Abstract

Background: GSK2251052 (formerly AN3365), a novel boron-containing leucyl-tRNA synthetase inhibitor with in vitro activity against Pseudomonas aeruginosa and multidrug-resistant Enterobacteriaceae, is currently being developed for the treatment of serious Gram-negative bacterial infections. The in vitro activity of GSK2251052 was assessed against a large global collection of recent P. aeruginosa isolates. Methods: The in vitro activity of GSK2251052 and 9 comparators was assessed by broth microdilution (CLSI M7-A8) against 2,008 isolates of P. aeruginosa. All study isolates were from hospital-associated isolates, with more than 30% of the isolates from severe infections. Breakpoints were defined as susceptible ≤0.25 µg/mL, intermediate 0.5-4 µg/mL, and resistant >4 µg/mL. Results: The in vitro activity of GSK2251052 was compared to 9 comparators, including meropenem, imipenem, ceftazidime, cefepime, ticarcillin-clavulanate, and amikacin. All comparators had susceptible MICs ranging from 0.12 to 0.25 µg/mL, whereas GSK2251052 showed increased activity against P. aeruginosa with MICs ranging from 0.06 to 0.5 µg/mL. Conclusions: This study demonstrates the in vitro activity of GSK2251052 against a large global collection of P. aeruginosa isolates with an MIC of 0.5 µg/mL, which suggests that GSK2251052 is a potential alternative treatment against P. aeruginosa.

Methods

Organisms All study organisms were clinically isolated previously collected from a diverse global population and frozen at -70 °C in the years 2009-2010. All P. aeruginosa were hospital-associated isolates from a multi-national geographic population. Each isolate was a unique, non-replicate isolate, with no more than one isolate per patient represented. There were 2,008 P. aeruginosa isolates collected from 270 sites in 55 countries: North America (n=801), Europe (n=393), and other International regions (n=514).

Antimicrobial Susceptibility Testing

Minimal inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines in document M7-A8 [2]. Interpretive criteria were applied as defined in CLSI document M100-S21, where available [3]. Mueller Hinton broth was used as the test broth, and testing was performed using custom panels prepared fresh on the same day of testing. Quality control (QC) testing was performed each day as specified by CLSI using P. aeruginosa ATCC 27853 [3].

Results

Table 1. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 2008 Isolates of P. aeruginosa from a Global Population.

Table 2. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 581 Isolates of P. aeruginosa from a Global Population.

Table 3. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 2011 Isolates of P. aeruginosa from a Global Population.

Table 4. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 514 Isolates of P. aeruginosa from an International Population other than North America and Europe.

Conclusions

• GSK2251052 demonstrated in vitro activity when tested against a large global population of recent clinical P. aeruginosa isolates. Greater than 92% of all isolates tested had GSK2251052 MICs of ≤4 µg/mL.

• GSK2251052 maintained MIC50 values of 4 µg/mL in all regional populations of P. aeruginosa that were 2- to 32-fold lower than all other antibiotics tested against the global isolates including colistin (MIC50 >8 µg/mL) amikacin (MIC50 16 µg/mL), levofloxacin (MIC50 >8 µg/mL) and meropenem (MIC50 16 µg/mL).

These in vitro data suggest that further development of GSK2251052 as a possible alternative treatment against infections caused by P. aeruginosa is warranted.

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