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Role of Faecal Microbiota Transplantation for Maintenance of Remission in Patients With Ulcerative Colitis: A Pilot Study

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Abstract

Objectives: To study the role of faecal microbiota transplantation [FMT] in maintenance of remission in ulcerative colitis [UC].

Methods: In this pilot study, patients with UC in clinical remission achieved after multi-session FMT were randomly allocated to either maintenance FMT or placebo colonoscopic infusion every 8 weeks, for 48 weeks. The standard of care [SOC] therapy was continued in all patients. The primary endpoint was maintenance of steroid-free clinical remission [Mayo score ≤2, all subscores ≤1] at Week 48. Secondary endpoints were achievement of endoscopic remission [endoscopic Mayo score 0] and histological remission [Nancy grade 0, 1] at Week 48.

Results: In all, 61 patients in clinical remission were randomised to receive either FMT [$n = 31$] or placebo [$n = 30$]. The primary outcome was achieved in 27/31 [87.1%] patients allocated FMT versus 20/30 [66.7%] patients assigned placebo [$p = 0.111$]. Secondary endpoints of endoscopic remission (FMT: 18/31 [58.1%] versus placebo: 8/30 [26.7%], $p = 0.026$) and histological remission (FMT: 14/31 [45.2%] versus placebo: 5/30 [16.7%], $p = 0.033$) were achieved in a significantly higher number of patients with FMT. Three patients receiving FMT [9.7%] and 8 patients on placebo [26.7%] relapsed. There were no serious adverse events necessitating discontinuation in patients on FMT; one patient who relapsed on placebo required colectomy.

Conclusions: Maintenance FMT in patients who are in clinical remission may help sustain clinical, endoscopic and histological remission in patients with UC.

Key Words: Inflammatory bowel disease; clinical remission; endoscopic remission; histological remission, faecal microbiota transplantation

1. Introduction

Ulcerative colitis [UC] is a chronic and progressive inflammatory disease with a relapsing and remitting course.[1] Conventionally, induction of remission in patients with UC is achieved with 5-aminosalicylates [5-ASAs], corticosteroids, and biologics. Subsequently, these patients are maintained on 5-ASAs, thiopurines, or biologics. However, 5-ASAs have modest efficacy, and corticosteroids and thiopurines have substantial adverse events with long-term

use.[2–5] In addition to this, annual relapse rates of up to 25–40% have been reported despite use of optimal doses of 5-ASAs and/or thiopurines.[5–12] Biologics [infliximab, adalimumab, and vedolizumab] are approved for induction and maintenance of remission.[13–15] Though efficacious, these agents are expensive, can cause potentially serious adverse events, and despite use of these drugs, less than half of the patients maintain remission and up to one-fifth of patients with inflammatory bowel disease [IBD] may require surgical interventions.[16–18] Therefore, newer treatment strategies are being evaluated for the induction and maintenance of remission in patients with active UC.

Faecal microbiota transplantation [FMT] is emerging as a novel therapy for UC as it targets gut microbial dysbiosis, which in addition to the host's genetic susceptibility and immune response, contributes to the pathogenesis of UC.[19] Transplantation of faecal matter from a healthy individual to a patient with active UC has been proposed to correct dysbiosis-mediated immunological disturbances by inhibiting Th1 differentiation, activity of T cells, leukocyte adhesion, and production of inflammatory mediators.[19] Several studies have reported the efficacy of FMT for the induction of remission in patients with active UC.[20–23] However, except for a small series of three paediatric patients with UC where 22–30 treatments with FMT aided withdrawal of immunotherapy [infliximab, 6-mercaptopurine, and steroids],[24] the role of FMT as a maintenance therapy in patients who have achieved clinical remission on this therapy has not been reported so far.

2. Materials and Methods

2.1. Study design

This was a pilot randomised study conducted in the Department of Gastroenterology, Dayanand Medical College and Hospital, a tertiary care hospital in northern India. The study was approved by the Institutional Review Board and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects. The study was registered with Clinical Trials Registry-India [CTRI/2018/02/012148].

2.2. Study population

Since September 2015, patients with active UC [Mayo score 4–10] who were being treated with standard of care therapy [5-ASAs, corticosteroids, and thiopurines] have been offered FMT as an add-on therapy. Those with proctitis [E1 disease] and on topical 5-ASAs were excluded. Patients who consented underwent seven sessions of FMT via a colonoscopic route for induction of remission [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online]. These patients have been analysed in part and have been reported.[25] Patients who achieved clinical remission [defined as Mayo score ≤2, with each subscore ≤1] with FMT and were on stable medication regimens [5-ASA and azathioprine for 6 months] were eligible for this study. Eligible patients who consented were then randomised in a 1:1 ratio according to a computer-generated randomisation list, to receive either FMT or placebo by a colonoscopic route every 8 weeks,for a further 48 weeks. The standard of care, i.e. 5-ASA with/without azathioprine, in a stable dose [5-ASA 4-4.8 g/day, azathioprine 2 mg/kg/day] was continued in all patients.

2.3. Intervention

The interventions [colonoscopic infusion of FMT or placebo] were scheduled at Weeks 0, 8, 16, 24, 32, 40, and 48. Both patients and treating physicians were blinded to the nature of intervention done. Bowel preparation was done with polyethylene glycol lavage, a night before the procedure. Ileocolonoscopy was performed under conscious sedation by two endoscopists [VMe, YG] and the slurry [faecal slurry or placebo] was administered into the ileum and/or caecum. A single donor was used for all the patients. He was a healthy, unrelated, voluntary individual aged 32 years, with no personal or family history of UC or any other autoimmune disease. He was screened by stool microscopy and culture for common detectable enteric pathogens [*Salmonella*, *Shigella*, *Campylobacter*, *Vibrio cholera*, *Entamoeba coli*, *Clostridium difficile*, *Giardia lamblia*, and *Cryptosporidium*] and also for antibodies against hepatitis A, C, and E, hepatitis B surface antigen [HBsAg], syphilis, and human immunodeficiency virus [HIV]. In order to ensure an uninterrupted supply of faecal slurry, stool samples of the donor were stored at -80^{0}C in a stool bank and used after thawing, in case the fresh stool sample was either not available or not suitable for processing.

The faecal slurry was prepared from freshly passed stools by the donor on the morning of the procedure. These stool samples were inspected visually on the day of procedure and only those with Bristol stool score 3 or 4 were used. The sample [100 g] was diluted with preservative-free normal saline [200 ml] and homogenised using a blender [Stomacher® 400 Circulator, Seward, UK, at 230 rpm for 1 min] till it reached a liquid consistency. This slurry was filtered to remove the particulate matter, filled into four syringes [50 ml each] and used within 1 h of preparation or 6 h of passage of stools. Preservative-free normal saline with added food grade colour was used as placebo. Post FMT, recipients were encouraged to retain the slurry for 4–6 h. All patients were followed up during each session of intervention for disease activity and clinical outcomes, slurry retention time, and adverse events.

2.4. Clinical outcomes

The clinical status and laboratory and endoscopic findings were recorded at each visit, or earlier in case of worsening of symptoms. Disease activity was assessed by Mayo Score at each visit. Histological disease activity was assessed using the Nancy Index at Week 48, by a blinded pathologist [VN].[26] The worst site of inflammation was assessed using the Mayo endoscopic subscore and a blinded review, and consensus scoring of endoscopic images [photographs] was done by two gastroenterologists [AjS, RM]. The primary endpoint was maintenance of steroid-free clinical remission [Mayo score ≤2, all subscores ≤ 1] at Week 48. Secondary endpoints were achievement of endoscopic remission [endoscopic Mayo score 0] and histological remission [Nancy grade 0, 1] at Week 48. Clinical relapse was defined as worsening of diarrhoea, need for any treatment escalation [defined as the need for increasing the dose of ongoing drugs, including topical medication, or any drug changes] to induce remission, hospitalisation, or colectomy. All patients who relapsed on treatment and those who were lost to follow-up were considered as treatment failures. Adverse events like fever, abdominal pain or distension, nausea, vomiting, anorexia, worsening of diarrhoea, perianal or rectal pain, flatulence, borborygmi, bloating, constipation, urinary tract infection, respiratory tract infection, etc. were recorded at each visit. In addition, all patients were advised to inform about any post-FMT adverse events either by telephone or by visiting the outpatient department. A serious adverse event was defined as any untoward medical occurrence after enrolment into the study, resulting in inpatient hospitalisation or prolongation of hospitalisation, which was life-threatening or resulted in death of the patient.

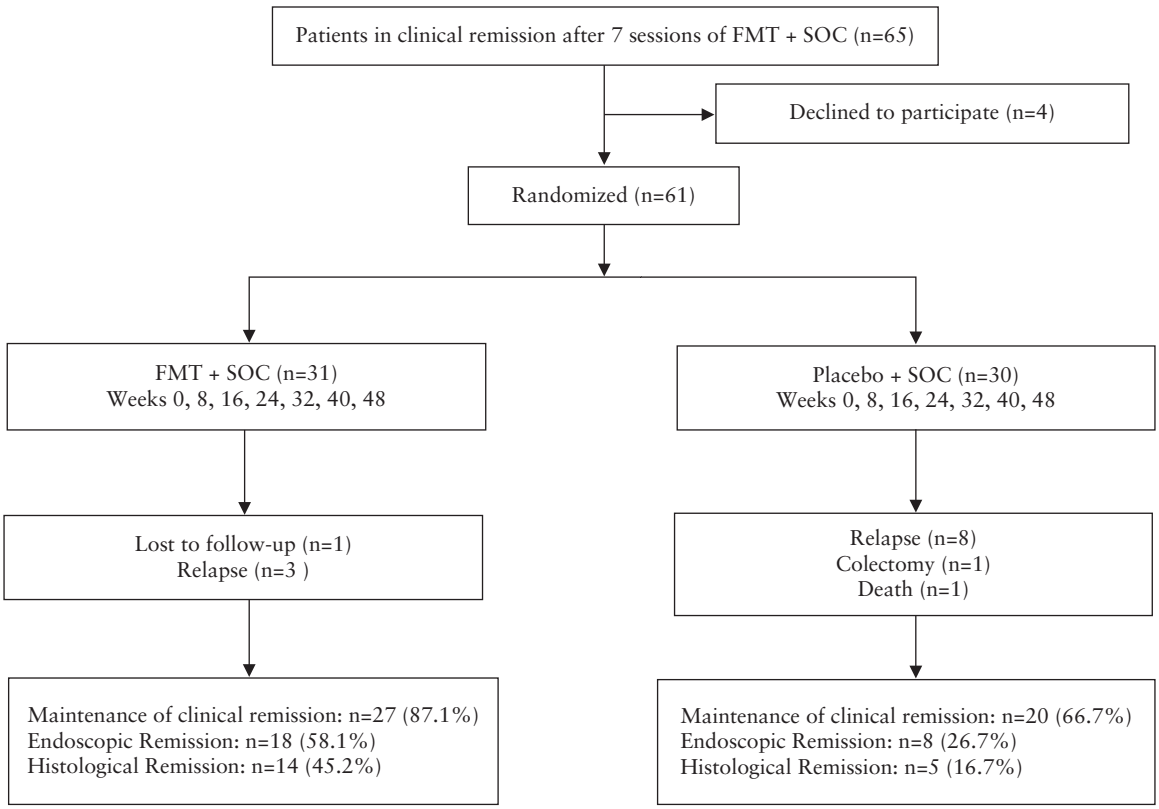

Figure 1. Flow diagram of patients included in the study. FMT, faecal microbiota transplantation; SOC, standard of care therapy; UC, ulcerative colitis.

2.5. Statistical analysis

An intention-to-treat analysis was done and included all patients who underwent one session of FMT after initial clinical remission. Data were described in terms of frequencies [number of cases] and relative frequencies [percentages], as appropriate. Normally distributed continuous data were expressed as mean (±standard deviation [SD]). Subjects [FMT] were compared with the controls [placebo]. The clinical response in both groups was compared at 48 weeks by using an unpaired Student's t test and a chi square test for continuous and categorical variables, respectively. SPSS Statistics v21.0 was used for statistical analysis. Using the standard $\alpha = 0.05$ cut off, $p < 0.05$ was considered as statistically significant.

3. Results

Between September 2015 and June 2017, 128 consecutive patients with active UC were offered FMT as an add-on therapy, of whom 112 patients consented for the same. Clinical remission with FMT [seven sessions] was achieved in 65/112 patients [58%] [Supplementary Figure 1]. Eight weeks after the last session of FMT in induction phase, the patients in remission were then offered maintenance therapy with FMT. Four patients refused to consent for the same; the remaining 61 patients were randomly allocated to receive either FMT [$n = 31$] or placebo [$n = 30$], in addition to the standard of care therapies, every 8 weeks [Figure 1]. The baseline characteristics of both groups were similar, except for a higher erythrocyte sedimentation rate [ESR] in the FMT group [Table 1]. None of the patients was on maintenance biologics during the study. Ileocolonoscopy was performed under conscious sedation and faecal slurry delivered into ileum/caecum. The mean slurry retention times [hours] were 4.51 ± 0.4 and 4.64 ± 0.70, respectively, for patients on FMT and placebo infusion.

Table 1. Baseline characteristics of the enrolled population

	FMT [$n = 31$]	Placebo [$n = 30$]	p-value
Mean age [years]	33 ± 12.4	34.6 ± 12.3	0.622
Males [**n**] [%]	22 [70.9]	22 [73.3]	0.837
Non-smokers [*n*] [%]	28 [90.3]	26 [86.7]	0.654
Disease extent			
Left-sided colitis	25 [80.6]	22 [73.3]	0.49
Extensive colitis	6 [19.4]	8 [26.7]	
Disease duration [mean ± SD] [years]	4.1 ± 2.9	4.5 ± 3.5	0.658
Number of relapses in past	1 [0–5]	1 [0–5]	
Median [range]			0.592
Concomitant medications [*n*][%]			
5-ASA	31 [100]	30 [100]	
AZA/6-MP	19 [61.3]	16 [53.3]	0.53
Previous exposure to biologics			
Infliximab	5 [16.1]	3 [10]	0.48
Adalimumab biosimilar	2 [6.5]	4 [13.3]	0.37
Mean CRP [mg/L]	5.1 ± 2.1	4.5 ± 1.9	0.224
Mean ESR [mm/1st h]	15.8 ± 6.8	12.3 ± 4.5	0.020
Mean Mayo Score	1.9 ± 0.3	1.8 ± 0.4	0.297
Mean Endoscopic Mayo Score	0.9 ± 0.3	0.8 ± 0.4	0.685

SD, standard deviation; 5-ASA, 5-aminosalicylates; 6-MP, 6-mercaptopurine; AZA, azathiopurine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMT, faecal microbiota transplantation.

The primary outcome of maintenance of clinical remission at 48 weeks was achieved in 27/31 [87.1%] patients allocated FMT versus 20/30 [66.7%] patients assigned placebo (Yates corrected chi

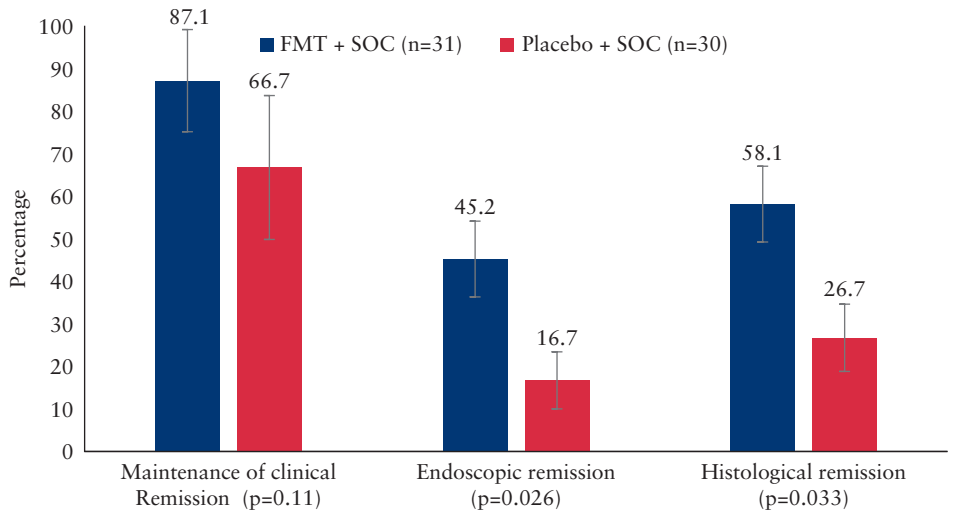

Figure 2. Bar graph showing clinical outcomes of patients. FMT, faecal microbiota transplantation; SOC, standard of care therapy.

square = 2.54, p = 0.111 [Figure 2, Table 2]). Secondary endpoints of endoscopic remission (18/31 [58.1%] with FMT versus 8/30 [26.7%] with placebo), [Yates corrected chi square = 4.93, p = 0.026] and histological remission (14/31 [45.2%] with FMT versus 5/30 [16.7%] with placebo) [Yates corrected chi square = 4.52, p = 0.033] were achieved in a significantly higher number of patients with FMT [Figure 2, Table 2]. Inflammatory markers (ESR and C-reactive protein [CRP]) were both significantly higher in the placebo arm at Week 48 [Table 2].

Of the 61 patients in clinical remission, only nine were in endoscopic remission [FMT: n = 4, placebo: n = 5] at the start of the study [Week 0]. At 48 weeks, addition of FMT to standard of care resulted in maintenance of endoscopic remission in all four patients, and 14 additional patients achieved endoscopic mucosal healing [before and after treatment, Yates corrected chi square = 11.91, p <0.001]. On the other hand, in the placebo group, all five patients maintained endoscopic remission and three more patients achieved endoscopic mucosal healing[before and after treatment, Yates corrected chi square = 0.398, p = 0.538].

Three patients receiving FMT [9.7%] and eight patients on placebo [26.7%] relapsed [Yates corrected chi square = 1.94, p = 0.164]. The likelihood of a relapse was higher in the placebo group (risk ratio: 2.6 [0.9–7.3, p = 0.07]). A majority of the relapses [FMT: 2/3; placebo: 8/8] were noted after Week 24. All relapses were treated with steroids along with the standard of care. One patient on FMT discontinued therapy as he was asymptomatic and refused repeated interventions. There were no serious adverse events necessitating discontinuation of treatment in patients on FMT [Table 3]. One patient relapsed on placebo and did not respond to steroids, thus requiring colectomy. Another patient in the placebo group died of myocardial infarction [unrelated to FMT].

4. Discussion

Faecal microbiota transplant is a novel therapeutic tool in UC. Three of the four randomised controlled trials [RCTs] to date, along with several case series, suggest its efficacy for inducing remission in active UC.[20–23,27–33] Ours is a pilot study to assess the role of FMT in maintenance of remission in patients with UC. A trend towards a higher rate of maintenance of steroid-free clinical remission was noted with addition of FMT to SOC, though this did not achieve statistical significance. However, the pre-specified secondary endpoints of both endoscopic and histological remission were statistically superior in patients receiving FMT as compared with those receiving placebo.

Table 2. Outcome measures comparing faecal microbiota transplantation with placebo for maintenance of remission at Week 48.

Outcome Measure	FMT	Placebo	p-value
Clinical remission	27/31	20/30	0.111
Endoscopic remission	18/31	8/30	0.026
Histological remission	14/31	5/30	0.033
ESR [mm/h] [mean ± std. dev]	10.1 ± 2.8	20.5 [5.3]	<0.001
CRP [mg/L] [mean ± std. dev]	4.5 ± 1.9	7.2 [2.5]	<0.001
Serious adverse events	0	0	—

FMT, faecal microbiota transplantation; CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

FMT is a robust method of manipulation of gut microbiota, which has emerged as a potential therapy for patients with UC, after its success in treatment of *Clostridium difficile* infection.[34]It has been shown to increase the diversity of the faecal bacterial populations in the recipients,[35,36]and this donor microbiota engraftment may result in long-lasting response in patients with *Clostridium difficile* infection.[37] An early study on the use of FMT for active UC suggested that it was efficacious and achieved long-term [1–13 years] clinical, endoscopic, and histological remission.[38] Subsequent case series and reports showed mixed results, and none showed a sustained long-term benefit with a limited duration of FMT.[39–41] Our study suggests that FMT-induced remission is not sustained; more patients in the placebo group suffered relapses, though the difference was not statistically significant. Our protocol of sustaining clinical remission with 8-weekly FMT was found to be effective.

The therapeutic goal of treatment in IBD has evolved from mere control of symptoms [i.e. resolution of diarrhea and control of rectal bleeding] to achievement of deep remission. In UC, there is no validated definition of deep remission; however, it has been defined as achievement of both clinical and endoscopic mucosal healing.[42] Once deep remission is achieved, the risk of relapse, hospitalisation, development of colorectal malignancy, and need for colectomy is reduced.[43,44] We observed that 52/61 [85.2%] of our patients [FMT: 27/31, placebo:25/30] in clinical remission still had an inflamed

Table 3. Adverse events experienced by the patients and controls during the study period.

Time	Week 0		Week 8		Week 16		Week 24		Week 32		Week 40		Week 48	
Adverse events	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo	FMT	Placebo
Fever[a]	1	0	1	0	1	1	0	0	0	0	0	0	0	0
Transient abdominal pain/distension	2	2	2	2	2	2	1	1	1	0	1	1	1	0
Nausea/vomiting	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Transient worsening of diarrhoea[b]	1	0	1	1	1	1	0	0	1	1	0	0	0	0
Perianal or rectal pain	1	1	0	1	0	0	0	0	0	0	0	0	0	0
Flatulance	2	1	2	2	1	1	1	0	0	0	0	1	0	0
Others	0	0	0	0	0	0	0	0	0	0	0	1	0	0

FMT, faecal microbiota transplantation.

[a]Fever was low-grade and self-limiting in all patients.

[b]Managed conservatively, no antibiotics or probiotics were given.

mucosa on endoscopy [Mayo endoscopic score 1] at baseline. With continuation of FMT, at 48 weeks all the patients in endoscopic remission initially at Week 0 maintained the same, and an additional 14 patients [45.2%] in the FMT group and three patients [10%] in placebo group achieved endoscopic mucosal healing. Thus, a total of 18/31 [58.1%] patients achieved endoscopic mucosal healing with FMT at 48 weeks, as compared with 8/30 [26.7%] with placebo, and this was significantly higher than the pre-treatment status. Unlike what can occur with thiopurines and biologics, maintenance therapy with FMT in this small pilot study was associated with few adverse events, none of which was serious to warrant discontinuation.

In patients with UC in clinical and endoscopic remission, histological activity is an independent risk factor for clinical relapse and thus histological remission is now being considered as an endpoint in clinical trials and a treatment goal in clinical practice in patients with UC.[45–47] There are very few studies assessing the rates of histological healing with conventional therapies in UC; 5-ASA compounds can improve histology in 30–60% of the patients, but only 10–30% achieve histological remission.[48–51] A study on 32 refractory active UC patients maintained on azathioprine showed 78% histological remission, but 90% of these patients relapsed within a median duration of 4 years.[52] Biologics have also shown significant reduction in the histological score [67%] but histological remission was noted in only one-third of the patients.[53] In our study, among patients maintained on FMT, histological remission was achieved in 45.2% which was statistically greater than among those on placebo [6.7%]. Thus, FMT seems to be an effective therapy for maintenance of long-term remission in UC patients.

The positive outcomes achieved in our study could be attributed to various factors. First, we used a colonoscopic route for administration of faecal slurry into the ileum. Of the four RCTs on FMT in UC published so far, those with a colonic or rectal instillation of faecal slurry[23,54] have shown better response compared with the upper gastrointestinal [GI] route of administration.[21] It has been hypothesised that instillation of the faecal slurry in the upper GI tract may not be effective, as gastric acid can destroy *Bacteroides* and *Firmicutes*.[55] Furthermore, the microbial uptake may be better when faecal samples are administered by colonoscopy, as inflammation in UC starts in rectum and proceeds proximally and dysbiosis is expected to be more in inflamed areas than in the non-inflamed areas.[56] In addition to this, colonoscopic administration ensured a directly observed therapy [as opposed to home enemas] and larger volumes of donor faeces could be administered, with a good retention time. Another factor which may have resulted in positive results was pre-FMT bowel preparation. The role of bowel preparation in published literature is controversial. However, an adequate bowel preparation before the procedure may help in successful colonisation of donor microbiota in the recipient by clearing the pro-inflammatory bacteria before the introduction of new flora.[57] In addition, it has additional benefits of adequate mucosal assessment during each session. However, bowel preparation with polyethylene glycol may itself cause changes in microbiome and thus produce results not attributable to FMT alone.[58]

Our study had a few limitations. The power achieved with the current sample size was 49%. To achieve power of 80%, an alpha error of 5%, and assuming similar outcomes, the sample size required is 80 in each arm. It was difficult to attain this sample size at a single centre; however, our pilot study was randomised and had a control group, which imparts strength to the same. Though the colonoscopic route is more efficacious than an upper GI administration as already discussed, repeated procedures with previous preparation may not be accepted by many patients. Using oral encapsulated FMT with a colonic release may increase the acceptance of FMT for maintenance of remission over longer periods of time.[59] The data for maintenance of remission is for 48 weeks only, and microbiome analysis of the patients and donors has not been done yet. However, despite these limitations, there certainly is a signal that FMT for maintenance of remission in UC may be effective and larger multicentre studies with an adequate sample size, long-term follow-up, and detailed microbiome analysis of the patients and donors may be planned in future to substantiate the same.

To conclude, addition of FMT to the standard of care may aid in maintenance of steroid-free clinical remission in a larger number of patients. It also enhances the achievement of endoscopic and histological remission. Larger multicentre studies with a longer follow-up and data on serial changes in histology and microbiome are needed to establish FMT as a treatment option for maintenance of remission.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

AjS: concept and design; collection, analysis, and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article. RM: concept and design; collection, analysis, and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article. ArS: collection, analysis, and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article. VMi: concept and design; analysis and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article. VMe: analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article. VN: data analysis; critical revision of the article for important intellectual content; final approval of the article. TS: data analysis; critical revision of the article for important intellectual content; final approval of the article. ASP: data collection; critical revision of the article for important intellectual content; final approval of the article.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;**105**:501–23; quiz 524.
2. Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for inducing remission in ulcerative colitis. *Cochrane Database Syst Rev* 2000;CD000543.
3. Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for maintaining remission in ulcerative colitis. *Cochrane Database Syst Rev* 2000;CD000544.
4. Ford AC, Khan KJ, Achkar J-P, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2012;**107**:167–76; author reply 177.
5. Timmer A, Patton PH, Chande N, McDonald JWD, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;CD000478.
6. Hosseini SV, Taghavi SA, Jafari P, *et al*. Incidence of ulcerative colitis relapse: a prospective cohort study in Southern Iran. *Ann Colorectal Res* 2016;**4**. doi:10.17795/acr-34565.
7. Nagahori M, Kochi S, Hanai H, *et al.*; OPTIMUM Study Group. Real life results in using 5-ASA for maintaining mild to moderate UC patients in Japan, a multi-center study, OPTIMUM Study. *BMC Gastroenterol* 2017;**17**:47.
8. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;CD000544.
9. Sandborn WJ, Korzenik J, Lashner B, *et al*. Once-daily dosing of delayed-release oral mesalamine [400-mg tablet] is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology* 2010;**138**:1286–96, 1296.e1–3.
10. Kamm MA, Lichtenstein GR, Sandborn WJ, *et al*. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008;**57**:893–902.
11. Ford AC, Achkar J-P, Khan KJ, *et al*. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:601–16.
12. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016;CD000544.
13. Rutgeerts P, Sandborn WJ, Feagan BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76.
14. Sandborn WJ, van Assche G, Reinisch W, *et al*. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;**142**:257–65.e1–3.
15. Feagan BG, Rutgeerts P, Sands BE, *et al.*; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;**369**:699–710.
16. Keane J, Gershon S, Wise RP, *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;**345**:1098–104.
17. Puri AS, Desai D, Sood A, Sachdeva S. Infliximab-induced tuberculosis in patients with UC: experience from India - a country with high prevalence of tuberculosis. *J Gastroenterol Hepatol* 2017;**32**:1191–4.
18. Peyrin-Biroulet L, Lémann M. Review article: remission rates achievable by current therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;**33**:870–9. doi:10.1111/j.1365-2036.2011.04599.x
19. Shen ZH, Zhu CX, Quan YS, *et al*. Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation. *World J Gastroenterol* 2018;**24**:5–14.
20. Moayyedi P, Surette MG, Kim PT, *et al*. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* 2015;**149**:102–9.e6.
21. Rossen NG, Fuentes S, van der Spek MJ, *et al*. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology* 2015;**149**:110–8.e4.
22. Costello SP, Hughes PA, Waters O, *et al*. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA* 2019;**321**:156–64.
23. Paramsothy S, Kamm MA, Kaakoush NO, *et al*. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017;**389**:1218–28.
24. Kellermayer R, Nagy-Szakal D, Harris RA, *et al*. Serial fecal microbiota transplantation alters mucosal gene expression in pediatric ulcerative colitis. *Am J Gastroenterol* 2015;**110**:604–6.
25. Sood A, Mahajan R, Juyal G, *et al*. Efficacy of fecal microbiota therapy in steroid dependent ulcerative colitis: a real world intention-to-treat analysis. *Intest Res* 2019;**17**:78–86.
26. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, *et al*. Development and validation of the Nancy histological index for UC. *Gut* 2017;**66**:43–9.
27. Kump PK, Gröchenig HP, Lackner S, *et al*. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. *Inflamm Bowel Dis* 2013;**19**:2155–65.
28. Kunde S, Pham A, Bonczyk S, *et al*. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013;**56**:597–601.
29. Ren R, Sun G, Yang Y, *et al*. [A pilot study of treating ulcerative colitis with fecal microbiota transplantation]. *Zhonghua Nei Ke Za Zhi* 2015;**54**:411–5.
30. Wei Y, Zhu W, Gong J, *et al*. Fecal microbiota transplantation improves the quality of life in patients with inflammatory bowel disease. *Gastroenterol Res Pract* 2015;**2015**:517597.
31. Suskind DL, Singh N, Nielson H, Wahbeh G. Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2015;**60**:27–9.
32. Angelberger S, Reinisch W, Makristathis A, *et al*. Temporal bacterial community dynamics vary among ulcerative colitis patients after fecal microbiota transplantation. *Am J Gastroenterol* 2013;**108**:1620–30.
33. Cui B, Li P, Xu L, *et al*. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. *J Transl Med* 2015;**13**:298.

34. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* 1958;**44**:854–9.
35. Khoruts A, Dicksved J, Jansson JK, Sadowsky MJ. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. *J Clin Gastroenterol* 2010;**44**:354–60.
36. Hamilton MJ, Weingarden AR, Unno T, Khoruts A, Sadowsky MJ. High-throughput DNA sequence analysis reveals stable engraftment of gut microbiota following transplantation of previously frozen fecal bacteria. *Gut Microbes* 2013;**4**:125–35.
37. Weingarden A, González A, Vázquez-Baeza Y, *et al*. Dynamic changes in short- and long-term bacterial composition following fecal microbiota transplantation for recurrent Clostridium difficile infection. *Microbiome* 2015;**3**:10.
38. Borody TJ, Warren EF, Leis S, Surace R, Ashman O. Treatment of ulcerative colitis using fecal bacteriotherapy. *J Clin Gastroenterol* 2003;**37**:42–7.
39. Brandt LJ, Aroniadis OC, Mellow M, *et al*. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012;**107**:1079–87.
40. Kump PK, Gröchenig HP, Lackner S, *et al*. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. *Inflamm Bowel Dis* 2013;**19**:2155–65.
41. Vermeire S, Joossens M, Verbeke K, *et al*. Donor species richness determines faecal microbiota transplantation success in inflammatory bowel disease. *J Crohns Colitis* 2016;**10**:387–94.
42. Zallot C, Peyrin-Biroulet L. Deep remission in inflammatory bowel disease: looking beyond symptoms. *Curr Gastroenterol Rep* 2013;**15**:315.
43. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al*. Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE]: determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;**110**:1324–38.
44. Rutter M, Saunders B, Wilkinson K, *et al*. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;**126**:451–9.
45. Peyrin–Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? *Clin Gastroenterol Hepatol* 2014;**12**:929–34.e2.
46. Narang V, Kaur R, Garg B, *et al*. Association of endoscopic and histological remission with clinical course in patients of ulcerative colitis. *Intest Res* 2018;**16**:55–61.
47. Lobatón T, Bessissow T, Ruiz-Cerulla A, *et al*. Prognostic value of histological activity in patients with ulcerative colitis in deep remission: A prospective multicenter study. *United European Gastroenterol J* 2018;**6**:765–72.
48. Kruis W, Kiudelis G, Rácz I, *et al*.; International Salofalk OD Study Group. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009;**58**:233–40.
49. Prantera C, Viscido A, Biancone L, Francavilla A, Giglio L, Campieri M. A new oral delivery system for 5-ASA: preliminary clinical findings for MMx. *Inflamm Bowel Dis* 2005;**11**:421–7.
50. Kruis W, Bar-Meir S, Feher J, *et al*. The optimal dose of 5-aminosalicylic acid in active ulcerative colitis: a dose-finding study with newly developed mesalamine. *Clin Gastroenterol Hepatol* 2003;**1**:36–43.
51. Green JR, Mansfield JC, Gibson JA, Kerr GD, Thornton PC. A double-blind comparison of balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in patients with newly diagnosed or relapsed active ulcerative colitis. *Aliment Pharmacol Ther* 2002;**16**:61–8.
52. Paoluzi OA, Pica R, Marcheggiano A, *et al*. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002;**16**:1751–9.
53. Hassan C, Ierardi E, Burattini O, *et al*. Tumour necrosis factor alpha down-regulation parallels inflammatory regression in ulcerative colitis patients treated with infliximab. *Dig Liver Dis* 2007;**39**:811–7.
54. Costello SP, Waters O, Bryant RV, *et al*. Short duration, low intensity, pooled fecal microbiota transplantation induces remission in patients with mild-moderately active ulcerative colitis: a randomised controlled trial. *Gastroenterology* 2017;**152**:S198–9.
55. Damman CJ, Miller SI, Surawicz CM, Zisman TL. The microbiome and inflammatory bowel disease: is there a therapeutic role for fecal microbiota transplantation? *Am J Gastroenterol* 2012;**107**:1452–9.
56. Walker AW, Sanderson JD, Churcher C, *et al*. High-throughput clone library analysis of the mucosa-associated microbiota reveals dysbiosis and differences between inflamed and non-inflamed regions of the intestine in inflammatory bowel disease. *BMC Microbiol* 2011;**11**:7.
57. Agrawal M, Aroniadis OC, Brandt LJ, *et al*. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated clostridium difficile infection in 146 elderly individuals. *J Clin Gastroenterol* 2016;**50**:403–7.
58. Jalanka J, Salonen A, Salojärvi J, *et al*. Effects of bowel cleansing on the intestinal microbiota. *Gut* 2015;**64**:1562–8.
59. Allegretti JR, Fischer M, Sagi SV, *et al*. Fecal microbiota transplantation capsules with targeted colonic versus gastric delivery in recurrent clostridium difficile infection: a comparative cohort analysis of high and lose dose. *Dig Dis Sci* 2018, Dec 5. doi: 10.1007/s10620-018-5396-6. [Epub ahead of print.]