Antimicrobial Characterization of CEM-101: Single Step, Selection by Passaging and Inducible Resistances

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Background:

CEM-101, an orally administered macrolide-ketolide for respiratory tract infections (RTI), has potent activity against Gram-positive pathogens, *H. influenzae* and *M. catarrhalis*. To further define resistance (R) potential to CEM-101, 3 studies determined single step mutational rates, passaging selection and R induction by erythromycin (ERY).

Methods:

Single step R used 1 *S. aureus* (SA), 1 *E. faecalis*, 2 *S. pneumoniae* (SPN), exposed to 4X, 8X and 16X MIC of CEM-101. Selection by passaging (7 days), used subinhibitory concentrations of CEM-101 and 3 comparators (azithromycin, clarithromycin, telithromycin [TEL]) with 18 strains including SA, CA-MRSA USA300, enterococci and SPN with various ERY-R patterns. Induction experiments with D-test (ERY inducer + CEM-101, clindamycin [CC] and TEL) tested 81 ERY-R, CC-S strains (17 spp).

Results:

In R selection passaging, no significant variation was observed for 8 strains (44.4%; 4 spp). The remaining 10 strains exhibited modest CEM-101 MIC increases of 4-(7 strains) or 8-fold (3) without reversion of the MIC in drug-free media. R-selection during passaging was less for CEM-101 compared to other agents evaluated. No CEM-101 single-step mutations were observed at 4X, 8X or 16X CEM-101 MIC using inocula of 6.5×10^8 (SPN) to 6.0×10^9 (SA; see Table). Four patterns of ERY induction of CEM-101/TEL/CC-R were noted as follows: +/+/+ (39; 10 spp, *erm* A, B and C); -/+/+ (7; 2 spp, *erm* A); +/+/- (10; 4 spp, *msr* A) and -/-/- (25; 10 spp, none).

Table. Results of the single-step mutation studies

Organism	Single step mutation rate[a]
E. faecalis ATCC 29212	$<4.0 \times 10^{-9}$
S. aureus ATCC 29213	$<6.0 \times 10^{-9}$
S. pneumoniae 063-1085A (wild-type)	$<1.4 \times 10^{-9}$
S. pneumoniae 075-241B (*erm*B)	$<6.5 \times 10^{-8}$

a. Strains were exposed at 4x, 8x, and 16x CEM-101 MIC.

Conclusions:

CEM-101 propensity for R was considered low for single step at $< 10^{-8}$ or 10^{-9}; infrequent by selection (passaging) and induction was comparable to CC but less than TEL. CEM-101 warrants further consideration as a RTI treatment agent.