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Paper Poster Session
New antibiotics against Gram-negative bacteria

S-649266, a novel siderophore cephalosporin: in vitro combination effect of S-649266 and other antibiotics against Gram-negative bacteria

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Background: The increase of carbapenem-resistant and multi-drug resistant (MDR) Gram-negative bacteria has become a serious healthcare problem all over the world. However, the current available therapeutic option for infections caused by MDR Gram-negative bacteria is scarce or limited to polypeptides and tetracycline antibiotic such as colistin and tigecycline. S-649266, catechol-substituted siderophore cephalosporin, showed potent *in vitro* activity against Gram-negative bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* including carbapenem-resistant *A. baumannii* and metallo β-lactamase-producing *P. aeruginosa*. Combination therapy is often used for the treatment of the MDR Gram-negative bacterial infections. It is important to evaluate the combination effect of the compound with the marketed antibiotics which has the possibility to be used for the combination therapy. In this study, *in vitro* combination activities of S-649466 with other antibiotics were evaluated against Gram-negative bacteria.

Material/methods: Combination effects of S-649266 and other antibiotics were evaluated by checkerboard methods and time-kill studies using iron-deficient medium, which was modified by the treatment with Chelex resin. A total of 82 meropenem (MEPM) non-susceptible strains which were isolated from the US based surveillance study conducted in 2012. It included 41 Enterobacteriaceae (1 *Escherichia coli*, 38 *Klebsiella pneumoniae*, 1 *Enterobacter cloacae*, and 1 *Citrobacter freundii*), 20 *P. aeruginosa*, and 21 *Acinetobacter* species, all of which produced KPC carbapenemase. Tested antibiotics for the combination were MEPM, amikacin (AMK), and colistin (CL). In checkerboard studies, the lowest FIC index was used to determine the combination effect which was categorized into three groups: synergy, indifference, and antagonism. In the time-kill studies, combination of 1/2-MIC concentration of S-649266 with either of 1/2-MIC concentration of MEPM, AMK, or CPFX were evaluated against KPC-producing *K. pneumoniae* KAM, VIM-10-producing MDR-*P. aeruginosa* NCTC13437, and MDR-*A. baumannii* 1485247.

Results: The combination of S-649266 and MEPM showed synergistic effect in 25.6% of Enterobacteriaceae, 42.9% of *Acinetobacter spp.*, and 11.1% of *P. aeruginosa*. On the other hand, when combined with AMK or CPFX, synergistic effects were observed in 9.5% to 15.0% of either Enterobacteriaceae or *Acinetobacter* spp but no strains in *P. aeruginosa*. None of the combinations of S-649266 with the reference agents (MEPM, AMK and CL) showed antagonism. Against all 3 test strains in the time-kill studies, the synergistic effects were observed when combined with MEPM or AMK that the number of viable cells 24 hours after treatment were decreased by more than 3-$\log_{10}$ compared to each antibiotic treatment. The significant synergistic effect between S-649266 and CPFX was observed only against *A. baumannii* 1485247.

Conclusions: The combinations of S-649266 and other antibiotics showed synergistic effects and did not show antagonism, suggesting the potential use of S-649266 combined with other antibiotics for the treatment of MDR Gram-negative bacterial infections.