In vitro Antibacterial Activity and in vivo Efficacy of Sulbactam-Durlobactam (ETX2514) against Pathogenic Burkholderia Species

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Abstract

Background

The genus Burkholderia contains several pathogenic species with distinct pathogenicities, including Burkholderia pseudomallei (Bp), the biothreat pathogen responsible for melioidosis, and Burkholderia mallei (Bm), the agent of glanders. B. pseudomallei, such as cellulitis and meningitis, are important as potential bioterrorism-causing options for these infections. However, there is no standard treatment for B. pseudomallei, which is primarily mediated by multiple types of β-lactamases in these classes, which is a growing concern. Concerning B. mallei infection, an effective β-lactamase inhibitor with broad spectrum activity against Anthel critique C. A. D. and E. aspergillaceae is needed. Additionally, Sulbactam (SUL) and Durlobactam (DUR) have in vitro antibacterial activity against a limited number of species, including Burkholderia spp. SUL-DUR is currently in Phase 3 clinical trials for the treatment of carbapenem-resistant infections caused by Burkholderia spp. In this study, SUL-DUR was evaluated in combination with Bp and Bm, as well as in vivo efficacy in a preclinical model of melioidosis.

Key Features of Sulbactam-Durlobactam

- Sulbactam-durlobactam is a β-lactam-β-lactamase inhibitor (SBL/BLI) combination which is efficacious against resistant Acinetobacter baumannii carbapenemase complex (ABC) organisms.

- Durlobactam (ETX2514) is a novel diazabicyclooctane BSL2 with best-in-class broad spectrum activity against class A, C, and D β-lactamases.

- Subclam in an approved BSL2 with intrinsic antibacterial activity that is limited to only a few bacterial species This activity in Acinetobacter baumannii (Ab), which is responsible for nosocomial infections, is due to inhibition of PBP2, an enzyme required for cell wall biosynthesis.

Study Design

All studies were performed under a CRADA with Entasis Therapeutics by the Therapeutics Discovery Group, Division of Countermeasures at USAMRMC, and were carried out in accordance with accepted ethical standards for this type of work, which is early stage research. No adverse events occurred during the study. Both in vitro and in vivo testing studies followed CLSI guidelines, including testing control compounds against QC organisms. SUL-DUR was assayed by twofold dilution of subsaturation in the presence of a fixed concentration of 4 µg/mL durlobactam.

Subclam-durlobactam and comparator compounds were evaluated in in vivo efficacy vs. Burkholderia pseudomallei in an acute murine model of melioidosis using the sentient strain KM9423 (MIC = 1 µg/mL). This strain, which was isolated from a lung abscess, was selected because it is one of the most commonly used isolates in preclinical models of melioidosis.

Durlobactam is able to cross the blood-brain barrier and 65% of the brain tissue of mice with a 100 mg/kg dose. This could be of clinical importance in the treatment of patients with melioidosis and in the treatment of patients with brain abscesses.

Conclusions

- Durlobactam restored subclam antibacterial activity against a collection of B. mallei and B. pseudomallei isolates.

- The subclam-durlobactam combination was efficacious in a murine model of melioidosis.

- Subclam-durlobactam was more efficacious over time in this model than either comparator agent, with 90% vs. 60% survival at day 35 and 60% vs. 40% survival at day 45 for SUL-DUR vs. comparator, respectively. These data support further evaluation of the subclam-durlobactam combination for the treatment of infections caused by pathogenic Burkholderia species.

References

8. Burkholderia genome database (www.burkholderia.org)

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