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**Can control of gut microbiota be a future therapeutic option for inflammatory bowel disease?**

Nishida A *et al.* Control of gut microbiota in IBD

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**Abstract**

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract encompassing two main clinical entities, Crohn’s disease and ulcerative colitis. Accumulated evidence indicates that an aberrant immune activation caused by the interplay of genetic susceptibility and environmental impact on the gut microbiota may be involved in the pathogenesis of IBD. Rapid advances in next-generation sequencing technology have enabled a number of studies to identify the alteration of the gut microbiota, termed dysbiosis, in IBD. Moreover, the alteration in the metabolites derived from the gut microbiota in IBD has also been described in many studies. Therefore, microbiota-based interventions such as fecal microbiota transplantation (FMT) have attracted attention as a novel therapeutic option in IBD. However, in clinical trials, the efficacy of FMT for IBD remains controversial. Additional basic and clinical studies are required to validate whether FMT can assume a complementary role in the treatment of IBD. The present review provides a synopsis on dysbiosis in IBD and on the association between the gut microbiota and the pathogenesis of IBD. In addition, we summarize the use of probiotics in IBD and the results of current clinical trials of FMT for IBD.

**Key Words:** Inflammatory bowel disease; Dysbiosis; Fecal microbiota transplantation; Short chain fatty acid; Probiotics

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**Core Tip:** In this review, we discuss the gut microbiota in inflammatory bowel disease and gut microbiota-derived metabolites, especially short chain fatty acids. The anti-inflammatory function of short chain fatty acids on the mucosal immune system in the gastrointestinal tract is also discussed. In addition, we review the efficacy of probiotics on inflammatory bowel disease and the current clinical trials on the effectiveness of fecal microbiota transplantation on inflammatory bowel disease.

**INTRODUCTION**

Crohn’s disease (CD) and ulcerative colitis (UC), which are known as inflammatory bowel diseases (IBD), are chronic and relapsing inflammatory disorders of the gastrointestinal tract[1,2]. The precise etiology and pathogenesis remain to be elucidated. Genome-wide association studies have identified over 200 IBD associated-susceptible genes, some of which are known to be involved or implicated in mediating host responses to the gut microbiota[3]. This has evoked the possibility that the gut microbiota is implicated in the pathogenesis of IBD[4-7].

The human digestive tract is inhabited by more than 100 trillion commensal bacteria, which exceeds the total number of human cells of 37 trillion[8,9]. The concentration of human intestinal bacteria has been estimated to be from 1011 to 1012 cells per gram of luminal contents[10,11]. The intestinal bacteria regulate the balance between each bacterium by interacting with each other, thereby maintaining the homeostasis of the intestinal environment. More than 99% of the bacteria that live in the human intestine belong to the four major phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, of which Firmicutes is the most predominant phylum followed by Bacteroidetes[10,12].

Recent studies have shown that the composition of human gut microbiota is closely linked to health and disease[13,14]. Moreover, the gut microbiota contributes to the differentiation and maturation of intestinal epithelial cells and immune cells, the supply of energy to the host through metabolic processes, and protection against infection by pathogens[10]. Humans, on the other hand, provide the gut microbiota with an anaerobic place to reside. In this way, a symbiotic relationship is established between the gut microbiota and human host[15].

Developments in gene sequencing technologies as well as the increased availability of powerful bioinformatic tools have enabled novel insights into the microbial composition of human gut microbiota and the effect of microbial communities on human physiology and disease[16,17]. Recent studies using these technologies have indicated that abnormal microbiota composition, known as “dysbiosis,” and a decreased complexity of the gut microbial ecosystem are common features in patients with IBD. Moreover, it has been demonstrated that dysbiosis is involved in the pathophysiology of non-gastrointestinal diseases such as obesity and diabetes[17,18], in addition to gastrointestinal diseases such as IBD and irritable bowel syndrome[6,7,19].

Recently, it has been widely recognized that the gut microbiota plays a vital role in human immunity, metabolism, and diseases[4,6,20-22], leading to the idea of considering it as an organ. Based on this idea, the gut microbiota is sometimes called a “superorganism” or “forgotten organ”[23]. Considering these various functions of the gut microbiota on human biological functions, controlling its composition and diversity might allow us to treat or cure human diseases.

In this review, we will discuss the relationship between the gut microbiota and IBD, the efficacy of probiotics on IBD, and the current status of fecal microbiota transplantation (FMT) as a therapeutic option for IBD.

**The gut microbiota in IBD**

Various alterations of the gut microbiota have been reported in patients with IBD. The most consistent findings of the gut microbiota in IBD patients are a reduction of diversity and a reduction of Firmicutes compared to healthy individuals[6,7,16]. Some studies on IBD patients have reported an increase in the phyla Proteobacteria and Bacteroidetes, while others have reported a decrease in these phyla[5,7].

*Faecalibacterium* *prausnitzii* (*F. prausnitzii*), which belongs to *Clostridium* cluster IV, has been reported to have an anti-inflammatory effect by producing short-chain fatty acids (SCFAs: C2-C6), especially butyrate[24]. It has been reported that there is a reduced abundance of *F. prausnitzii* in patients with CD and that this deficiency is associated with postoperative recurrence of CD[25]. It has been demonstrated that *F. prausnitzii*, *Blautia faecis*, *Roseburia inulinivorans*, *Ruminococcus torques*, and *Clostridium lavalense* are decreased in patients with CD when compared to healthy subjects[25,26] and that the number of *F. prausnitzii* is correlated with the risk of relapse of ileal CD after surgery[27]. Deficient colonization of *F. prausnitzii* was observed in UC patients during remission, and the recovery of the *F. prausnitzii* population after relapse is associated with the maintenance of clinical remission[27]. Moreover, Sokol *et al*[28] showed that human peripheral blood mononuclear cells stimulated with *F. prausnitzii* induce the production of interleukin (IL)-10 and inhibit the production of inflammatory cytokines, such as IL-12 and interferon-γ. Furthermore, a significant decrease of *Roseburia spp*. was shown in the gut microbiota of healthy individuals with a high genetic risk for IBD[29].

Another consistent finding from a number of reports is the relative increase in the phylum Proteobacteria, especially *Escherichia coli* *(E. coli)*, in CD patients. The CD-associated[30] proinflammatory *E. coli* is known as adhesion-invasive *E. coli*, which is a bacterium isolated from CD patients. Adhesion-invasive *E. coli* has been reported to increase the permeability of the intestinal epithelium and induce intestinal inflammation by adhering directly to it[31].

Thus, in IBD enterobacteria, along with a decrease in diversity, a decrease in anti-inflammatory bacteria (Firmicutes phylum) and an increase in proinflammatory bacteria (Proteobacteria phylum) were observed, and these changes have also been observed in IBD. It is possible that these factors contribute to chronic inflammation of the intestinal tract. It is possible that it contributes to chronic inflammation of the intestinal tract.

**Role of short-chain fatty acids in the intestinal tract**

Although most nutrients are digested and absorbed in the duodenum and small intestine, dietary fiber remains intact until it reaches the colon. Dietary fibers are complex carbohydrates of plant origin broken down by specialized enzymes produced by gut bacteria but indigestible by the host[32]. They have recently been redefined as microbiota-accessible carbohydrates (MACs) and represent the major energy source for colonic bacteria[33]. MACs favor an increase in beneficial bacteria. The composition and function of the gut microbiota are dependent on the availability of MACs[34]. In preclinical studies, low dietary MACs have been shown to aggravate the development of inflammatory diseases, including autoimmune diseases, infections, and allergies[35-38] (Figure 1).

SCFAs, namely, acetate, propionate, and butyrate, are produced in the intestinal tract by the gut microbiota during fermentation of dietary fibers under anaerobic conditions[17]. Among these SCFAs, butyrate is the main energy source for the intestinal epithelial cells. Butyric acid positively modulates mitochondrial function, such as enhancing oxidative phosphorylation and β-oxidation, leading to an increase in oxygen consumption of colonic epithelial cells[32,33,39,40]. As a result, the concentration of oxygen in the intestinal tract decreases, and the number of obligate anaerobic bacteria, including those Firmicutes phylum that produce butyrate, increases[41]. As mentioned above, there is a decrease in butyrate-producing bacteria, such as *F. prausnitzii*, *Clostridium* cluster IV and XIVa, and a decrease in the concentration of butyrate in the gut microbiota in IBD patients[26,42]. Therefore, the decrease of both butyrate-producing bacteria and concentration of butyrate may be involved in the development of IBD and the persistence of chronic intestinal inflammation.

It has been reported that the genus *Clostridium* is important for the induction of regulatory T cells with an immunosuppressive function by producing butyrate from MACs, and in turn, the butyrate suppresses inflammatory cytokines *via* mucin and antimicrobial peptides from intestinal epithelial cells[22,43-45]. Moreover, it has been reported that the genus *Clostridium* promotes the differentiation and proliferation of regulatory T cells by enhancing the production of transforming growth factor β from intestinal epithelial cells[43]. In addition to the direct function of butyrate on T cells, butyrate suppresses the induction of the inflammatory cytokine, IL-6, and enhances the production of the anti-inflammatory cytokine, IL-10, produced by macrophages and dendritic cells through GPR109a, which is the G protein-coupled receptor for butyrate[43,44]. Butyrate is also known to regulate gene expression epigenetically by inhibiting histone deacetylases. Recent studies have demonstrated that butyrate upregulates histone H3 acetylation at regulatory regions of the *Foxp3* gene and promotes the differentiation of naïve CD4+ T cells into regulatory T cells[45].

Based on these findings, SCFAs play an important role in maintaining intestinal homeostasis through their anti-inflammatory properties. Thus, the decreased concentration of SCFAs in the feces of IBD patients may be involved in the pathophysiology of IBD through multiple points of action.

**The effect of probiotics on IBD**

Probiotics are defined as “live microorganisms that when administered in adequate amounts confer a health benefit on the host”[46]. Over the past decade, there has been a great interest in the use of probiotics as a therapeutic option in IBD. However, highly reliable scientific evidence regarding the efficacy of probiotics in IBD has been lacking.

There is a large double-blind clinical trial to investigate the efficacy of *E. coli* Nissle 1917 on maintaining remission in comparison to mesalamine (1500 mg/d) in UC patients in clinical remission (*n* = 120). The clinical trial showed the similar relapse rate between *E. coli* Nissle 1917 and mesalamine (*E. coli* Nissle 1917 group: 14%, mesalamine group: 16%)[47]. This group conducted a second large trial to examine the efficacy of *E. coli* Nissle 1917 on maintaining UC remission compared to mesalamine (1500 mg/d). This study revealed a comparable clinical relapse rate (*E. coli* Nissle 1917 group: 36%, mesalamine group: 34%)[48].

There is one randomized clinical trial that examined whether the addition of *E. coli* Nissle 1917 to standard therapy increased the rate of remission of patients with active UC. While undergoing the induction therapy, subjects were randomized to *E. coli* Nissle 1917 group and mesalamine group (2400 mg/d). After remission, patients ware maintained on either mesalamine or *E. coli* Nissle 1917. The remission rates were similar in the mesalamine group (75%) and *E. coli* Nissle 1917 group (68%). Moreover, the relapse rates were also similar in mesalamine group (73%) and *E. coli* Nissle 1917 group (67%). Notably, it is the only probiotic mentioned in the European Crohn’s and Colitis Organization guidelines as an effective alternative to mesalamine in maintenance of remission in UC patients[49]. Collectively, the efficacy of *E. coli* Nissle 1917 on maintenance of remission was comparable to mesalamine.

To date, the evidence of the use of VSL#3 in UC patients has been accumulated. VAL#3 is a combination of four strains of *Lactobacillus* (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbruekii* subsp. *bulgaricus*), three strains of *Bifidobacteria* (*Bifidobacteria longim*, *Bifidobacteria breve*, and *Bifidobacteria infants*) and *Streptococcus salivarius* subsp. *Thermophilus*. Sood *et al*[50] conducted a randomized, double-blind clinical trial to investigate the efficacy of VSL#3 on mild-to-moderately active UC compared to placebo. By week 12, more patients given VSL#3 achieved remission (43%) as compared with those given placebo (15.7%; *P* < 0.001). Furthermore, by week 12, more patients in the VSL#3 group achieved mucosal healing (32%) as compared to the placebo group (15%; *P* < 0.03). Another study with similar design conducted by Tursi *et al*[51] also showed that the remission rate in VSL#3 group was higher than in the placebo group (44% *vs* 32%; *P* = 0.13). Collectively, these results suggest that the use of VSL#3 has a benefit in inducing remission in active UC.

There has been a lack of large clinical trials assessing the efficacy of probiotics in both inducing and maintaining the remission for patients with CD. A Cochrane review published in 2020 assessing the efficacy of probiotics to induce remission in CD patients found two studies that met criteria for inclusion[52]. One study had 11 subjects with mild-to-moderately active CD that randomized assignment to *Lactobacillus rhamnosus* strain GG or placebo. The other study had 35 subjects with active CD, whose CD activity index score of 150 to 450 randomized to receive a symbiotic treatment (freeze-dried *Bifidobacterium longum* and a commercial product) or placebo. The review concluded that there was no evidence to support the use of probiotics for the induction of remission in CD.

A Cochran systematic review published in 2006 assessing the efficacy of probiotics to maintain the remission in CD found seven small controlled studies worthy of inclusion in their review[53]. The review concluded that there was no evidence to suggest that probiotics are beneficial for the maintenance of remission in CD. In summary, large clinical trials in the efficacy of probiotics on active and quiescent CD should be conducted to change these conclusions in the future.

**The effect of FMT on IBD**

FMT aims to restore the intestinal microbiota in diseased individuals by transplanting intestinal microbiota from healthy donors[10]. FMT has been reported to be highly effective against recurrent *Clostridium difficile* infection[54]. The success of FMT in treating *Clostridium difficile* infection has attracted attention as a new therapeutic option for IBD. Several clinical studies have been conducted to examine the effect of FMT on IBD, but the results have been inconsistent so it cannot be stated with confidence whether or not the treatment is effective. Furthermore, in these studies, the protocols including donor selection, method of stool administration, and method of stool preparation are not consistent. Collectively, at present FMT has not yet been used clinically as a therapeutic option.

To date, the findings of four randomized controlled trials (RCTs) of FMT for UC patients have been published: two in Gastroenterology in 2015[55,56], one in The Lancet in 2017[57], and the other in the Journal of the American Medical Association in 2019[58] (Table 1). In a report from Canada in 2015, 50 mL of donor stool was administered six times by enema in an FMT group, and 50 mL of water was administered in the same manner in a placebo group. The remission rate in the FMT group was significantly higher than the placebo group [9/38 (24%) *vs* 2/37 (5%); *P* = 0.03][55]. On the other hand, according to a report from the Netherlands in 2015, donor stool was administered to patients at day 0 and 3 wk later using a nasoduodenal tube in an FMT group, and autologous stool was administered to patients in the same manner in a control group. In this study, there was no significant difference in the effect of FMT between the two groups[56]. More recently, two RCTs in patients with mild-to-moderately active UC were reported in 2017 and in 2019. Paramsothy *et al*[57] reported in 2017 that 81 UC patients were randomly assigned FMT or placebo and that the primary outcome was defined as steroid-free clinical remission with endoscopic remission or response at week 8. The rate of primary outcome of the FMT group was significantly higher than the placebo group [11/41 (27%) *vs* 3/40 (8%); *P* = 0.02]. Costello *et al*[58] reported that 73 patients with active UC were enrolled to an FMT group or autologous FMT group (placebo group). The steroid-free remission rate of the FMT group was significantly higher than that of the placebo group [12/38 (32%) *vs* 3/35 (9%); *P* = 0.03].

Since these four RCTs differ in donor selection, method of fecal administration, and the number of fecal administrations, it is difficult to make a direct comparison. It is presumed that increasing the number of FMT will be effective for UC. Based on the clinical data, FMT for UC may remain in clinical trials but not be adopted in practice. More high-quality RCTs are needed to optimize the protocol for FMT.

Sood *et al*[59] reported the effect of FMT in maintenance of remission in UC patients who had achieved clinical remission by FMT. In this pilot study, 61 patients with UC in clinical remission achieved after multisession FMT were randomized to an FMT group (*n* = 31) or placebo group (*n* = 30). There was no significant difference in the rate of steroid-free clinical remission between the FMT group and placebo group [27/31 (87.1%) *vs* 20/30 (66.7%); *P* = 0.111]. Secondary endpoints of endoscopic remission [FMT group: 18/31 (58.1%) *vs* placebo group: 8/30 (26.7%); *P* = 0.026] and histological remission [FMT group: 14/31 (45.2%) *vs* placebo group: 5/30 (16.7%); *P* = 0. 033] were achieved in a significantly higher number of patients with FMT. This pilot study suggested that maintenance FMT therapy may be one of the therapeutic options for UC patients in clinical remission.

To date, one pilot randomized controlled study has reported the effects of a single FMT administered *via* colonoscopy in patients with colonic or ileo-colonic CD who achieved clinical remission with systemic corticosteroids[60]. In this pilot study, 8 patients received FMT, and 9 patients received sham transplantation. The primary endpoint was the implantation of the donor microbiota at week 6. None of patients reached the primary endpoint. There was no significant difference in the steroid-free remission rate at week 10 between the FMT group and the sham group Stood [7/8 (87.5%) *vs* 4/9 (44.4%); *P* = 0.13]. The CD Endoscopic Index of Severity decreased significantly 6 wk after FMT [8.5 (4.6; 13.0) *vs* 3.5 (1.0; 8.9); *P* = 0.03] but not after sham [2.4 (0.0; 8.3) *vs* 2.7 (0.7; 10.0); *P* = 0.8]. Moreover, 6 wk after FMT, C-reactive protein levels remained stable [3.0 (3.0; 3.0) *vs* 3.0 (3.0; 14.2) mg/L; *P* = 0.05], while they had already started to increase in the sham group [3.0 (3.0; 4.2) *vs* 6.9 (4.0; 8.7) mg/L; *P* = 0.008). This pilot study indicated that the benefit of FMT over sham transplantation was observed for several clinically relevant endpoints, including CD Endoscopic Index of Severity and C-reactive protein level. Several reports have been published on the effects of FMT for CD on a small number of cases, but the results have been inconsistent. A recent systematic review and meta-analysis of 11 studies (four case reports and seven prospective uncontrolled cohort studies) on FMT for CD that included 83 CD patients showed an overall clinical remission rate of 50.5% (42/83)[61]. However, the result of one large study had a great influence on the remission rate. The authors indicated that their overall findings should therefore be treated with caution because of the potential bias from this one study[30].

**CONCLUSION**

A convergence of technology, data from clinical studies, and experimental insights have revealed that the gut microbiota and its metabolites markedly contribute to the pathogenesis of IBD. However, it remains unclear whether the dysbiosis of the gut microbiota observed in IBD is a cause or a consequence of chronic intestinal inflammation. To answer this question, more basic approaches to reveal the precise effects of the gut microbiota on intestinal functions, including immune system and barrier system, will be essential. Moreover, intestinal microorganisms other than bacteria, such as viruses, archaea, and fungi should be investigated. The results from these basic studies may help to clarify the situation.

Although there is great promise for novel probiotics, we need to be circumspect when there was a lack of proof in efficacy of probiotics on IBD. There are promising results for *E. coli* Nissle 1917 in maintenance of quiescent UC and VSL#3 in active UC. There is no evidence available to support the use of probiotics in CD. The same results were found in a recently published systematic review[62]. In the future, large clinical trials should be essential to determine the effect of probiotics on IBD.

FMT has attracted attention as a new therapeutic option for IBD. However, despite its significant effect in the treatment of *Clostridium difficile* infection, its therapeutic efficacy in IBD still remains limited. There are many factors that should be taken into consideration to increase the success rate of FMT in IBD, including disease state, selection of stool donors, route of fecal administration, number of infusions, and use of antibiotic pretreatment. Therefore, further basic research as well as clinical studies are required to understand the mechanisms of action of FMT and to improve FMT preparations, modes of administration, and donor selection.

Recently, the techniques of genetic engineering have been introduced into treatments with gut microbiota. Various genetic platforms to deliver therapeutic molecules have been developed and transformed into microorganisms[63]. For disease treatment, the microbial delivery of various therapeutic molecules has been tested[64]. Host proteins, bacterial therapeutic proteins, antigens, and synthetic metabolic pathways have been introduced into the host through heterogeneous production in microbes[64]. As part of another microbiome-based therapy, engineered microbes may open new avenues for the treatment for IBD.

In the future, the combination of gut microbiology, gastroenterology, and epidemiology with advances in the rapid analysis of the gut microbiota, metabolites, molecular signals, and genetic engineering promises the development of novel therapeutic strategies in IBD.

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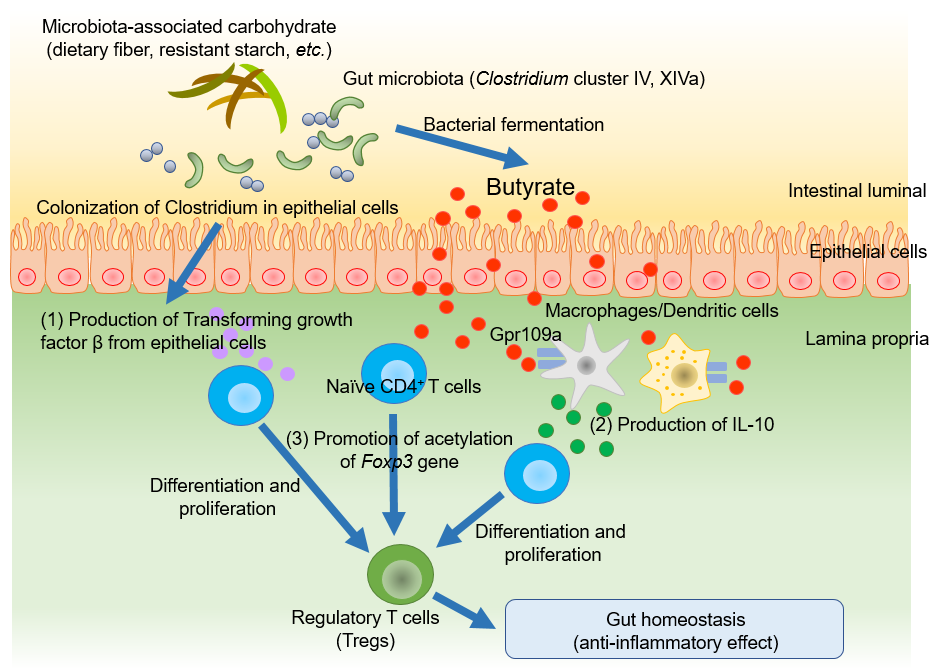
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**Figure Legends**



**Figure 1 Function of butyrate in intestinal mucosa.** Butyrate contributes to the maintenance of gut homeostasis by multiple mechanisms. Butyrate is mainly produced in the intestinal tract by bacteria of the Firmicutes phylum during fermentation of dietary fibers under anaerobic conditions. Butyrate is the main energy source for the intestinal epithelial cells. (1) The genus *Clostridium* promotes the differentiation and proliferation of regulatory T cells by enhancing the production of transforming growth factor β from intestinal epithelial cells; (2) Butyrate enhances the production of the anti-inflammatory cytokine, interleukin-10, produced by macrophages and dendritic cells through GPR109a, which is the G protein-coupled receptor for butyrate; and (3) Butyrate upregulates histone H3 acetylation at regulatory regions of the *Foxp3* gene and promotes the differentiation of naïve CD4+ T cells into regulatory T cells. IL: Interleukin.

**Table 1 Randomized controlled studies of fecal microbiota transplantation in ulcerative colitis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Moayyedi *et al*[55]** | **Rossen *et al*[56]** | **Paramsothy *et al*[57]** | **Costello *et al*[58]** |
| Date of publication | 2015 | 2015 | 2017 | 2019 |
| Reference number | 55 | 56 | 57 | 58 |
| Number of patients | 38 | 23 | 41 | 38 |
| Number of controls | 37 | 25 | 40 | 35 |
| Severity of UC | Mayo 4-12 (mild to severe) | SCCAI 4-11 (mild to moderate) | Mayo 4-10 (mild to moderate) | Mayo 3-10 (mild to moderate) |
| Donor and Donor stool | 6 volunteers | 15 donors | Multi-donors | Multi-donors |
| fresh or frozen | fresh | (3-7 donors), frozen | (3-4 donors), frozen |
| Mode of FMT | Retention enema | Nasoduodenal tube | Colonoscopy and enema | Colonoscopy and enema |
| Number of FMT | 6 | 2 | 41 | 3 |
| 1/wk × 6 wk | 0 and 3 wk | First infusion by colonoscopy + 5/wk for 8 wk by enema | 3/wk (colonoscopy followed by 2 enemas) |
| Follow-up | 6 wk | 12 wk | 8 wk | 8 wk |
| Pretreatment with antibiotics | No | No | No | No |
| Primary endpoint | Remission (Mayo ≤ 2 with an endoscopic score of 0) | Remission (SCCAI ≤ 2) combined with ≥ 1-point decrease in Mayo endoscopic score | Steroid-free clinical remission with endoscopic remission or response (Mayo ≤ 2, all subscores ≤ 1, and ≥ 1-point reduction in endoscopy subscore) | Steroid-free remission with endoscopic remission (Mayo ≤ 2 with endoscopic subscore ≤ 1) |
| Subjects who achieved the primary endpoint | 9/38 (24%) treated with FMT *vs* 2/37 (5%) control (*P* = 0.03) | 7/23 (30.4%) treated with FMT *vs* 5/25 (20.0%) control (*P* = 0.51) | 11/41 (27%) treated with FMT *vs* 3/40 (8%) control (*P* = 0.021) | 12/38 (32%) treated with FMT *vs* 3/35 (9%) control (*P* = 0.03) |

SCCAI: Simple Clinical Colitis Activity Index; FMT: Fecal microbiota transplantation; UC: Ulcerative colitis.