Engraftment of SER-109 Spores was Rapid and Durable in Patients with Recurrent *Clostridium difficile* infection

L-836

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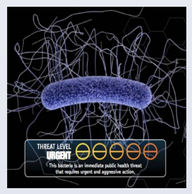
Abstract

Patients with recurrent *Clostridium difficile* infection (RCDI) have a ≥60% risk of relapse because antibiotics cannot correct the underlying dysbiosis. In a single-arm open-label study in 30 patients with ≥3 episodes of RCDI within 9 months, SER-109, an ecology of bacteria in spore form, prevented RCDI in 87% patients over 8 weeks. Three patients with transient *C. difficile* positive diarrhea achieved clinical resolution without additional antibiotic treatment, leading to an overall clinical response of 97%. We compared kinetics and durability of spore engraftment by clinical outcome.

Background

***Clostridium difficile* infection (CDI)** designated in 2013 as a top urgent threat by the Centers for Disease Control and Prevention (CDC)



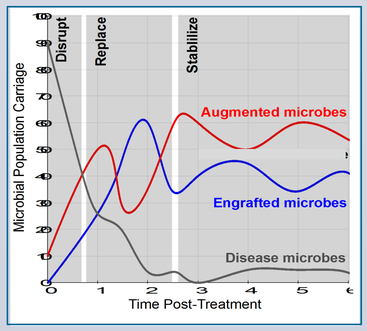
- Leading cause of hospital-acquired infection in the U.S. and in Europe
- Approximately 29,000 deaths in the U.S. each year (Lessa et al., NEJM 2015)
- 25% of patients experience a recurrence after the first episode; the risk of recurrence is >60% among those with ≥2 relapses (Vardakas et al., Int J Antimicrob Agents 2012)
- Patients with RCDI have a microbiome with significantly decreased diversity (Chang et al., JID 2008)

Antibiotics do not treat root cause of the disease - dysbiosis of the microbiome

Microbiome-based therapeutics are consortia of microbes designed to catalyze the transition of the microbiome from a disease state to a state of health.

Treatment Process

Disrupt diseased ecology → **Replace diseased ecology** → **Stabilize healthy ecology function**



Stabilization of the microbiome is dependent on both
a) **engraftment**, the germination and outgrowth of bacteria present in the dose administered and not present in the patient pre-treatment, and
b) **augmentation**, the outgrowth of bacteria not detected in the dose administered.

Methods

In an open-label phase 1b/2 clinical study (SERES-001), 30 patients with a history of RCDI were enrolled in two different dosing cohorts. Patients were given SER-109 oral capsules 48 hours after completing therapy for CDI. The primary clinical endpoint was prevention of RCDI (>3 loose C difficile+ stools in 24 hours). Kinetics and durability of engraftment were evaluated at day 4 and weeks 1, 2, 4, 8 and 24.

- SER-109 was developed as a microbiome-based therapy composed of spore-forming Firmicutes derived from the stool of healthy donors.
- Spore purification with ethanol selectively kills vegetative bacteria, fungi, parasites and most viruses, reducing the risk of pathogen transmission.

Demographics

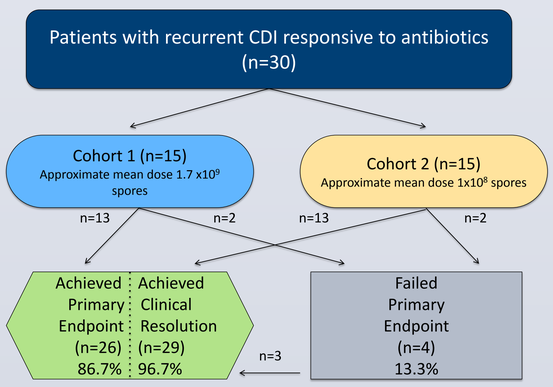
Sex and Age

	Number	Mean Age	Stdev
Female	20	56.6	18.0
Male	10	68.0	15.0

Last Antibiotic Received and # Recurrences

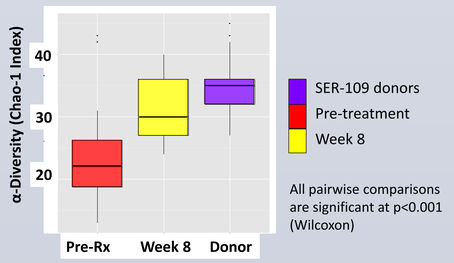
	Number	Mean Recurrences	Stdev
fidaxomicin	5	3.2	1.1
metronidazole	1	2	N/A
rifaximin	1	4	N/A
vancomycin	23	3.3	1.1

Results



1 patient received a second dose of SER-109 following a CDI recurrence in the first 8 weeks after the original SER-109 dose

Treatment with SER-109 increased the diversity of bacteria in the gastrointestinal ecology

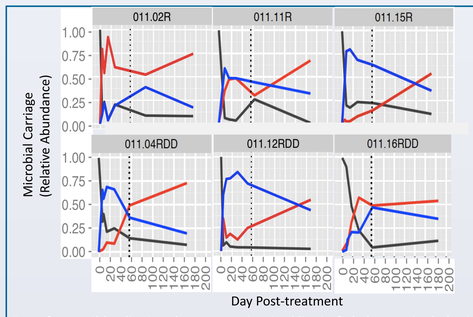


All pairwise comparisons are significant at p<0.001 (Wilcoxon)

Average microbiome α-diversity in patients pre- and post-treatment with SER-109. Diversity indices are calculated based on taxonomic assignments to phylogenetic clades.

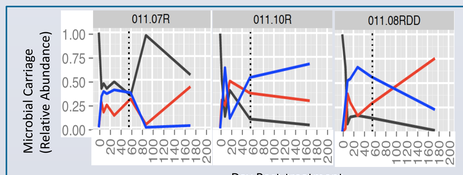
Changes in gut microbiome composition post-treatment with SER-109 resulted from both engraftment and augmentation. Engraftment was rapidly achieved (within 4-7 days). Engraftment and augmentation dynamics were variable across patients, but in all patients both were observed. Representative results are shown below.

SER-109 treatment was associated with a shift in microbiome composition

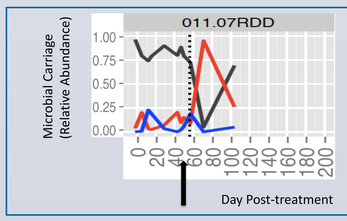


Engraftment (blue line) and augmentation (red line) of phylogenetic clades in gastrointestinal tract post-treatment with SER-109 in patients of the SERES-001 Phase 1b/2 trial is shown. Clades that are not part of the engrafting or augmenting ecologies are designated as "other" (grey line). Dotted line denotes week 8, primary clinical endpoint.

Of the 4 patients who did not achieve the primary endpoint, 3 had transient *C. difficile*+ diarrhea (days 5-9) but did not receive antibiotics and were subsequently *C. difficile* negative at week 8. Rates of engraftment/augmentation in these 3 patients were similar to responders through week 8.

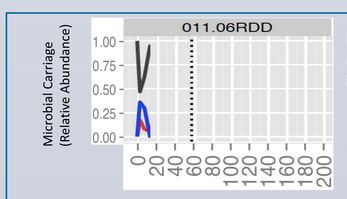


One patient with CDI at day 26 was subsequently CDI free at week 8 after a second dose of SER-109, as per protocol. Although the time to engraftment was comparable, augmentation, which was limited after the first dose, accelerated following retreatment.



Patient received 2nd SER-109 dose on day 48 (arrow)

Engraftment/augmentation were only transient in the fourth patient with persistent CDI+ diarrhea.



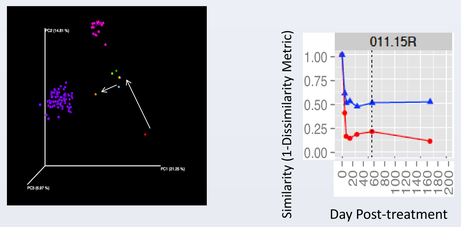
No engraftment/augmentation signal at day 14

Patient declined 2nd dose

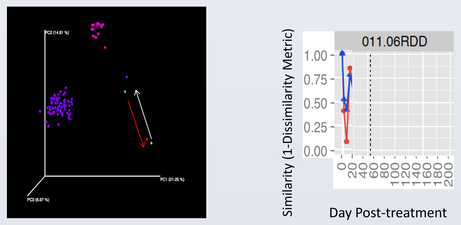
In most patients we observed a durable shift in microbiome composition away from the pre-treatment low diversity state towards a higher diversity state similar to that observed in healthy donors (e.g. Patient 15R).

In contrast, the patient who developed RCDI and refused a second dose appeared to revert to a low diversity state by day 14 (Patient 6RDD).

Patient 15R: achieved primary endpoint

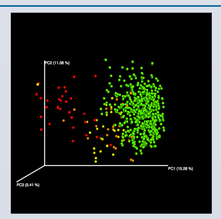


Patient 6RDD: no clinical resolution



LEFT: Principle Coordinates Analysis (PCoA) showing similarity of SER-109 doses (magenta), healthy donors (purple), and patient microbial ecologies pre- and post-treatment with SER-109 based on unweighted UniFrac (Lozupone et al., ISME 2011). Patient samples are color coded by time point: pre-treatment (red), 1 week (blue), 2 weeks (light green), 4 weeks (green), 8 weeks (yellow) and 16 weeks (orange). RIGHT: Similarity of GI microbiome post-treatment with SER-109 relative to pre-treatment state computed as (1 - dissimilarity metric). Results are presented for Bray-Curtis (red circles) and unweighted UniFrac (blue triangles) dissimilarity metrics.

Overall, microbial ecology in patients ≥ 8 weeks post-treatment was comparable to healthy individuals sampled as part of the Human Microbiome Project (HMP)



HMP = green
Pre-treatment = red
8-16 wks = yellow
24-27 wks = orange

PCoA showing comparability of GI microbiome of patients at ≥ 8 weeks post-treatment with SER-109 to microbiome of healthy individuals sampled as part of the Human Microbiome Project based on unweighted UniFrac.

Conclusions

- In patients at high risk of recurrent CDI, rapid and durable engraftment of spores from SER-109, with additional outgrowth of commensals not found in SER-109, were observed in both dosing cohorts.
- Kinetics of engraftment/augmentation were generally comparable among patients who achieved a clinical response suggesting that increased diversity restores the microbiome's protective function against CDI.
- SER-109, a first-in-field microbiome-based therapeutic agent, is being further investigated in an ongoing phase II randomized, placebo-controlled clinical trial.