# Hope Remains for Fecal Transplant in Ulcerative Colitis

Caroline Helwick | May 09, 2014

CHICAGO — Although results from the first randomized placebo-controlled trial of fecal microbiota transplant in patients with active ulcerative colitis are negative, study investigators remain convinced that it can be effective in some patients.

"There was a trend toward benefit in our study, but it was modest," said investigator Paul Moayyedi, MD, from McMaster University in Hamilton, Ontario, Canada.

"I am an evidence-based medicine guy. In those terms, this is a negative study. That being said, it does not mean this is completely negative," he told *Medscape Medical News*.

Dr. Moayyedi presented results for the first 61 of an anticipated 130 patients to complete the trial here at Digestive Disease Week 2014.

It is believed that ulcerative colitis involves a triad of immune dysregulation, abnormal environment, and genetic susceptibility, and much of the focus has been on altering the immune system with drugs, explained Dr. Moayyedi.

"Less attention has been paid to what drives the immune response," he said. "Surely, there is something driving the immune dysregulation. It's likely that the antigen causing ulcerative colitis is food-ingested or in the gut microbiome."

The environment can be altered with prebiotics, probiotics, and antibiotics; however, in small randomized trials, these approaches have been disappointing.

**I am an evidence-based medicine guy. In those terms, this is a negative study.**

"Fecal microbiota transplant is the new kid on the block for altering gut flora. We have seen dramatic efficacy in *C difficile*, where the success rate in this difficult-to-treat group is around 90%," Dr. Moayyedi reported.

He and his colleagues evaluated ambulatory patients with active ulcerative colitis, defined as a Mayo score of at least 4 and an endoscopic Mayo score of at least 1, who tested negative for the *C difficile* toxin gene. Participants were allowed to be on other ulcerative colitis medications provided doses were stable, but antibiotics had to be discontinued for 30 days.

All participants underwent flexible sigmoidoscopy at baseline.

Patients were randomized to receive a 50 mL retention enema of fecal microbiota from an anonymous donor once per week for 6 weeks or a placebo enema (50 mL water). Patients, clinicians, and investigators were blinded to treatment allocation.

Baseline characteristics were similar in the transplant and placebo groups, although pancolitis was more common in the transplant group (64% vs 36%).

The primary outcome was remission of ulcerative colitis, defined as a Mayo score of 2 or less and an endoscopic Mayo score of 0 at week 7. Secondary outcomes included change in Mayo score and change in quality of life, assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ) and EQ-5D.

Patients gave stool samples at baseline and each week before the enema, and the fecal microbiome was assessed using amplification of the V3 ribosomal RNA region and MiSeq Illumina sequencing.

**End Point Not Met**

There was no difference in the primary outcome or any of the secondary outcomes between the 2 groups.

**Table. Outcomes at 6 Weeks**

| Outcome | Transplant Group, n = 31 | Placebo Group, n = 30 | *P* Value |
|---|---|---|---|
| Remission | 7 (23%) | 2 (7%) | 0.15 |
| Mayo score | 6.36 | 6.30 | 0.95 |
| IBDQ score | 148.4 | 146.4 | 0.85 |
| EQ5D score | 61.0 | 66.2 | 0.34 |

Fecal transplant was well tolerated, but 3 patients experienced "a change in diagnosis that was bigger than expected," said Dr. Moayyedi. Two patients in the transplant group and 1 in the placebo group had their diagnoses upgraded to Crohn's colitis.

"We are not sure why; our worry is that fecal transplant may change the phenotype," he said.

Fecal transplant "is an interesting approach to treating ulcerative colitis, but our randomized controlled trial does not support its use," Dr. Moayyedi concluded.

**Case Report of Success**

The overall study was negative but some patients had a very good response to the treatment. Dr. Moayyedi presented a case that "typifies a few patients in the study."

The man had a 20-year history of ulcerative colitis and had responded to steroids and 5-aminosalicylic acid for most of his illness. Two years before study entry, the medications became ineffective and he developed severe disease. He refused immunosuppressive therapies and surgery. He was randomized to the placebo group and showed no improvement during the study. He was then offered fecal transplant.

At 20 weeks, "his Mayo score is 0, his mucosa looks good, and he is fine without medication, after having had severe disease for 2 years," Dr. Moayyedi reported. This patient had a "diverse, unstable" microbiome at baseline. With treatment, his microbiome became enriched with *Ruminococcus* and began to resemble the donor's.

Transplants from some donors seemed to be more effective than others, indicating a need to better understand the transplanted microbiome, he said.

**Length of Treatment and Severity of Disease**

A number of patients who subjectively reported improvement but did not achieve remission continued on treatment, and approximately one-third achieved remission with extended treatment. This suggests that the study treatment period could have been too short, said Dr. Moayyedi.

"I am very optimistic about this approach," said Scott Harris, MD, a gastroenterologist from Washington, DC, who attended the presentation. "Six weeks of treatment may not be long enough. We see that with drugs in other trials," he said.

The study also involved patients with less severe disease than would be included in some drug trials, said Dr. Harris. "You have selected patients with a large range of disease. A Mayo score of 3 wouldn't get a patient into most trials, and if you pick less severe patients, it is difficult to see treatment effects. The study, by most drug trials, is also underpowered."

Other attendees wondered how rectally administered enemas could treat the entire colon, and noted that most of the patients had pancolitis.

**This study does not tell us to stop exploring.**

"We have done pilot studies where this seemed to work," one audience member explained. "The problem is that we need to keep giving it, and we cannot colonoscope everyone, all the time, to administer it throughout the colon. It's indeed interesting to us that the people for whom fecal transplant is effective are not just those with distal disease. In patients with pancolitis, rectal enemas can induce remission."

Dr. Moayyedi said that if future studies are conducted, they will evaluate fecal transplant given over long periods of time, perhaps more intensively. Meanwhile, he cautioned, this approach should only be offered to ulcerative colitis patients in the context of a clinical study.

"We need more data on the microbiome, and we need to understand how best to use this approach. This study does not tell us to stop exploring," he said.

"There is hope that gut microbiome research will enable us to figure out ways to modulate bacteria" in inflammatory bowel disease, said Colleen Kelly, MD, clinical assistant professor of medicine at Brown University in Providence, Rhode Island, during a press briefing. Her research focus is fecal transplant for *C difficile* infection.

Perhaps a modified version of fecal transplant will be effective. "The question is whether dysbiosis — altered bacterial population — is causing the disease or is a result of it," Dr. Kelly explained. "Patients are often treated with antibiotics, which can alter the microflora. We are starting to get evidence that specific microorganisms appear to be associated with disease at baseline. The hope is that we can get a beneficial effect by providing some different organisms."

*Dr. Moayyedi reports financial relationships with Forest Laboratories, AstraZeneca Pharmaceuticals, and Shire Canada. Dr. Kelly and Dr. Harris have disclosed no relevant financial relationships.*

Digestive Disease Week (DDW) 2014: Abstract 929c. Presented May 6, 2014.



Send comments and news tips to news@medscape.net.

Cite this article: Hope Remains for Fecal Transplant in Ulcerative Colitis. *Medscape*. May 09, 2014.