Oritavancin does not antagonise the activity of common antibacterial agents for Gram-positive and Gram-negative infections

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Objectives

Oritavancin has completed Phase 3 development as a single 1200 mg dose for treatment of complicated skin and soft-tissue infections caused by Gram-positive pathogens. The marketing authorisation application is currently under review by the European Medicines Agency. To investigate the pharmacodynamic interaction between oritavancin and other antibacterial agents that may be used concurrently in patients, the well-described in vitro checkerboard assay was used to evaluate antagonism, indifference or synergy of oritavancin combinations against Gram-positive and Gram-negative isolates.

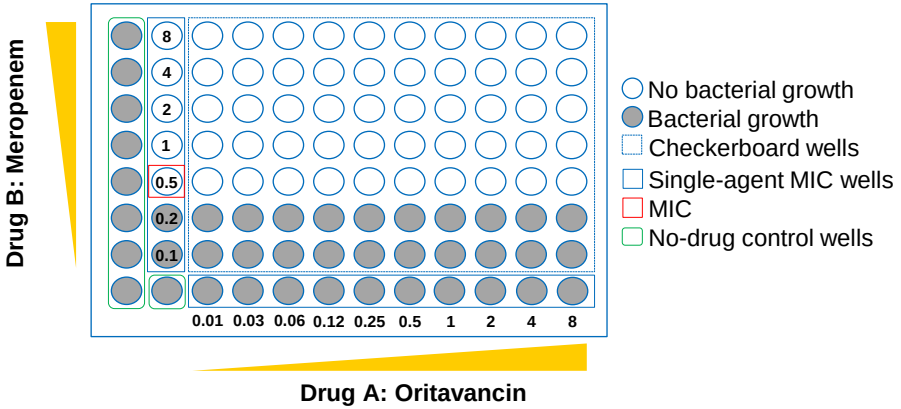
Materials and Methods

- The quality-control (QC) strains *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used. As per CLSI M07-A9 guidelines, testing was performed in cation-adjusted Mueller-Hinton broth containing 0.002% polysorbate-80 (for oritavancin) or with other indicated supplements (for other agents).
- The interaction of oritavancin with representatives of nine classes of antibacterial agents was assessed by the checkerboard assay (Figure 1). Single-agent MICs (solid outline) and MICs obtained in combination in the checkerboard wells (dashed outline) were used to calculate the fractional inhibitory concentration indices (FICi) as follows:

$$\text{FICi} = \frac{\text{MIC of Drug A}}{\text{MIC of Drug A in combination}} + \frac{\text{MIC of Drug B}}{\text{MIC of Drug B in combination}}$$

- The FICi were scored as follows: FICi ≤0.5, synergy; 0.5> FICi ≤4, indifference (I); and FICi >4, antagonism (AAC, 2014 Instructions to authors).

Figure 1: Illustration of checkerboard assay results exemplifying the in vitro activity of oritavancin and meropenem against *P. aeruginosa* ATCC 27853. The MIC for meropenem is 0.5 mg/l (red square) whereas the MIC for oritavancin is >8 mg/l. No change in MIC for either agent was observed in combination.



Results

- Oritavancin MICs were 0.06 mg/l for *S. aureus* ATCC 29213, 0.015 mg/l for *E. faecalis* ATCC 29212 and were within QC ranges (CLSI M100-S24). As expected, oritavancin did not exhibit an MIC against the two Gram-negative isolates within the range of concentrations tested (0.015-8 mg/l).
- The single-agent MICs for each agent used in combination with oritavancin were within the specified QC ranges (CLSI M100-S24) for the four organisms.
- All tested oritavancin combinations exhibited indifference (0.5> FICi ≤4) against the Gram-positive and Gram-negative isolates (table).

Isolates	FICi interpretation of oritavancin combinations												
	Ampicillin	*Azithromycin*	*Aztreonam*	*Cefepime*	*Daptomycin*	*Gentamicin*	*Levofloxacin*	*Linezolid*	*Meropenem*	*Minocycline*	*Piperacillin*	*Teicoplanin*	*Vancomycin*
Gram-positive													
S. aureus	I	I	-	-	I	I	I	I	-	I	-	I	I
E. faecalis	I	-	-	-	I	I	I	I	-	I	-	I	I
Gram-negative													
E. coli	I	-	-	I	-	I	I	-	I	I	-	-	-
P. aeruginosa	-	-	I	I	-	I	I	-	I	-	I	-	-

-, not tested; I, indifference (0.5> FICi ≤4)

Conclusions

Oritavancin does not antagonise the *in vitro* activity of common Gram-positive and Gram-negative antibacterial agents that may be used concurrently in patients.

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