *Klebsiella oxytoca* (5), *K. pneumoniae* (55), *Morganella morganii* (2), *Proteus mirabilis* (1) and *Serratia marcescens* (3). CLSI breakpoints were used to determine carbapenem susceptibility [M100-S23]. However, doripenem breakpoints are not provided for *A. baumannii* so the same breakpoints as for meropenem and imipenem were used. Chequerboard studies with BAL30072 in combination with the carbapenems were also carried out on a sub-set of 50 isolates and fractional inhibitory concentration indices (FICI) were calculated.

**Results:** BAL30072 MIC<sub>50/90</sub> values were 4/>32, 1/16 and 2/32 mg/L against *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii*, respectively. Doripenem MIC<sub>50/90</sub> values were 4/>32, 8/>32 and >32/>32 mg/L, respectively. Meropenem MIC<sub>50/90</sub> values were 4/>32, 16/>32 and >32/>32 mg/L, respectively. Imipenem MIC<sub>50/90</sub> values were 8/>32, 32/>32 and >32/>32 mg/L, respectively. Combination of a carbapenem with BAL30072 increased carbapenem susceptibility as shown in the Table below. Chequerboard experiments indicated ~26% of isolates showed synergy (average FICI ≤ 0.5) between BAL30072 and carbapenems and only a very small proportion (~3%) showed antagonism (average FICI >4). The remainder (~71%) showed an indifferent interaction.

Percent Carbapenem susceptible		Carbapenem: BAL30072 ratio			
Organism	Carbapenem	No BAL	1:1	2:1	4:1
<i>A. baumannii</i>	Doripenem	14.7	77.9	72.6	56.8
	Imipenem	13.7	73.7	65.3	37.9
	Meropenem	13.7	74.7	67.4	41.1
<i>P. aeruginosa</i>	Doripenem	20	79	68	45
	Imipenem	20	80	58	37
	Meropenem	22	76	63	43
<i>Enterobacteriaceae</i>	Doripenem	33.6	64	56.8	53.6
	Imipenem	26.4	57.6	49.6	33.9
	Meropenem	30.4	60.8	52	48.8

**Conclusions:** This study showed that combining a carbapenem with BAL30072 at a fixed ratio of 1:1 restored carbapenem susceptibility to ~75% of *A. baumannii*, ~78% of *P. aeruginosa* and ~60% of *Enterobacteriaceae*. A lesser effect was seen at 2:1 and 4:1. Classical chequerboard FICI data also confirmed a positive interaction between BAL30072 and carbapenems. These data suggest that there is a therapeutic advantage to be obtained by combining BAL30072 with carbapenems.