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Preliminary Results From a Multicenter, Randomized Trial Using Fecal Microbiota Transplantation to Induce Remission in Patients With Mild-to-Moderate Crohn's Disease

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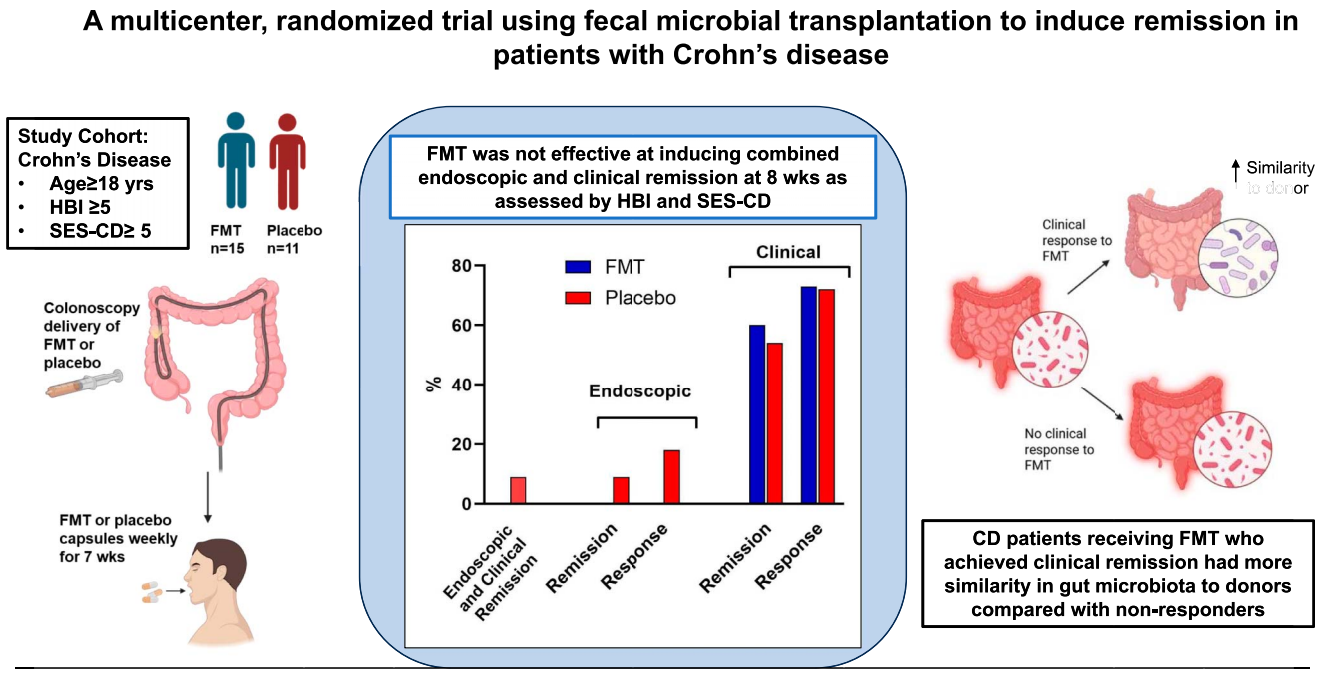
INTRODUCTION: **Fecal microbiota transplantation (FMT) has shown promise at inducing remission in ulcerative colitis. This study is the first of its kind to evaluate the efficacy and safety of FMT at inducing remission in Crohn's disease (CD).**



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METHODS: **This double-blind, placebo-controlled trial was conducted in 3 Canadian academic centers; randomized patients with mild-to-moderate CD received FMT or placebo. The first treatment was administered by colonoscopy followed by weekly oral capsules for 7 weeks. Primary end point was clinical and endoscopic remission at week 8. Secondary outcomes included clinical and endoscopic response, adverse events, and health-related quality of life using generic and disease-specific instruments.**

RESULTS: **From July 2017 to June 2021, 21 and 13 patients were randomized to FMT and placebo groups, respectively. The trial terminated early due to futility. At week 8, 0% (0/15) of patients in the FMT group versus 8.3% (1/11) in the placebo group reached the primary end point of combined clinical and endoscopic remission as per protocol analysis. There were no differences between the groups in clinical or endoscopic responses. One patient in each group had worsening of CD. Although both groups experienced statistically significant improvements in health-related quality of life, only the FMT group had a significant decrease in activity impairment. Although there were no significant changes in microbial diversity or composition, patients who achieved clinical response became more similar to their donors in stool microbial composition.**

DISCUSSION: **FMT was not effective at inducing clinical and endoscopic remission in CD using the FMT regimen in this study. Future studies may use other strategies to enhance treatment response, including longer intervention, antibiotic pretreatment, optimized donor-recipient pairing, and concomitant anti-inflammatory diet, and biologic or small molecule therapies.**

KEYWORDS: fecal microbiota transplantation; Crohn's disease; microbiome; patient-reported outcome measure; health-related quality of life

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D462

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INTRODUCTION

The pathogenesis of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), involves genetic predisposition, immune dysregulation, environmental triggers, and gut microbial dysbiosis (1). Current therapies often fail to achieve remission in many patients; none address gut dysbiosis.

Individuals with IBD have altered the structure and function of their intestinal microbiota, with reduced microbial diversity and relative abundance of beneficial or protective taxa (i.e., *Faecalibacterium prausnitzii* and *Roseburia*) and increased relative abundance of *Ruminococcus* and *Enterobacteriaceae* (2–11). This observation may extend beyond association: alteration in microbiota precedes the development of CD (12), and randomized trials using fecal microbiota transplantation (FMT) have shown promise in inducing UC remission (13–16) and maintaining steroid-induced CD remission (17). However, it is not known whether FMT is effective at inducing remission in CD.

Patients with IBD have lower health-related quality of life (HRQoL) than healthy individuals (18), even in disease remission (19). Consequently, many patients pursue complementary and alternative medicine and expect a higher degree of shared decision making with their physicians (20). Previous qualitative and mixed-methods studies have found that patients with IBD are willing to try FMT (21–23).

In this randomized trial, we compared FMT with placebo in patients with mild-to-moderate CD to test the efficacy and safety, and evaluated changes in patient-reported HRQoL, work productivity, and activity impairment. We hypothesized that sequential FMT is safe, necessary to induce remission in CD, and improves HRQoL and work and activity impairment.

METHODS

Study design

This multicenter, double-blind, placebo-controlled study randomized patients to either FMT or placebo at a 1:1 ratio, stratified by disease duration ($<$1 year or $\geq$1 year) and use of a biologic agent (yes or no) over 8 weeks. We recruited patients with mild-to-moderate CD from University of Alberta, University of Calgary, and McMaster University.

Study population

Main inclusion criteria were age 18 years and older; ileal, ileocolonic, or colonic CD; Harvey-Bradshaw Index (HBI) score $>$5; and active ileal and/or colonic disease on endoscopy using simplified endoscopic score for CD (SES-CD $\geq$5). Main exclusion criteria included severe CD (HBI $>$ 16) or hospitalization for CD; planned bowel resection within 3 months; intra-abdominal abscess; extensive colonic resection; ileostomy or colostomy; symptomatic stenosis or complex fistulae; active perianal disease; antibiotic exposure within 30 days; any conditions requiring concurrent antibiotics; topical therapy for IBD within 2 weeks; intestinal pathogens including *Clostridioides difficile* within 28 days; active substance abuse or active psychiatric problems; chronic hepatitis B, C, or HIV infection; pregnancy or planning to be pregnant; or breastfeeding during the trial.

Table 1. Secondary outcomes

	Definition	Secondary outcome timepoint
Clinical response	≥3 point reduction in HBI	W8
Clinical remission	HBI <5	W8
Endoscopic response	≥50% reduction in SES-CD	W8
Endoscopic remission	SES-CD score of <5	W8
Changes in patient-reported outcomes	HRQoL (EQ-5D-5L, SIBDQ) and WPAI:CD	W8
Serious adverse events	Death, colonic perforation, proven infections (presence of spontaneous bacteremia in the absence of any other potential source of infection that could be attributed to FMT), hospitalization due to CD, and worsening of CD	Up to W8
Minor adverse events	Fever (≥37.8 °C), nausea, vomiting, and perianal abscess	Up to W8

HBI, Harvey-Bradshaw Index; FMT, fecal microbiota transplantation; HRQoL, health-related quality of life; SES-CD, simplified endoscopic score for Crohn's disease; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; W8, week 8; WPAI, work productivity and activity impairment.

Baseline assessments

Baseline (BL) characteristics included age, sex, duration and extent of CD, HBI score, and previous and current therapy for CD. Blood work at BL included C-reactive protein (CRP), HIV, serology for viral hepatitis, and stool samples for enteric pathogens and fecal calprotectin. Extent of CD was confirmed by endoscopy (gastroscopy and colonoscopy), video capsule endoscopy, or computed tomograph/magnetic resonance enterography within 7 months of screening. If disease extent was not evaluated in the previous 7 months but all other criteria were met, a participant could be randomized but excluded at the first colonoscopy if SES-CD <5.

Permitted medications

Oral 5-aminosalicylates doses stable for at least 4 weeks; oral corticosteroid therapy (prednisone maximum 20 mg/d or budesonide up to 6 mg/d) permitted if taken for <4 weeks and remained at the same dose during the trial; immunomodulators and biologics were taken at stable dose for ≥12 weeks.

Interventions and follow-up

The first treatment (week 0) was delivered by colonoscopy, followed by weekly oral capsules for 7 weeks in the outpatient clinic under direct observation. The first colonoscopy was used to determine whether a patient met inclusion criteria, excluding those with SES-CD < 5. Endoscopically delivered treatments were 400 cc fecal slurry (equivalent to 100 g donor stool) in the FMT group or 400 cc water in the placebo group. Subsequent weekly treatment was 20 capsules/week (equivalent to 50 g donor stool or water). Bowel preparation was only required before colonoscopy. No antibiotic pretreatment was given. A follow-up colonoscopy was performed at week 8 (W8). Each colonoscopy was recorded and scored independently using the SES-CD by the local endoscopist and a central reader blinded to treatment assignment. The central reader's score was used unless there was a large discrepancy between the 2 scores, in which case a third investigator (unaware of treatment assignment) would adjudicate the score. At BL and W8, clinical assessment including EuroQoL-5D-5L (EQ-5D-5L), work productivity and activity impairment (WPAI:CD), and the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) were performed. Blood and stool samples were collected at BL and W8 for CRP, fecal calprotectin, and stool microbial composition.

Study outcomes

The primary outcome was the proportion of patients in clinical and endoscopic remission (HBI < 5 and SES-CD < 5) at W8. CD disease activity was assessed using HBI, which correlates with CD activity index (24). A 3-point drop in HBI corresponds to a 100-point change in CD activity index and indicates clinical response; HBI score of <5 indicates clinical remission.

Secondary outcomes are summarized in Table 1. Patient-reported outcomes including EQ-5D-5L, SIBDQ, and WPAI:CD were scored using established guidelines (see Supplementary Information, Supplementary Digital Content 1, http://links.lww.com/AJG/D462). EQ-5D-5L index value was calculated using the Canadian value set (25). Exploratory outcomes included changes in CRP, fecal calprotectin, and microbial composition between BL and W8.

Randomization and double blinding

Randomization (block size = 4) was done centrally through REDCap hosted by University of Alberta. Neither patients nor the study team knew the treatment assignment. Only the technician (not involved in clinical care) who manufactured the treatment knew the treatment assignment. The syringes containing either fecal slurry or water were covered, so patients remained unaware of which treatment they received during colonoscopy. The endoscopists performing the colonoscopy at week 0 were not involved in clinical assessment of that patient to maintain double blinding. The central reader was not involved in clinical assessment. All capsules appeared identical.

Stool donors

Four volunteer donors registered with the Edmonton FMT program provided stool. Donor inclusion and exclusion criteria are previously described (26); donor screenings also included testing for multidrug resistant organisms and SARS-CoV-2 as required by Health Canada. Donor materials were quarantined and released after negative bookend testing 8 weeks apart. Each patient received FMT from a single donor throughout the trial, unless the donor became unavailable.

FMT manufacturing

FMT manufacturing processes for fecal slurry and frozen capsules are previously described, with 10% glycerol (26). All investigational products were stored at −80 °C until use.

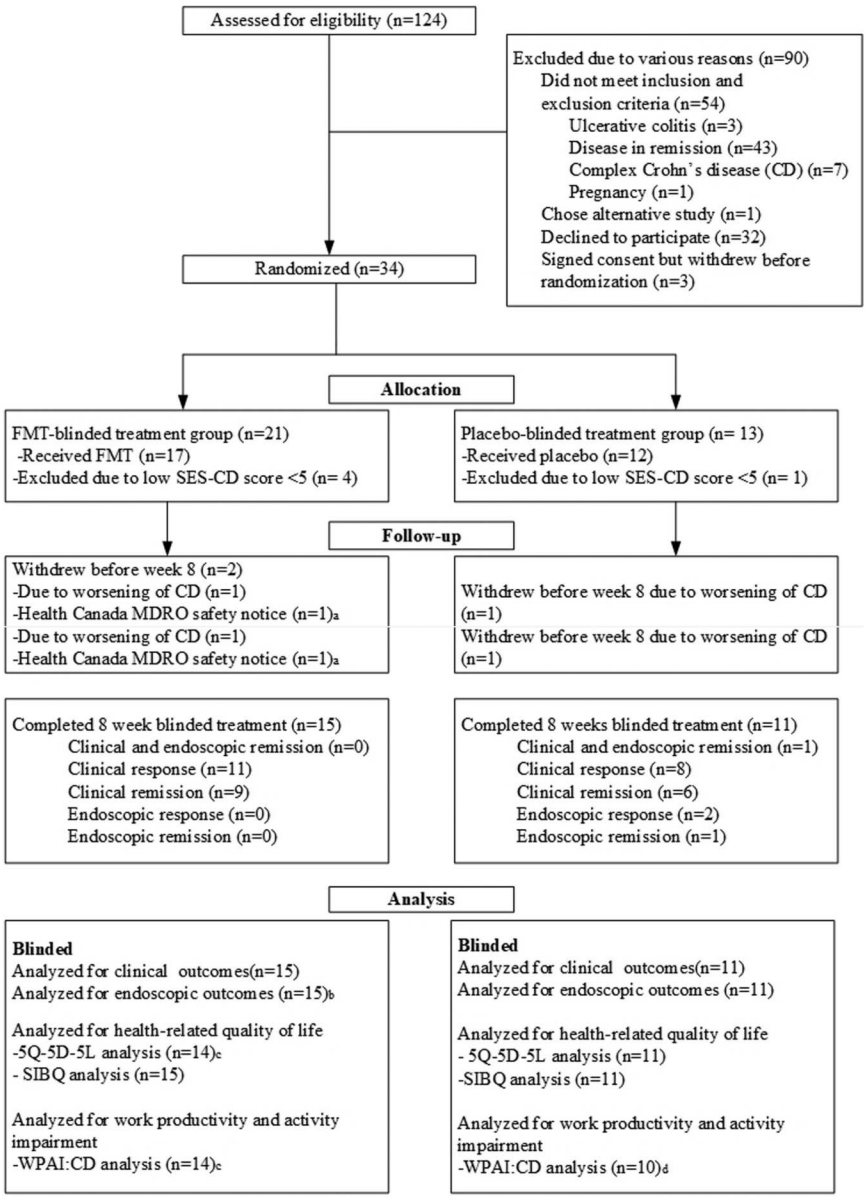


Figure 1. Consolidated Standards of Reporting Trials diagram. [a]Of the 2 patients who withdrew, 1 was unable to receive treatment due to voluntary donor program suspension as a result of Health Canada safety notice re multi-drug resistant organisms. [b]Of 15 patients who completed week 8 of the FMT-blinded treatment, 1 did not have repeat endoscopy at week 8 due to COVID-related endoscopy unit closure. [c]Of the 15 patients who complete week 8 of the FMT-blinded treatment, I did not complete that 5Q-5D-5L or Short Inflammatory Bowel Disease Questionnaire. [d]Of the 11 patients that completed week 8 of placebo treatment, 1 did not complete the WPAI:CD questionnaire. FMT, fecal microbiota transplantation; SES, simplified endoscopic score; WPAI, work productivity and activity impairment.

Microbial analysis

Microbial composition was characterized by 16S rRNA gene amplicon sequencing of the v4 region using MiSeq Illumina technology (2 × 300 bp) and primers 515F 5′-GTGCCAGCMGCCGCGGTA-3′ and 806R 5′-GGACTACHVGGGTWTCTAAT-3′ (Genome Canada, Montreal, Canada). QIIME2 and DADA2 were used for quality control and feature table construction (27). Taxonomic assignment (kingdom to genus level) of representative sequences of each sample were performed using the Silva 132 pretrained Naive Bayes classifier and the q2-feature-classifier plugin in the QIIME2 pipeline.

Sample size calculation

Our study was powered based on the primary outcome of clinical and endoscopic remission at W8. For sample size estimation, we planned to use an internal pilot study design (see Supplementary Information, Supplementary Digital Content 1, http://links.lww.com/AJG/D462). For the initial sample size calculation, we assumed the clinical and endoscopic remission rate for the placebo group to be between 5% and 20%, and a remission rate for the FMT group $\geq$20% greater than the placebo group. To achieve 80% power at the 5% alpha level to detect a 20% difference in remission rate, our sample size was estimated as 55–90 patients per group

Table 2. Patient baseline characteristics

Group assignment	FMT (N = 17)	Placebo (N = 12)
Age, mean (SD)	48.6 (12.7)	40.5 (13.2)
Body mass index, mean (SD)	25.3 (3.8)	29.7 (7.3)
Sex, female (%)	12 (70.6)	7 (58.3)
Disease duration (yr), mean (SD)	11.9 (7.2)	8.6 (7.0)
Surgical resection	4 (23.5)	2 (16.7)
Montreal classification		
Age of onset		
<16 yr old	0 (0)	3 (25.0)
17–40 yr old	10 (58.8)	5 (41.7)
>40 yr old	7 (41.2)	4 (33.3)
Disease location		
L1	0 (0)	1 (8.3)
L2	7 (41.2)	5 (41.7)
L3	10 (58.8)	6 (50.0)
Disease behavior		
B1	12 (70.6)	8 (66.7)
B2	4 (23.5)	3 (25.0)
B3	1 (5.9)	1 (8.3)
Perianal disease		
Yes (%)	2 (11.8)	4 (33.3)
5 ASA		
Yes (%)	7 (41.2)	5 (41.7)
Steroids		
Yes (%)	5 (29.4)	6 (50.0)
Immunomodulators		
Yes (%)	8 (47.1)	5 (41.7)
Imuran	3	1
Methotrexate	0	1
Biologics		
Infliximab	2	2
Adalimumab	1	1
Vedolizumab	3	2
Ustekinumab	1	1
Other	0	1
History of failed biologics		
Yes	5	5
Number of biologics failed		
1	2	2
2	1	1
3	0	1
4	1	0
5	1	0
6	0	1
Smoking status		
Current	2 (11.8)	1 (8.3)
Former	7 (41.2)	4 (33.3)
Never	8 (47.1)	7 (58.3)
Baseline HBI, mean (SD)	8.6 (4.6)	11.1 (5.5)
Hemoglobin (g/L), mean (SD)	126.8 (16.7)	135.7 (18.9)
CRP (mg/L), mean (SD)	16.5 (32.2)	20.4 (24.8)
Albumin (g/L), mean (SD)	37.6 (3.9)	39.4 (4.2)
Fecal calprotectin (μg/g), mean (SD)	1,430.5 (1,230.1)	906.8 (708.9)

5 ASA, 5 aminosalicylates; CRP, C-reactive protein; FMT, fecal microbiota transplantation; HBI, Harvey-Bradshaw Index;

based on the Fisher exact test. We planned to enroll 30 patients in each treatment group, re-estimate the sample size, and enroll additional patients until the adjusted sample size was achieved.

Statistical analyses

BL characteristics of all subjects were reported as means and SDs for continuous variables and frequencies and proportions for categorical variables. Per protocol analyses were conducted since not all randomized patients were eligible for the study. Binary outcomes were performed using the χ^2 test or Fischer exact test. EQ-5D-5L, SIBDQ, and WPAI:CD were summarized using median and interquartile range, with between-group comparisons (FMT vs placebo) using Mann-Whitney *U* test and within-group comparisons (BL vs W8) using paired sign test (36–40). Between-group and within-group comparisons of HBI and SES-CD score were conducted using two-sample *t* test and paired-sample *t* test, while fecal calprotectin and CRP were compared using Mann-Whitney *U* test and paired sign test. All statistical analyses were performed using Stata SE 16.1 (College Station, TX).

Microbial α-diversity was calculated by Chao1 and Shannon indices using QIIME2. Further details are provided in Supplementary File (Supplementary Digital Content 1, http://links.lww.com/AJG/D462).

Data availability

The data generated or analyzed during this study are included in the article and Supplementary Information (Supplementary Digital Content 1, http://links.lww.com/AJG/D462). Raw sequencing data are available under BioProject accession number PRJNA1178690. https://www.ncbi.nlm.nih.gov/sra/PRJNA1178690.

Ethics

This study was approved by the Institutional Review Boards of each participating center and by Health Canada (HC6-024-c176567, Control# 201939), and was registered with clinicaltrials.gov (NCT03078803). Written informed consent was obtained from each enrolled patient. All procedures were conducted in accordance with Good Clinical Practice.

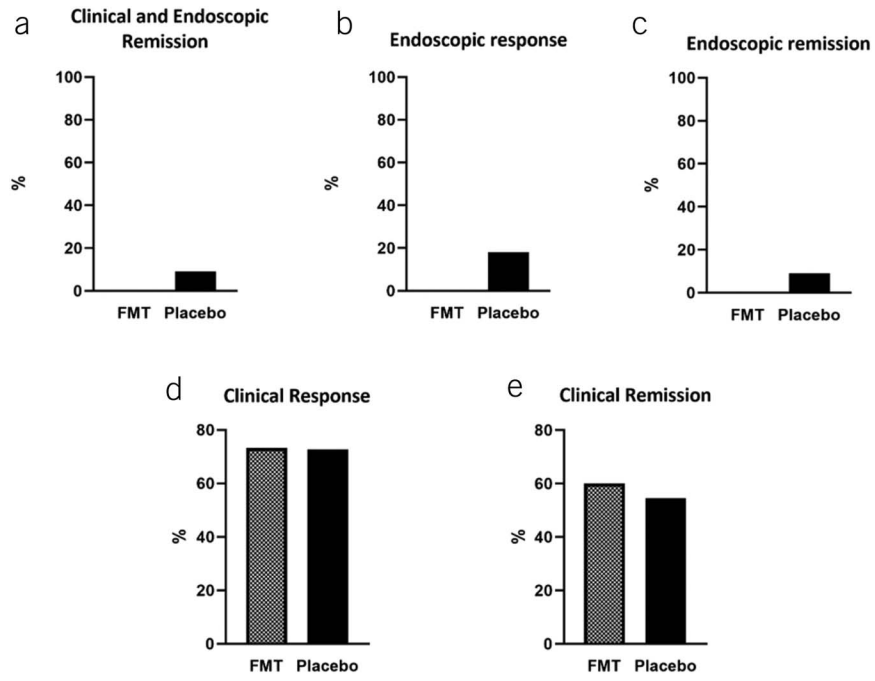


Figure 2. Primary and secondary outcomes at week 8. Primary outcome of combined clinical and endoscopic remission was achieved in 1/11 patients in the placebo group (**a**). Endoscopic response (**b**) was achieved in 2/11 patients in the placebo group and endoscopic remission (**c**) in 1/11 patients in the placebo group. Clinical response (**d**) was achieved in 11/15 patients in the FMT group and 8/11 patients in the placebo group. Clinical remission was achieved in 9/15 patients in the FMT group and 6/11 patients in the placebo group. There were no significant differences in outcomes between the groups. FMT, n = 15; Placebo, n = 11. FMT, fecal microbiota transplantation.

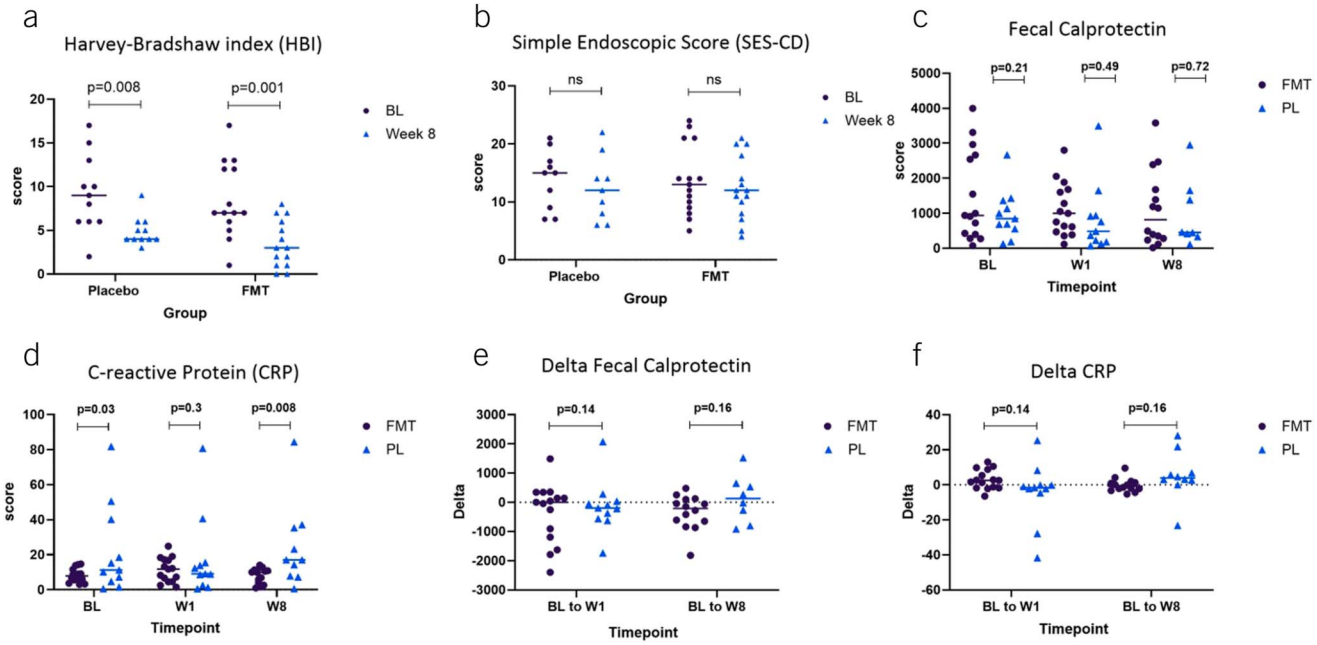


Figure 3. There was a significant improvement in HBI (**a**) between BL and W8 in both groups. There was no change in SES-CD scores in either the placebo or the FMT group (**b**). Levels of fecal calprotectin (**c**) and CRP (**e**) in individual patients at BL, W1, and W8. There were no significant changes in CRP or fecal calprotectin within the FMT or the placebo group between BL, W1, and W8. CRP was higher in the placebo group than in the FMT group at BL and at W8 (**e**). Delta changes in fecal calprotectin (**d**) and CRP (**f**) between BL and W1 and between BL and W8 are shown. Data are shown as individual values and median and were analyzed using 2-way repeated measures or mixed-effect model. FMT, n = 15; Placebo, n = 11. BL, baseline; CRP, C-reactive protein, FMT, fecal microbiota transplantation; HBI, Harvey-Bradshaw Index; SES-CD, simplified endoscopic score for Crohn's disease, W1, week 1; W8, week 8.

Table 3. Safety outcomes

Number of patients	FMT group (N = 17)	Placebo group (N = 12)
Death	0	0
Colonic perforation	0	0
Infection attributable to FMT	0	0
Hospitalization due to CD	0	0
Worsening of CD	1	1
Fever	1	0
Nausea	0	0
Vomiting	0	0

CD, Crohn's disease; FMT, fecal microbiota transplantation.

RESULTS

Study patients and trial interruptions/termination

Patient recruitment began in July 2017 and was interrupted twice by Health Canada safety warnings (concerns of FMT transmitting multidrug-resistant organisms in July-September 2019 and SARS-CoV-2 in March-August 2020); we voluntarily suspended our donor program until we modified donor screening to mitigate these concerns. The final follow-up visit occurred in Jun 2021.

Of 124 patients assessed for eligibility, 90 were excluded during initial screening. The remaining 34 patients were randomized at the first Data Monitoring and Safety Board (DSMB) meeting: 21 to FMT and 13 to placebo (Figure 1). Four patients with SES-CD <5 at colonoscopy were excluded from the FMT group and one from the placebo group; a total of 17 patients received FMT, and 12 patients received placebo. BL characteristics are presented in Table 2.

Study outcomes

Primary outcome. Three patients withdrew before W8; therefore, we could not assess the SES-CD score at W8. One patient in each group had worsening CD, and one (FMT group) could not receive assigned treatment during suspension of the stool donor program.

Data were reviewed in May 2022: 0/15 patients in the FMT group and 1/11 (9.1%) in the placebo group were in combined clinical and endoscopic remission at W8 ($P = 0.42$). Our DSMB advised that we discontinue the trial because the study was unlikely to achieve the primary outcome.

Secondary outcomes. Figure 2 shows W8 combined endoscopic and clinical remission rates (Figure 2a), endoscopic response and remission rates (Figure 2b,c, respectively), and clinical response and remission rates (Figure 2d,e, respectively). There was a significant decrease in HBI scores between BL and W8 in both the placebo (mean decrease = 5, 95% CI: 2.5–7.5, $P = 0.001$) and FMT group (mean decrease = 5.3, 95% CI: 3.1–7.5, $P < 0.001$) (Figure 3a). However, the decreases in HBI scores were not significantly different between the FMT group and placebo ($P = 0.83$). There were no statistical differences in SES-CD (Figure 3b) between the groups or between BL and W8.

There was no death, colonic perforation, and infection attributed to FMT, or hospitalization due to CD. One patient in each group had worsening CD. One patient in the FMT group had transient fever (Table 3).

Patients in the FMT group had statistically significant improvements in EQ-5D-5L Visual Analog Scale from BL to W8 (Table 4). There were no statistically significant differences between the FMT and placebo groups for EQ-5D-5L Visual Analog Scale or index values at BL or W8. Patients in both groups also had statistically significant improvements in overall SIBDQ score from BL to W8 (FMT group: 42 to 56, $P < 0.001$; placebo group: 36 to 49, $P < 0.01$). Five patients in the FMT group and 7 patients in the placebo group were employed and completed the WPAI: CD at BL and W8. Those patients did not exhibit statistically significant changes in overall work impairment between BL and W8. However, patients in the FMT group did have a statistically significant decrease in activity impairment from BL to W8 (median: 40%–10% impairment; $P < 0.01$). At W8, the median activity impairment in the FMT group (10% impairment) was statistically lower than that of the placebo group (30% impairment; $P < 0.05$).

Exploratory outcomes

CRP and fecal calprotectin. There were no significant changes in fecal calprotectin (Figure 3c,d) or CRP (Figure 3e,f) within the FMT or the placebo group between BL, week 1, and W8. CRP was significantly higher in the placebo group than in the FMT group at BL ($P = 0.03$) and at W8 ($P = 0.008$) (Figure 3e).

Microbial analysis. The α-diversity (Shannon Index) was significantly lower in the placebo group than in the donors (Figure 4a). There was no change in α-diversity between week 0 and W8 in either the FMT or placebo group. The α-diversities of the donors were not different (Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D462). Microbial composition at BL and W8 differed between the placebo and FMT groups (Figure 4b), with each group having several different taxa at W8 (Figure 4c). The FMT group had higher Bacteroidales (Bacteroidaceae, Tannerellaceae, Marinifilaceae, and Barnesiellaceae); Eubacteriales (Eubacteriaceae, Butyricicoccaceae, and Oscillospiraceae); Burkholderiales (Sutterellaceae); and Acidaminococcales (Acidamincoccaceae) while Eubacteriales (Lachnospiraceae) were reduced. The FMT group had higher Bacteroidaceae, Sutterellaceae, Staphylococcaceae, Eubacteriaceae, Gemellaceae, Tannerellaceae, Marinifilacae, Oscillospirales, Acidamincoccaceae, and Barnesiellaceae, while Lachnospiraceae and Clostridia were reduced (Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D462). There were no significant compositional changes between BL and W8 in the placebo or FMT groups. However, subgroup analysis of the patients who achieved clinical remission (responders) and those who did not (nonresponders) revealed that responders were significantly more similar to the donor than nonresponders (Supplementary Figure 2, Supplementary Digital Content 1, http://links.lww.com/AJG/D462).

DISCUSSION

This is the first placebo-controlled, randomized, multicenter trial to evaluate the efficacy of FMT on patients with active CD. Although no patients in the FMT group and 1/11 patients in the placebo group were in clinical and endoscopic remission, both groups experienced improvements in HRQoL. Overall, 9/15 patients receiving FMT and 6/11 patients receiving placebo were in clinical remission at W8.

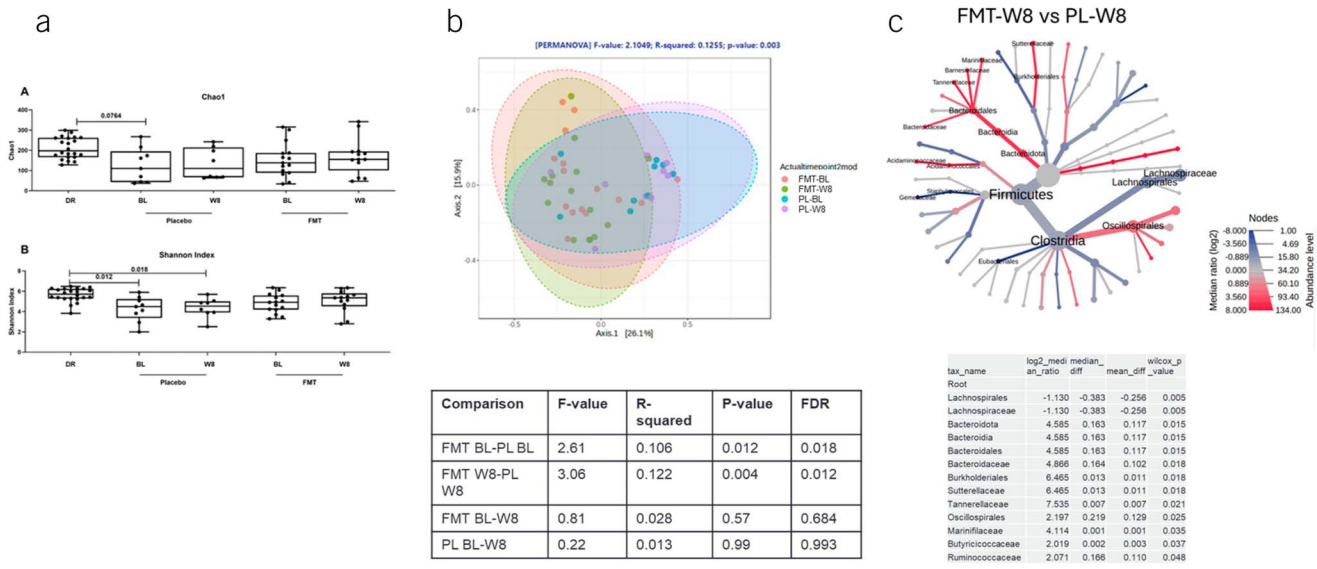
Table 4. Changes in patient-reported HRQOL (EQ-5D-5L, SIBDQ) and WPAI:CD between baseline and week 8

		Baseline			Week 8			Baseline vs Week 8
	N	Median	IQR	*P*-value	Median	IQR	*P*-value	*P*-value
EQ-5D-5L								
VAS[a]								
FMT	14	60	30	0.30	75	25	1.00	<0.01
Placebo	11	70	25		70	20		0.070
Missing	1							
Index value[b]								
FMT	14	0.83	0.20	0.12	0.90	0.10	0.05	<0.01
Placebo	11	0.77	0.19		0.85	0.16		<0.01
Missing	1							
SIBDQ								
Overall score[c]								
FMT	15	42	15	0.70	56	16	0.23	<0.001
Placebo	11	36	19		49	16		<0.01
Missing	0							
WPAI:SHP								
Currently used								
FMT	8							
Placebo	8							
Percent overall work impairment due to CD[d]								
FMT	5	20	3.81	0.17	20	10	0.09	0.25
Placebo	7	40	20		30	30		1.00
Missing[e]	14							
Percent activity impairment due to CD[f]								
FMT	14	40	20	0.36	10	20	<0.05	<0.01
Placebo	10	50	40		30	30		0.18
Missing	2							

Between group differences in medians (FMT vs placebo) and within group differences in medians (baseline vs week 8 for each group) were tested using nonparametric statistical tests (2-tailed Mann-Whitney *U* test and paired sign test, respectively).
CD, CD, Crohn's disease; EQ-5D-5L, EuroQoL-5D-5L; FMT, fecal microbiota transplantation; HRQOL; health-related quality of life; IQR, interquartile range; SHP, Specific Health Problem; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; VAS, Visual Analog Scale; WPAI, work productivity and activity impairment.
[a]EQ-5D-5L VAS values range from 0 (lowest/worst HRQOL) to 100 (highest/best HRQOL).
[b]EQ-5D-5L index value based on Canadian value set.
[c]SIBDQ overall score values range from 10 (lowest/worst HRQOL) to 70 (highest/best HRQOL).
[d]WPAI:SHP percent overall work impairment values range from 0% to 100% impairment, with higher values indicating greater overall work impairment/less productivity.
[e]Patients only completed WPAI:SHP questions related to work if they were employed at the time of the survey; N reported is only those who were employed and completed the WPAI:SHP at both baseline and week 8.
[f]WPAI: SHP percent activity impairment values range from 0% to 100% impairment with higher values indicating greater activity impairment.

The placebo rate in our study was similar to that of other clinical trials with biologics, although we only included mild-to-moderate patients with CD. In a recent meta-analysis, the endoscopic remission rates in those receiving placebo were 10% and 4% for biologic naive and biologic experienced patients, respectively, during induction (28). A recent meta-analysis showed that in trials using FMT for UC, the placebo rate for endoscopic remission was approximately 10% (29). However, we did see a significant improvement in activity impairment following FMT, but not with placebo. All other statistically significant improvements in HRQoL, as assessed by EQ-5D-5L and SIBDQ, occurred in both the FMT and placebo groups.

A recent systematic review and meta-analysis of studies using FMT to induce remission in patients with CD found 11 non-comparative cohort studies and one non-placebo-controlled randomized trial comparing endoscopic delivery through small bowel to colon (30). Similar to the results in our study, the pooled proportion of patients with CD achieving clinical response was 72% (95% CI = 65%–79%) and clinical remission was 57% (95% CI = 49%–64%), with no patient achieving endoscopic remission. The high response rates likely reflect the nature of these open-label cohort series. Comparatively, the clinical remission rate in UC was only 37% in those receiving FMT compared with 18% in the placebo group, while the endoscopic remission rate was 30% in patients receiving FMT compared with the control



Comparison	F-value	R-squared	P-value	FDR
FMT BL-PL BL	2.61	0.106	0.012	0.018
FMT W8-PL W8	3.06	0.122	0.004	0.012
FMT BL-W8	0.81	0.028	0.57	0.684
PL BL-W8	0.22	0.013	0.99	0.993

tax_name	log2_median_ratio	median_diff	mean_diff	wilcox_p_value
Root				
Lachnospirales	-1.130	-0.383	-0.256	0.005
Lachnospiraceae	-1.130	-0.383	-0.256	0.005
Bacteroidota	4.585	0.163	0.117	0.015
Bacteroidia	4.585	0.163	0.117	0.015
Bacteroidales	4.585	0.163	0.117	0.015
Bacteroidaceae	4.866	0.164	0.102	0.018
Burkholderiales	6.465	0.013	0.011	0.018
Sutterellaceae	6.465	0.013	0.011	0.018
Tannerellaceae	7.535	0.007	0.007	0.021
Oscillospirales	2.197	0.219	0.129	0.025
Marinifilaceae	4.114	0.001	0.001	0.035
Butyricicoccaceae	2.019	0.002	0.003	0.037
Ruminococcaceae	2.071	0.166	0.110	0.048

Figure 4. Gut microbial diversity of FMT donors and subjects. Alpha-diversity (**a**) of fecal microbiota was assessed using the Chao1 and Shannon indices. There was no change in α-diversity between baseline and week 8 in either the FMT or the placebo group. Both baseline and week 8 α-diversity, as assessed by the Shannon index, was lower in the placebo group compared with the donors. Beta diversity (**b**) was calculated using the Bray-Curtis dissimilarity index. Significant differences were observed in microbial composition between the FMT and placebo groups at week 8 (**c**). Differences of beta diversity were analyzed via permutational multivariate analysis of variance ($n = 999$) using the "Adonis" function in "vegan". for the microbiota compositional features, α-diversity index and centered log-ratio-transformed bacterial taxa counts, repeated measures linear regression, and paired *t*-tests were applied to compare within-group differences relative to baseline. Between-group differences were assessed by linear regression, and pairwise comparisons used unpaired *t*-tests. *P*-values were adjusted by the Benjamin-Hochberg FDR method. FMT, n = 15; Placebo, n = 11. . BL, baseline; DR, donors; FDR, false discovery rate; FMT, fecal microbiota transplantation; W8, week 8.

(10%) at W8 in a recent Cochrane review of randomized controlled trials comparing FMT with controls (29). Adverse events were infrequent, self-limited, and resolved spontaneously within hours to days, similar to our study.

Engraftment of donor microbial strains is likely required for FMT efficacy. Although the dynamics and determinants of engraftment are not well understood, donor and recipient complementarity may be a key factor (31,32). Many ecological principles are at play, including competition, exclusion, and priority effect. Furthermore, a lower degree of engraftment is expected than that observed in recurrent *Clostridioides difficile* infection (33). Fecal microbiota analyses indicate that patients with CD had lower microbial diversity than healthy donors; however, α-diversity did not increase in either FMT or placebo groups during treatment. Despite having well-matched clinical characteristics, BL microbiota of the FMT and placebo groups differed throughout the study. There were no significant changes in microbial composition in either group during the study; however, patients with CD who achieved clinical remission in response to FMT were more similar to their donor after 8 weeks, similar to a previous study (30). The reasons for varying engraftment are unknown but may be related to BL microbiota of the donor or recipient, CD phenotype or duration, or the diet of the recipient.

Several challenges resulted in slow recruitment. Patients received their treatments at weekly clinical visits, which proved difficult. Many patients with active CD did not have sufficient symptoms to qualify for this study; by contrast, some were excluded because of insufficient endoscopic disease. The COVID-19 pandemic closed endoscopy units and reduced our capacity to enroll and assess patients. Last, Health Canada safety warnings regarding SARS-CoV-2 led us to temporarily suspend our stool donor program. These issues, combined with early interim analysis, resulted in our DSMB advising to terminate our trial.

We intentionally set a high threshold for clinical and endoscopic remission; in retrospect, this may be impossible to achieve over the 8-week period. A longer duration of treatment may improve response rate. Using lyophilized FMT capsules (stored at 4 °C at home) may facilitate recruitment. Lyophilized FMT has shown the similar efficacy to frozen FMT in recurrent clostridioides difficile infection and UC (16,34). Antibiotic pretreatment before FMT may improve bacterial engraftment and improve response (32). FMT combined with an anti-inflammatory diet induced remission in UC in a recent randomized trial (35). FMT combined with therapy to block specific cytokines or modulate the immune system may be beneficial in patients with CD.

This is the first placebo-controlled randomized controlled trial examining the effect of FMT on inducing remission in CD. We used a pragmatic approach for inclusion and exclusion criteria, and we included patients taking biologics, so the results can be generalizable. The small number of donors also reduced the number of potential variables. Limitations of our study included a small sample size, short duration, and an intensive study regimen requiring weekly in-person visits. The small number of stool donors may have also limited our ability to optimize donor-recipient pairing.

Future studies should use an adequately powered multicenter trial and use a longer intervention period to improve the clinical efficacy. Lyophilized FMT can also improve treatment logistics.

Antibiotic pretreatment, anti-inflammatory diet, or concurrent biologics or small molecules may also potentiate microbial engraftment and augment efficacy.

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CONFLICTS OF INTEREST

Guarantor of the article: Dina Kao, MD.

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Potential competing interests: K.W. has received honoraria from AbbVie, Janssen. H.J. has received honoraria from AbbVie, Ferring, Pendopharm, Takeda. K.K. has received honoraria from AbbVie, Janssen, Celltrion, Pfizer, Takeda. F.P. has consulted for Takeda, Ferring; received speaker fees for Janssen, Takeda, AbbVie, Pfizer; served on Advisory Board for Janssen, Fresenius Kabi, Ferring, Takeda, AbbVie, BioJAMP. N.N. holds a McMaster University AFP Clinician Researcher Award; received honoraria from Janssen, AbbVie, Takeda, Pfizer, Sandoz, Novartis, Iterative Health, Innomar Strategies, Fresinius Kabi, Amgen, Organon, Eli Lilly, and Ferring. R.P. has consulted for Abbott, AbbVie, Abivax, Alimentiv (formerly Robarts), Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Fresenius Kabi, Genentech, Gilead Sciences, Glaxo-Smith Kline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pendopharm, Pfizer, Progenity, Prometheus Biosciences, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Sublimity Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus, Viatris, Ventyx, UCB; received Speaker's Fees for: AbbVie, Amgen, Arena Pharmaceuticals, Bristol-Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Gilead Sciences, Janssen, Merck, Organon, Pfizer, Roche, Sandoz, Shire, Takeda Pharmaceuticals; served on Advisory Boards for AbbVie, Alimentiv (formerly Robarts), Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Genentech, Gilead Sciences, Glaxo-Smith Kline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, SandozShire, Sublimity Therapeutics, Takeda Pharmaceuticals, Ventyx. D.M. is supported by the Svare Chair in Health Economics, Value and Impact, University of Calgary DM reports nonfinancial support from consultancy from Illumina, nonfinancial support from ISPOR, personal fees from Office of Health Economics, Novartis and Astellas on preferences methods outside the submitted work. D.M. is supported by the Svare Chair in Health Economics, Value and Impact, University of Calgary. Other authors declared no COI.

Study Highlights

WHAT IS KNOWN

- ✓ Fecal microbiota transplantation (FMT) induces remission in patients with ulcerative colitis in randomized controlled trials.
- ✓ FMT has been shown to maintain steroid induced remission in Crohn's disease (CD) in a preliminary study.
- ✓ It is not known whether FMT can induce remission in patients with CD.

WHAT IS NEW HERE

- ✓ FMT given weekly by colonoscopy then oral capsules over 7 weeks did not induce remission in CD compared with placebo
- ✓ Participants in both groups had significant improvements in health-related quality of life.
- ✓ Participants in the FMT group, but not placebo group, had a significant decrease in activity impairment.
- ✓ Participants in the FMT group in clinical remission had shifted microbial composition toward the stool donors.

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