Background: VRE infections are a worldwide problem due to increasing prevalence, lack of effective therapies and modest impact of infection control policies. A leading risk factor for VRE is prior antibiotic use, which disrupts the healthy microbiome. In a study of patients with recurrent Clostridium difficile infection (CDI), we assessed the prevalence of VRE before and after administration of SER-109, a novel microbiome-based agent for the prevention of CDI.

Methods: SER-109 is an ecology of bacterial spores enriched from stool of healthy, screened donors. The efficacy and safety of SER-109 was evaluated for prevention of CDI in an open-label study of 30 outpatients with episodes of CDI in the past 12 months who had responded to standard antibiotics. During 8 weeks following SER-109, 26/30 patients (87%) had no transient diarrhea and 25/30 patients (83%) had no further episodes of CDI. The primary clinical endpoint was prevention of CDI (>3 loose C. difficile-positive stools in 24 hours). The diversity of the GI microbiome was assessed pre-treatment with SER-109 and at weeks 1, 2, 4, 8, and 24.

Results: Of the 30 patients (67% female, mean age 66.5 years), 25 (83.3%) had been treated with vancomycin for CDI. At baseline, 8 of 28 patients (28.6%) had VRE (e. E. fecium) and in all 8 VRE titers decreased by 2-6 logs (to below the limit of detection) after 8 weeks completing therapy for CDI. The primary clinical endpoint was prevention of CDI (>3 loose C. difficile-positive stools in 24 hours). The diversity of the GI microbiome was assessed pre-treatment with SER-109 and at weeks 1, 2, 4, 8, and 24. Titers (CFU/g) of vancomycin-resistant Enterococcus were determined by plating on Enterococcus agar plus 8 μg/ml vancomycin. To positively identify isolates as VRE, colonies were purified, and MICs and species identity were determined via Vitek 2 cards (AST-GP07) and GP, respectively.

Methods

In an open-label phase 1b/2 clinical study (SERES-001), 30 patients with a history of CDI were enrolled in two different cohorts in two centers. Patients were given SER-109 oral capsules 48 hours after completing therapy for CDI. The primary clinical endpoint was prevention of CDI (>3 loose C. difficile-positive stools in 24 hours). The diversity of the GI microbiome was assessed pre-treatment with SER-109 and at weeks 1, 2, 4, 8, and 24. Titers (CFU/g) of vancomycin-resistant Enterococcus were determined by plating on Enterococcus agar plus 8 μg/ml vancomycin. To positively identify isolates as VRE, colonies were purified, and MICs and species identity were determined via Vitek 2 cards (AST-GP07) and GP, respectively.

Titers of VRE (CFU/g) were significantly reduced at week 8 post-treatment with SER-109 compared with baseline (p < 0.01). Treatment with SER-109 led to a significant increase in diversity compared with pre-treatment (p < 0.0001). The diversity of the gut microbiome of patients increased post-treatment with SER-109.

Conclusion: VRE colonization was commonly observed among outpatients with CDI. SER-109, an ecology of bacterial spores enriched from stool of healthy, screened donors, reduced the prevalence of VRE and showed significant increase in gut microbiome diversity post-treatment with SER-109.

Abstract

Effect of SER-109 on VRE carriage and gut microbiome diversity

Methods

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Overview of SERES-001 Recurrent CDI Trial Results

Patient Demographics

Patients enrolled in the SERES-001 study must have experienced clinical improvement on their most recent antibiotic course of therapy. For twenty-three of the 30 patients, based on genomics analyses and coded to potential pathobionts within the microbiome to defend against colonization by potential pathogens.

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Conclusion: VRE colonization was commonly observed among outpatients with CDI. SER-109, an ecology of bacterial spores enriched from stool of healthy, screened donors, reduced the prevalence of VRE and showed significant increase in gut microbiome diversity post-treatment with SER-109.

Increased diversity was achieved via engraftment of SER-109 species and augmentation of species not present within SER-109.

Engraftment was defined as species that were detected in SER-109, and detected post-treatment in patients, but not detected pre-treatment. The top figure below presents engraftment data for all patients, based on genomics analyses and coded to species that were present in each of the 7 donors in the study. In all patients, multiple phylogenetic clades of organisms are found to engrat and engraffment is independent of the dose of the species. The bottom figure presents augmentation data from culture-based analysis of the B. fragilis clade. Augmentation was defined as species not present in SER-109 that are detected at greater than 10-fold higher relative abundance post-treatment than pre-treatment. In 11 of 23 patients, the CFU/ml of Bacteroides and Parabacteroides in stool were increased by 38 to 1.2 million fold.

Summary

In the 8 patients in whom VRE were detected at baseline, VRE titers were reduced to below the limit of detection post-treatment with SER-109.

The increased diversity of host microbiota post-treatment with SER-109 is associated with reduced VRE colonization and expansion of the Enterobacteriaceae family. Patients with sensitive strains (2) and currently available antibiotics (3) are provided.