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Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

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BACKGROUND & AIMS: Ulcerative colitis (UC) is difficult to treat, and standard therapy does not always induce remission. Fecal microbiota transplantation (FMT) is an alternative approach that induced remission in small series of patients with active UC. We investigated its safety and efficacy in a placebo-controlled randomized trial. **METHODS:** We performed a parallel study of patients with active UC without infectious diarrhea. Participants were examined by flexible sigmoidoscopy when the study began and then were randomly assigned to groups that received FMT (50 mL, via enema, from healthy anonymous donors; n = 38) or placebo (50 mL water enema; n = 37) once weekly for 6 weeks. Patients, clinicians, and investigators were blinded to the groups. The primary outcome was remission of UC, defined as a Mayo score ≤2 with an endoscopic Mayo score of 0, at week 7. Patients provided stool samples when the study began and during each week of FMT for microbiome analysis. The trial was stopped early for futility by the Data Monitoring and Safety Committee, but all patients already enrolled in the trial were allowed to complete the study. **RESULTS:** Seventy patients completed the trial (3 dropped out from the placebo group and 2 from the FMT group). Nine patients who received FMT (24%) and 2 who received placebo (5%) were in remission at 7 weeks (a statistically significant difference in risk of 17%; 95% confidence interval, 2%−33%). There was no significant difference in adverse events between groups. Seven of the 9 patients in remission after FMT received fecal material from a single donor. Three of the 4 patients with UC ≤1 year entered remission, compared with 6 of 34 of those with UC >1 year ($P = .04$, Fisher's exact test). Stool from patients receiving FMT had greater microbial diversity, compared with baseline, than that of patients given the placebo ($P = .02$, Mann-Whitney U test). **CONCLUSIONS:** FMT induces remission in a significantly greater percentage of patients with active UC than placebo, with no difference in adverse events. Fecal donor and time of UC appear to affect outcomes. ClinicalTrials.gov Number: NCT01545908.

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Ulcerative colitis (UC) is a chronic inflammatory disorder of the colorectum that has a peak incidence in early adulthood.[1] The cardinal symptom of UC is bloody diarrhea,[2] which is associated with a significant reduction in quality of life.[3] The etiology of the disease is unknown, but it is thought to arise from an aberrant immune response to a change in colonic environment in a genetically susceptible individual.[2,4] Current medical treatment remains imperfect[5] and a significant minority of patients need colectomy to manage their disease.[6] There have been advances in therapy,[7] but gains have been modest. The focus of drug development has been on altering the immune response[8] rather than reducing factors that stimulate the aberrant immune response.[9] A likely candidate that could drive the immune response in UC is the colonic microbiome, as this is altered in patients with the disease compared with healthy controls[10] and animal models of colitis require gut bacteria to induce inflammation.[11] Fecal microbiota transplantation (FMT) has emerged as a novel approach to altering the colonic microbiome and can successfully treat antibiotic-resistant *Clostridium difficile* colitis.[12,13] The concept of FMT has captured the imagination of the public, and this approach is being advocated for a number of diseases, including UC. The efficacy of FMT is unclear in other situations and there have only been a few case reports of FMT in UC, with conflicting results.[14,15] We report the first randomized trial of FMT to treat active UC.

Methods

Study Design

This is a double-blind randomized controlled trial of FMT vs placebo in active UC conducted in Hamilton Health Sciences, St Joseph's Healthcare Hamilton, and McMaster University, Hamilton, Canada. The local research ethics committee at McMaster University approved the trial and Health Canada had no objection to the use of FMT for this study. All participants

Abbreviations used in this paper: **FMT, fecal microbial transplantation; UC, ulcerative colitis.**

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provided written informed consent and an independent Data Monitoring and Safety Committee evaluated the trial annually.

Study Population

Eligible patients were 18 years or older with active UC defined as a Mayo Clinic score[16] ≥4 with an endoscopic Mayo Clinic score ≥1. Concomitant treatments for UC, such as mesalamine, glucocorticoids, immunosuppressive therapy (eg, azathioprine), or tumor necrosis factor antagonists were permitted, provided these had been used at a stable dose for at least 12 weeks (4 weeks for glucocorticoids) and disease remained active. Five patients who were previously exposed to topical mesalamine or steroids had a 30-day washout period before being enrolled. Patients were excluded if they had taken antibiotics or probiotics in the last 30 days, had concomitant *C difficile* infection or another enteric pathogen, had a disease severity that required hospitalization, were pregnant, or were unable to give informed consent.

Baseline Assessments

Potentially eligible patients were scheduled for a flexible sigmoidoscopy and also completed baseline questionnaires to obtain demographic information, Mayo score,[16] Inflammatory Bowel Disease Questionnaire score (a validated disease specific quality of life measure; range of scores from 0 to 224 with higher score indicating better quality of life),[17] and EuroQol (EQ-5D) score (a validated general quality of life measure; range score 0 to 100 with higher score indicating better quality of life).[18] Blood samples were drawn for inflammatory markers (complete blood count, erythromycin sedimentation rate, and C-reactive protein) and serology for human immunodeficiency virus; hepatitis A, B, and C; and syphilis. Stool samples were provided by the participant and were screened for ova, cysts, and parasites, as well *C difficile* toxin gene tested by polymerase chain reaction. In addition, stool samples were collected in a sterile, airtight container for microbiota assessment.

Randomization

Eligible patients were randomized 1:1 according to a computer-generated randomization list that was stratified for patients with UC diagnosed within 1 year. The randomization was held centrally at the McMaster Gastroenterology Clinical Trials Unit to ensure concealment of allocation. The treatment location was masked to the patient, health care workers caring for the patient, and investigators. The technician administering FMT or placebo was aware of the treatment being administered, as the nature of the intervention meant that it was not possible to make it identical to the placebo.

Interventions and Follow-Up

FMT was prepared from stool donated by volunteers who were between 18 and 60 years of age and were otherwise healthy, as assessed by a screening questionnaire (see Supplementary Material). Donor stool was screened for enteric pathogens, including *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli* O157 H7, *Yersinia*, as well as ova, cysts, and parasites and *C difficile* toxin. The donor had to have negative serology for human immunodeficiency 1/2, hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody, syphilis, and human T- lymphotrophic virus 1/II and be screened negative for vancomycin-resistant *Enterococcus* or methicillin-resistant *Staphylococcus aureus*. All donors were prospectively screened and rescreened every 6 months. Stool was retested whenever a donor returned from travel outside of North America. The donor could not provide stool samples if they had taken antibiotics in the previous 3 months. Donor stool was delivered for processing within 5 h of collection. Fifty grams of donor stool was collected in the preweighed container and mixed with 300 mL commercial bottled drinking water. The mixture was emulsified for 3 to 5 minutes using a clean wooden/plastic spatula and then allowed to settle for 5 minutes. Filter paper was placed over the mixture until the supernatant filtered to the top and this was then decanted using a 60-mL syringe. The supernatant was either administered immediately to the patient or stored at −20°C.

Participants were randomized to receive 50 mL FMT or placebo consisting of 50 mL water given as a retention enema once per week for 6 weeks. The enema was administered with the patient in the left lateral position with instructions to retain this for at least 20 minutes. Patients provided stool samples each week before receiving their retention enema and samples were stored at −20°C for fecal microbiota analysis. The donor samples that were analyzed were those that were given to the patient. If the samples were frozen−thawed, it was the thawed sample that was sent for microbiome analysis. Adverse events were assessed at every weekly visit and the intervention was administered in a different hospital from where the patient was assessed for response to therapy.

Participants returned to complete a further Mayo Clinic score, Inflammatory Bowel Disease Questionnaire, EQ-5D, and have an exit flexible sigmoidoscopy at week 7 (±3 days). One investigator (PM) performed all flexible sigmoidoscopies at baseline and week 7, with the exception of 2 baseline sigmoidoscopies and 1 exit sigmoidoscopy (performed by JKM). Two rectal, sigmoid, and descending colon biopsies were taken for histology at baseline and at week 7.

Clinical Outcomes

The primary outcome was UC remission at week 7, defined as a full Mayo score <3 and complete healing of the mucosa at flexible sigmoidoscopy (endoscopic Mayo score = 0). Secondary outcomes included improvement in UC symptoms (defined as ≥3 improvement in full Mayo score), as well as change in Mayo, Inflammatory Bowel Disease Questionnaire, and EQ-5D scores. There was a 12-month follow-up phase of the trial planned with re-randomization to either open label no therapy or FMT once per month for 12 months. This part of the trial was discontinued, as there were insufficient patients entering remission at week 7. We did, however, record changes in UC medication, serious adverse events, hospitalization for UC and colectomies, as well as partial Mayo score at month 12.

Assessment and Analysis of the Microbiome

Microbial community profiling was conducted by extracting genomic DNA from patient and donor stool samples using a protocol described previously,[19] which enhances total DNA recovery. After genomic DNA extraction, the V3 region of the 16s ribosomal RNA gene was amplified (total polymerase chain reaction volume of 50 μL [25 pmol of each