ABSTRACT

Background: Antibiotics can damage the gut microbiome leading to dysbiosis, which is comprised of perturbations to the normal composition of the gut microbiome. SYN-004 (ribaxamase) is a clinical-stage beta-lactamase formed in Bacillus subtilis that cleaves beta-lactam antibiotics, such as extended spectrum beta-lactam antibiotics (ESBLs), and reduces them to their active component in the GI tract to prevent the gut microbiome. Ribaxamase was evaluated in a phase 2b clinical study that met primary endpoint of significantly reducing C. difficile infection in patients treated with IV ceftaroline and demonstrated protection of the gut microbiome with reduced emergence of antibiotic-resistant C. difficile including ribaxamase-sensitive but not ribaxamase-resistant strains. A subsequent study evaluated the beta-lactamase-mediated microbiome protection and expanded to include oral and carbapenem antibiotics.

Methods: For use with oral beta-lactams, a ribaxamase formulation, SYN-004, was designed for release in the lower small intestine, distal to the site of antibiotic absorption. For use with IV ceftaroline, SYN-006 (a novel metallo-beta-lactamase, was formulated for oral delivery: SYN-007 (10 mg, P.O.), TID) was evaluated in dogs treated with oral ceftaroline (30 mg/kg, IV, SID) for 4 days. Serum antibiotic levels were measured and fecal DNA whole genome shotgun sequence analyses were performed.

Results: In dogs and pigs, systemic antibiotic levels were significantly different across antibiotic formulations. SYN-007 or SYN-006. Fecal metagenomics analyses demonstrated that oral amoxicillin and IV etepame in pigs resulted in significant changes to the gut microbiome. SYN-007 and SYN-006 attenuated microbiome dysbiosis.

Conclusion: Ribaxamase, SYN-007, and SYN-006 have the potential to protect human gut microbiota from antibiotic-mediated collateral damage and to mitigate emergence and spread of antibiotic-resistant pathogens. SYN-007 or SYN-006 with oral beta-lactams or SYN-006 with IV beta-lactam antibiotics designed to preserve the gut microbiota by degrading medical antibiotics in the GI tract. A phase 2b study met its primary endpoint of significantly reducing C. difficile infection (CDI) in patients treated with ceftaroline and ribaxamase.

BACKGROUND

IV beta-lactam antibiotics, including cephalosporins, are aerocined via the bile into the intestine where they can disrupt the intestinal microbiota and potentially lead to the outgrowth of pathogens like Clostridioides difficile. SYN-006 has a novel enteric coating that effectively protects SYN-006 from systemic antibiotic absorption during the small intestine, 2 hrs at pH 5.5, conditions of the upper small intestine, and 4 hrs at pH 7.1, conditions of the lower small intestine/colostrum. For SYN-006, capsules were held in 0.1 N HCl for 2 hrs, and pH 6.5 for 4 hrs.

RESULTS

Enteric Coated Beta-Lactamase Formulations

SYN-007 is a dual dose 16 doses of oral amoxicillin (PO) + SYN-007 (TID). Ribaxame was collected after the first and last doses. Pigs received 4 doses of IV etepame (SID) + SYN-006 (QID), starting the day before antibiotic administration. Blood was collected day 2, day 3, after 4 doses of etepame. Serum was evaluated for antibiotic levels.

For SYN-007, amoxicillin serum levels were not significantly different in the presence of SYN-007 indicating that SYN-007 did not interfere with systemic absorption. For SYN-006, etepame serum levels were not significantly different in the presence of SYN-006, indicating that SYN-006 did not interfere with etepame blood levels.

SYN-007 and SYN-006 Protect the Gut Microbiome

For microbiome analyses, fecal DNA, collected prior to and after the last antibiotic (-5/-6) or SYN-007 (-3/-4) doses, were subjected to whole genome shotgun sequence analyses using CosmosID, Inc. metagenomics software.

DISCUSSIONS

SYN-007 and SYN-006 have the potential to expand microbiome protection to oral, as well as IV beta-lactam antibiotics, and all classes of beta-lactams including penicillins, cephalosporins, and carbapenems.

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