Pharmacodynamic evaluation of AA101, a novel extended-spectrum beta-lactamase inhibitor (BLI), with piperacillin against ESBL producers in a hollow fiber infection model

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Abstract

Background: AA101 is a novel extended-spectrum BLI with potent activity against diverse beta-lactamases. Its activity against Pseudomonas aeruginosa and Enterobacteriaceae has been demonstrated in vitro and in vivo, with optimal PK/PD parameters for achieving efficacious concentrations for killing of the organism. The pharmacodynamic driver for AA101 activity against ESBL-producing K. pneumoniae is yet to be determined by dose fractionation studies.

Methods: Methods: AA101 and reference beta-lactam antibiotics (BLAs) were evaluated in vitro against a panel of ESBL-producing strains isolated from clinical infections. Class-specific susceptibility breakpoints were used to determine if ESBL-producing strains were susceptible or resistant to an agent. Tests were performed using standard CLSI broth microdilution procedures.

Results: Test results indicated that AA101 is an investigational beta-lactamase inhibitor with broader activity against class A, class C beta-lactamases and ESBL producers. MICs and minimum bactericidal concentrations were determined for each isolate. AA101 and PIP had similar MICs, Cmax/MIC and AUC/MIC values for all ESBL-producing strains tested. For K. pneumoniae, the PK/PD targets for achieving efficacious concentrations for killing of the organism were defined as Cmax/MIC ≥ 32 and AUC/MIC ≥ 512 mg·h/L.

Conclusions: AA101 is an investigational beta-lactamase inhibitor with broader activity against class A, class C beta-lactamases and ESBL producers. MICs and minimum bactericidal concentrations were determined for each isolate. AA101 and PIP had similar MICs, Cmax/MIC and AUC/MIC values for all ESBL-producing strains tested. For K. pneumoniae, the PK/PD targets for achieving efficacious concentrations for killing of the organism were defined as Cmax/MIC ≥ 32 and AUC/MIC ≥ 512 mg·h/L.

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