SER-109 and the Prevention of Clostridium difficile Infection (CDI) in Patients with Multiple Recurrent Infections

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August 2015
SER-109 and the Prevention of Recurrent *Clostridium difficile* infection (CDI)
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- The foundation for the SER-109 development program is based on scientific knowledge that has emerged on the importance of the human microbiome in states of health and disease.
The Human Microbiome Project
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• The Human Microbiome Project has shown that 100 trillion bacteria live in a healthy person’s gut

• The diversity of the bacteria in our gut help us live a healthy life by:
  • Breaking down sugars
  • Releasing energy from dietary sources
  • Building up proteins
  • Reducing inflammation
  • Other important functions
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- Although there are more than 50 identified bacterial phyla to date, only a few dominate in the healthy gut microbiome, including the:
  - Firmicutes
  - Bacteroidetes
- Thus, there is great similarity among the phyla that exist among healthy persons.
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• On the family, genus and species level, there is a wide variety of what constitutes “health” from person to person
• This is likely influenced by host genetics, the immune system, and the person’s age, environment and diet. Microbial coadaptation may be important as well.
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• This is likely influenced by host genetics, the immune system, and the person’s age, environment and diet. Microbial coadaptation may be important as well.

• Thus, there is no single profile of a “healthy microbiome”
Diversity vs Function

• Although there may be wide diversity in the gut microbiome, there is functional redundancy…. 

Community A

Community B

Community C

Metabolism of sugars
Although there may be wide diversity in the gut microbiome, there is functional redundancy. The microbiome as a functional organ is similar among healthy individuals in terms of metabolism of sugars.
Where does Clostridia fit in the scheme of things?
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- *Clostridium difficile* is one of the Firmicutes, which includes other spore-forming bacteria
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- *Clostridium difficile* is one of the Firmicutes, which includes other spore-forming bacteria
- Within the Firmicutes, there are many other bacteria that are essential to the health of the host, including many helpful Clostridia. Thus, only some Clostridial species are potentially harmful.
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• We know that the leading risk factor for CDI are antibiotics, which disrupt the gut microbiome by wiping out important bacteria that live normally in a healthy person
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- We know that the leading risk factor for CDI are antibiotics, which disrupt the gut microbiome by wiping out important bacteria that live normally in a healthy person
  - Antibiotic use leads to a less diverse population of bacteria
- Hypothesis: This lack of diversity allows *C. difficile* to flourish and cause inflammation of the gut with diarrheal disease.
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  - *These concepts form the underlying rationale for the development of SER-109 to prevent recurrent C. difficile infection*
What is SER-109?

- SER-109 is an ecology of approximately 50 bacterial spores
- The spores are enriched from stool donations obtained from healthy, screened donors
- SER-109 has been shown to prevent recurrence of CDI in preclinical studies in animals
Why does SER-109 only use spores?

- Advantages of spores
  - Dormant forms of bacteria that are very hearty
    - Resistant to air, heat and many solvents
    - In the manufacturing of SER-109, we are able to use ethanol which kills other potentially harmful germs, including bacteria, fungi and viruses
      - *But the spores remain intact*
  - The potential for transmission of harmful pathogens is dramatically reduced
Why use only spores?

- The number of spores can be measured and calculated based on the composition of the spore wall
  - This provides consistency of dosing
  - These spores also represent only a fraction (<0.1%) of the complex species of organisms found in stool that have been identified to date (and many more that have not), thus allowing a more focused therapeutic approach
- In general, spores are resistant to stomach acid allowing them to reach the intestine where they can germinate and grow into a living ecology of bacteria.
- SER-109 is formulated into capsules for oral delivery
Donor Screening

- Lean donors <50 years of age undergo rigorous screening process including:
  - A thorough medical and family history
  - A general physical examination
  - Laboratory screening to eliminate donors with any signs of metabolic abnormalities (elevated sugars or fats) or autoimmune diseases (like Rheumatoid arthritis or Lupus)
  - Donors also undergo screening of blood and stool for any sign of infection
SER-001: Study design

- Open-label study conducted at four US sites with two dosing arms (Cohort 1 and Cohort 2)
- Adult patients (18 to 90 years of age) with ≥3 CDI episodes in the previous 12 months
- Eligible patients:
  - Clinical response to CDI antibiotics immediately before enrollment
  - Able to give informed consent to receive a donor-derived product
Treatment Protocol

- Day-2: Antibiotics for CDI completed
- Day-1: Bowel lavage
- Day-0: Enter one of the SER-109 dosing arms
  - If during 8-week period following dosing, CDI recurred, repeat administration of CDI antibiotics followed by SER-109 was allowed
SER-001: An investigative study evaluating SER-109 for prevention of recurrent CDI

**Efficacy phase**

- The primary efficacy measure was the ability of SER-109 to prevent recurrent CDI up to 8 weeks after dosing
  - CDI recurrence was defined as >3 unformed bowel movements in a 24-hour period with laboratory confirmation of *C. difficile* in the stool
SER-001: An investigative study evaluating SER-109 for prevention of recurrent CDI

Safety phase:

• Adverse events, laboratory values, vital signs, and physical examination findings were measured before and after SER-109 dosing over 24 weeks
Secondary objectives: Alterations in Gut Microbiota Composition

- The impact of SER-109 on the gut microbiome was examined by looking at microbial diversity - the number of different types of organisms in the gut.
# Patient Characteristics

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<tr>
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<th><strong>COHORT 1</strong></th>
<th><strong>COHORT 2</strong></th>
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<tbody>
<tr>
<td><strong>AGE</strong></td>
<td>64.7</td>
<td>59.1</td>
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<tr>
<td><strong>GENDER</strong></td>
<td>10 (66.7%)</td>
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Primary endpoint achieved in 26 of 30 patients (86.7%)

Patients with recurrent CDI responsive to antibiotics (n=30)

Cohort 1 (n=15)
- Approximate mean dose \(10^{9}\) spores

Cohort 2 (n=15)
- Approximate mean dose \(10^{8}\) spores

Primary Endpoint

Achieved

Cohort 1 (n=13)

Cohort 2 (n=2)

Cohort 1 (n=2)

Cohort 2 (n=13)

Only 1 patient required more than one SER-109 treatment
What happened to the four patients who did not meet the primary endpoint?

1 patient with recurrent diarrhea declined re-dosing with SER-109 and left study

Cohort 1 (n=2)
Cohort 2 (n=2)

—3 patients had transient diarrhea that resolved without CDI treatment
—Testing for *C. difficile* negative at week 8
Clinical Resolution Achieved in 29 of 30 patients (96.7%)

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No
Cohort 1 (n=2) Cohort 2 (n=2)

—3 patients had transient diarrhea that resolved without treatment for CDI
—Testing for *C. difficile* negative at week 8

Cohort 2 (n=15)
Approximate mean dose 10(8) spores

Yes
Achieved Primary Endpoint (n=13)

No

1 patient declined re-treatment
Adverse Events during 24 weeks of follow-up

• The most common drug-related adverse events included mild diarrhea, nausea and abdominal pain, which occurred mainly within the first 3 days following dosing.

• Seven serious adverse events documented in four patients considered not to be drug-related by the investigators.
Did any patients have recurrent CDI during the safety phase? (weeks 8-24)

29 patients entered safety phase

- 1 patient left for personal reasons
- 2 patients were lost to follow-up

26 of 29 patients completed the safety phase

- 1 patient relapsed without clear risk factors
- 2 patients relapse after non-CDI antibiotics
- 23 without CDI recurrence
Improvements in the Microbiome Occurred in Parallel with Clinical Resolution

SER-109 increases the microbiome diversity towards the level of diversity seen in healthy donors.

Chao-1 Diversity Index

- Pre-SER 109
- 8 weeks post SER-109
- Healthy Donors
Summary of SER-109 profile
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  - Clinical resolution observed in 29 of 30 patients.
- Adverse events included mild diarrhea, nausea and abdominal pain.
- Clinical improvement occurred in parallel with remodeling of the gut microbiome supporting hypothesis that a low diversity state is the root cause of CDI.
- Limitations of this trial are its small size and lack of a placebo-controlled design.
What’s next?
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- Primary endpoints are safety and efficacy
SER-004: Exploratory Objectives

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- Examine the numbers of deaths and hospitalizations among patients treated with SER-109 versus those treated with placebo
- Assess measures of quality of life and health outcomes through week 24 after dosing of SER-109 vs placebo