Pharmacodynamic evaluation of the Intracellular activity of CEM-101, a novel fluoroketolide, towards *Staphylococcus aureus*, *Listeria monocytogenes*, and *Legionella pneumophila* in human THP-1 macrophages

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Background:

Macrolides accumulate in eukaryotic cells and are considered advantageous for the treatment of intracellular infections. Ketolides recover activity against erythromycin-resistant organisms. CEM-101, a novel fluoroketolide with a 11,12 carbamate-butyl-[1,2,3]-triazolyl-phenylamino sidechain, demonstrates enhanced potency compared to telithromycin. We have assessed the cellular accumulation and intracellular activity of CEM-101 towards the intracellular forms of *Staphylococcus aureus*, *Listeria monocytogenes*, and *Legionella pneumophila* in comparison with azithromycin (AZM), clarithromycin (CLR), and telithromycin (TEL).

Methods:

All experiments were performed with the human macrophage cell line THP-1. Drug accumulation was measured using bioassay. Intracellular activity measured over time and concentration by following the change in cell-associated CFU compared to post-phagocytosis levels (see details in JAC 2004,54:288-9 [*L. monocytogenes* – strain EGD]; AAC 2006, 50:841-51 [*S. aureus*; strain ATCC 25923]; similar protocol for *L. pneumophila* [strain ATCC 33153]).

Results:

Uptake uptake of CEM-101 was linear over time, reaching accumulation levels about 375-fold within 24 h (AZM, 160 x, CLR, 30 x, TEL, 21 x). Accumulation was suppressed by acid pH or addition of the proton ionophore monensin, but not modified by verapamil or gemfibrozil (preferential inhibitors of P-gp and MRP, respectively). MIC and intracellular activities (developed in a concentration-dependent fashion [Hill equation] are shown in Table.

	CEM-101			AZM			CLR			TEL		
	MIC [a]	Cs [b]	E_{max} [c]	MIC [a]	Cs [b]	E_{max} [c]	MIC [a]	Cs [b]	E_{max} [c]	MIC [a]	Cs [b]	E_{max} [c]
S.a.	0.06	0.022	-0.86	0.5	> 50	0.04	0.5	0.84	-0.18	0.25	0.63	-0.29
L. m.	0.004	0.11	-0.66	1	11.6	-0.81						
L. p.	0.004	0.018	-1.03	0.016	2.90	-0.83	0.007	0.12	-0.71	0.007	0.06	-0.63

[a] mg/L; [b] static concentration (mg/L) at 24 h; [c] $\Delta \log_{10}$ CFU at 24 h compared to the post-phagocytosis inoculum

CEM-101 caused slightly higher or similar maximal efficacy compared to AZM, CLR or TEL, but considerably higher relative potency (lower EC_{50} and C_s), in relation to its lower MIC when expressed on a mass basis (differences in EC_{50} and C_s between drugs largely vanish if data are expressed as multiples of the MIC).

Conclusions:

CEM-101 is a ketolide with enhanced cellular accumulation. It shows improved intracellular potency (on a weight basis) in comparison with AZM, CLR and TEL in this in vitro model (mainly due to its larger intrinsic activity [lower MICs] against target organisms). This should lead to enhanced in vivo potency if using doses similar to those of the comparators tested here.