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REVIEW ARTICLE

Update on Fecal Microbiota Transplantation In Inflammatory Bowel Diseases

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Abstract

The microbiome in our digestive tract has beneficial and symbiotic effects on our health. Loss of this diversity may be associated with certain autoimmune diseases such as inflammatory bowel disease, a condition hallmarked by chronic inflammation of the gastrointestinal tract due to dysregulated immune response to host intestinal microflora. Fecal microbiota transplantation has been effective in treating medically refractory *Clostridium difficile* infection and is now being studied in other gastrointestinal diseases, including IBD. Several recent meta-analyses have been performed to determine the efficacy of using FMT in patients with Crohn's disease and Ulcerative Colitis. It has also been the focus of small trials in order to treat pouchitis and extraintestinal manifestations of IBD. This article is a systemic review of the up to date clinical trials and meta-analysis focusing on the use of FMT for patients with IBD.

Introduction

Inflammatory bowel disease (IBD) is a disorder characterized by chronic inflammation of the digestive tract. In 2015, the Centers for Disease Control and Prevention reported about 3 million new cases in the United States. What is alarming is that the incidence of IBD in our population is significantly increasing every year. Researchers believe that IBD is due to dysregulated immune response to host intestinal flora in genetically susceptible individuals. Common symptoms include persistent diarrhea, abdominal pain, gastrointestinal hemorrhage, fistulas, weight loss and chronic fatigue. Early trials using prebiotics and probiotics for treatment have yielded mixed results [1-3]. Due to its chronic nature, patients have a very poor quality of life and must endure long-term use of immunosuppressant therapy. While most patients respond to immunosuppressive therapy, in a subset of patients, even aggressive immunosuppression is not enough for the patient to enter remission. Due to the success of using fecal microbiota transplantation in treating *Clostridium difficile* infections [4-6], researchers are now looking at the possibility of using fecal microbiota transplantation (FMT) as a treatment for those who have few other non-surgical treatment options [7].

Search Methodology

Literature searches used for this article include PubMed, Medline, Embase and Google Scholar database ranging from the year 1950 to September 2018. This article is a systematic review of fecal microbiota transplantation as treatment in inflammatory bowel disease. Keywords used were “fecal microbiota transplantation” (fecal, faecal, or stool; microbiota or microbiome; transplantation, transplant, instillation, administration, infusion, or transfer), “inflammatory bowel disease,” “ulcerative colitis,” or “Crohn’s disease.” The reference lists of the clinical reviews, systematic reviews and meta-analyses identified with the above search criteria were also reviewed to identify any additional relevant publications that may have been missed.

Current Tests and Medical Therapy for Inflammatory bowel disease

IBD is an umbrella term that includes two major diseases: ulcerative colitis (UC) and Crohn’s disease. Treatment for patients with IBD is often based on severity, disease activity, IBD associated complications, and response to multidrug regimens. The Mayo Clinic Endoscopic Score and Simple Clinical Colitis Activity Index (SCCAI) help gauge the severity of ulcerative colitis and can assist the clinician in determining the choice of therapy for individual patients [8]. Simple Endoscopic Scores (SES) and Crohn’s disease Activity Index serve as a tool to help guide clinicians to determine optimal treatment options for patient with Crohn’s disease. The Index generally uses symptoms of diarrhea, abdominal pain, fever, fatigue, bloody stools, weight loss, and anorexia to determine the severity of disease. Patients with Crohn’s disease are at risk of severe malnutrition, bowel obstruction, ulcers, fistulas as well as side effects due to medical treatments and have higher risk of developing colon cancer [9,10]. Current guidelines require the patient’s symptomatology, laboratory findings and endoscopic findings to score the severity and activity of the patient’s disease [10].

Treatment is based on disease severity and presentation. Oral and/or topical mesalamine is the first line therapy for mild inflammatory bowel disease. Although mesalamine therapy has an excellent safety profile, clinical remission using mesalamine for mild to moderate disease ranges from 29 to 60%. Crohn's disease is more refractory than UC patients in achieving remission using mesalamine according to recent Cochrane meta-analysis [11,12]. Multiple immunomodulatory (azathioprine, mercaptopurine, methotrexate, cyclosporin, etc...) and biologic agents with immunosuppressive effects, including anti-tumor necrosis factor-alpha, anti-integrins, Janus Kinase inhibitors, and anti-IL12/IL23 agents, have been approved by the Food and Drug Administration for use in moderate to severe UC and Crohn's disease. However, up to one-half of the patients do not have clinical response, and less than 50% of responders maintaining clinical remission at 6 to 12 months with these biologic agents [13-16]. Additionally, there are the potential for serious adverse effects, including malignancy, sepsis, and demyelination, are major impediment to wider patient acceptability and long-term use of these drugs in clinical practice [17-20] Because of the limited efficacy and potential serious side-effects of the available treatment, novel therapies are being sought with fecal microbiota transplantation gaining interest as an alternative treatment for IBD.

"Dysbiosis" in inflammatory bowel disease

The human gastrointestinal tract is an immense microbial ecosystem composed of over 100 trillion microbes. There is mounting evidence that an imbalance of this ecosystem or "dysbiosis" plays a key role in developing IBD [21-23]. Studies using meta-genomic analysis in patients with IBD show overpopulation of certain taxa of microbes; specifically, overpopulation of *Enterobacteriaceae, Pasteurellacaea, Fusobacteriaceae* and decreased populations of *Bacteroides, Faecalibacterium, Rodeburia, Rumninococcus* species [22,24-26]. Dysbiosis may cause excessive toxin production by the harmful bacteria leading to inflammation of the intestinal mucosa [27,28]. Recognized factors that increase the risk of developing dysbiosis include age, heredity factors, diet, antibiotic treatment, intestinal mucosa, host immune system and overpopulation of certain bacterial microbes [29]. Alteration of microbiome such as the use of fecal diversion has been shown to induce remission in some Crohn's patients, which further suggests that FMT is a possible therapy for IBD [30,31].

Fecal Microbiota Transplantation in Inflammatory Bowel Disease: 1) Treatment of *Clostridium Difficile* Infection in Inflammatory Bowel Disease

Patients with IBD have frequent hospitalizations and are regularly exposed to antibiotic treatment. It is no surprise then that inflammatory bowel disease patients have increased incidence for developing colitis due to *Clostridium Difficile* Infection [32]. In patients without IBD, who develop a *Clostridium Difficile* Infection and fail standard treatments with standard antibiotics, FMT will achieve a 90% cure rate with the first FMT[6,33-37]. IBD patients with superimposed *Clostridium Difficile* Infection responds less well to FMT, but with successive FMT can achieve cure rate similar to patients without IBD. Studies show that IBD patients with *Clostridium Difficile* infection have a cure rate of 64% after first FMT but have increasing efficacy with subsequent treatments. For example, 90% of IBD patient will respond by the 3rd FMT; cure rates that are

equal to those patients without IBD [51]. A recent meta-analysis also showed that if initial treatment failed to treat *Clostridium Difficile* infection in IBD patients, multiple administrations of FMT would increase the cure rate and that the efficacy of FMT was similar to non-IBD patients. The cure rates were 78% with initial FMT and the overall successful cure rate was 87.7%. 10% of patients required more than 1 fecal microbiota transplantation to cure *Clostridium Difficile* infection. [52].

2) Effect of fecal microbiota transplantation Ulcerative Colitis

Recent randomized clinical trials provided evidence that FMT may be effective for IBD patients (Table 1).

Table 1- Result of randomized controlled trial on effectiveness of Fecal Microbiota Transplantation in UC.
Abbreviations: UC - Ulcerative Colitis
SSCAI – Simple Clinical Colitis Activity Index
FMT – Fecal Microbiota Transplantation

Parameter	Moayyedi et al (2015)	Rossen et al (2015)	Paramsothy et al (2016)	Costello et al (2017)
UC Activity	Any	Mild/Moderate	Mild/ Moderate	Mild/Moderate
Patients (FMT/Placebo)	75 (38/37)	48 (23/25)	81(41/40)	73 (38/35)
Stool Donor	Single	Single	Pooled Multidonor	Pooled Multidonor
Stool Preparation	Aerobic	Aerobic	Aerobic	Anaerioboic
Stool Form	Fresh or frozen	Fresh	Frozen	Frozen
Route Of Delivery	Enema	Nasoduodenal tube	Colonoscopy + Enema	Colonoscopy + Enema
Control	Water	Autologous stool	Colored saline	Autologous stool
FMT regimen	Once weekly enema x 6	Week 0 and 3	Day 0 colonoscopy + 5 times weekly enemas x 8 weeks	Day 0 colonoscopy + 2 enemas by day 7
Assessment	Week 7	Week 12	Week 8	Week 8
Primary Outcome	Composite Clinical and Endoscopic remission	Composite Clinical remission and Endoscopic improvement	Composite Clinical Remission and Endoscopic improvement	Composite Clinical and Endoscopic remission
Primary Outcome	FMT-24% Placebo-5% P=0.03	FMT-30% Placebo-20% P=0.51	FMT-27% Placebo-8% P=0.02	FMT-32% Placebo-9% P=0.02
Clinical Response	FMT-39% Placebo-24% P=0.16	FMT-43.5% Placebo-52% P=0.58	FMT-54% Placebo-23% P=0.004	FMT-55% Placebo-20% P<0.01

Three trials used FMT enemas vs. placebo administration [38-40] *Rossen et al* chose a nasoduodenal route with no notable difference in outcome However, this study is futile because of limited numbers of participants and lack of sufficiency [41]. The most recent meta-analysis from Paramsothy et al., showed that the pooled clinical remission and response rates of FMT in ulcerative colitis were 33% and 52%, respectively [42]. In addition, 140 patients in 4 randomized clinical trials within the same meta-analysis showed an odds ratio of 2.48 for clinical response and 2.89 for clinical remission with fecal microbiota transplantation in ulcerative colitis [42]. Based upon the available data, FMT is an effective treatment in moderate to severe ulcerative colitis. However, its efficacy appears to be lower than some of the currently available options. Additionally, long-term efficacy data with FMT in ulcerative colitis is also needed.

3) Treatment of Crohn's disease

The data on effectiveness of FMT in managing Crohn's disease is limited [42-46]. There was a meta-analysis study done which was composed of 6 cohort studies and it showed that 71 patients with Crohn's disease had a remission rate of 52% with fecal microbiota transplantation [43]. Nevertheless, the overall remission rate of this meta-analysis study was largely affected by one large cohort study from China with high treatment success rates [45]. Based upon the available data, more research on the safety and efficacy of FMT in Crohn's disease is needed.

Predictors of response to fecal microbiota transplantation

1) Disease severity

Patients with IBD are categorized as having mild, moderate, and severe disease. IBD patients with moderate to fulminant disease are less responsive to current medical therapy. Treatment efficacy with FMT also appears to have an inverse relationship with IBD disease severity. A study by *Paramsothy et al* found that success of FMT in ulcerative colitis was inversely related to clinical and endoscopic severity of ulcerative colitis[40]. Moreover, there is a concern regarding worsening of IBD after fecal microbiota transplantation that can be detrimental in patients with pre-existing severe IBD.

2) Donor type

The composition and quality of stool donor's gut microbiome may significantly impact clinical response of fecal microbiota transplantation in IBD. Several studies show a clear correlation between the donor's microbiome and the clinical response of the recipient after fecal microbiota transplantation treatment. The results of these studies showed that the responders to fecal microbiota transplantation would have diverse intestinal microbiome closely resembling the microbial composition of donors [38,43,46,47]. This result was observed in the clinical study on FMT in ulcerative colitis that shows the remission rate in recipients of donor B stool was 39% compared to 10% in recipients from another donor stool (P=0.06) [38]. *Paramsothy et al* used samples combined from multiple donors to theoretically increase the diversity of the donor sample and to circumvent the donor advantage by using multidonor stool. Post-hoc analysis showed that patients receiving multi sample donation had 18% response vs. single donor sample, which

showed 37% response [40]. Thus, it appears that there is an "ideal donor microbiome consortium" with higher IBD treatment effectiveness using stools from certain individuals. Diluting this "ideal donor consortium" (e.g. using pooled stool) would reduce the effectiveness of the FMT to treat IBD. The future success of FMT treatment for patients with IBD therefore requires more research in determining the ideal donor microbial type for improved treatment efficacy.

3) Donor stool type

FMT using fresh vs. frozen donor samples showed no statistically significant clinical response [48]. Notably, a clinical trial found that the remission rate of using frozen stool in FMT is significant higher compared to fresh stool (40% vs. 15% with P=0.06) [38]. In a similar meta-analysis study of FMT in ulcerative colitis, the overall remission rate with fecal microbiota transplantation using frozen stool is also significantly higher than fresh stool (36% vs. 28%; P=0.045). A reason that fresh stools are less effective in fecal microbiota transplantation could be that the anaerobic species can become depleted during the storage process. One of the anaerobic organisms, *Faecalibacterium puausnitzii,* has been identified as essential for a successful fecal microbiota transplantation treatment [49]. However, the clinical trial of FMT using anaerobic stool processing showed numerically similar efficacy to other trials using aerobic stool processing [38-40]. Currently, there is no therapeutic benefit when comparing frozen versus fresh stool samples.

4) Route of administration

The three routes of administration of fecal microbiota transplantation include depositing fecal microbiota directly into the colon (via colonoscopy or enema), administering via a naso-enteric tube, which delivers the fecal microbiota into the small bowel, or bypassing the stomach with capsules, which resist gastric acid degradation. Based on recent data of FMT treatment, the optimal route is by directly depositing the microbiota into the colon. Based on the clinical research of general fecal microbiota transplantation, clinical cure rate and improvement rate is 43% and 58.6% via the naso-enteric route, 41.5% and 61% respectively through colonoscopy, and 37% and 63% with the use of a capsule [50]. A recent meta-analysis looking at the route of administration only for patients with ulcerative colitis showed 20% via colonoscopy and 10% via naso-enteric route [38,40,41,51]. There are limited randomized controlled trials and meta-analysis with Crohn's disease and only positive outcomes have only been shown on a few cohort studies. Adverse effects, safeties and long-term outcomes of FMT for Crohn's disease are still unknown. Studies of FMT treatment for Crohn's patients are currently limited and larger studies are needed [52,53].

5) Timing and duration of administration

Recent meta-analysis and randomized controlled trials have shown that the timing and duration of FMT can affect the therapeutic effectiveness in IBD. More frequent and longer duration of FMT is of benefit to patients with IBD. This is the reason why protocols were set up using many trials instead of using two FMT sessions [38,40,41]. For ulcerative colitis, the clinical remission rate is higher when using 10 or more infusions (49%) when compared to 10 or less infusions (27%) [40]. However, the clinical study by Costello *et al* showed no difference in frequency of FMT adminis-

tration [24]. This may represent a scenario where too little is not enough and too much is unnecessary. More data clarifying the optimal intensity of FMT regimen is needed.

6) Pretreatment with antibiotics

Antibiotic pre-treatment may remove the dysbiotic microbial environment and enhance the engraftment of donor microbiota. Thus, research with regards to antibiotic administration 2-3 days before FMT for pretreatment has gained traction with many researchers [54,55]. A meta-analysis showed that pretreatment with antibiotics may increase the success rate of FMT in patients with ulcerative colitis (54% vs. 25.1, p=xx) [56,57]. Despite limited data, studies show possible beneficial effect of antibiotic pretreatment. If antibiotic pretreatment is used, it may be prudent to wait 48-72 hours before performing FMT. This would allow for the washout of antibiotics before proceeding with the transplantation of donor microbiota.

Safety of fecal microbiota transplantation in inflammatory bowel disease

FMT has several benefits compared to immunosuppressive therapy and other drugs. FMT, however, may involve invasive procedures such as colonoscopic administration and naso-enteric tube insertions. There are several concerns regarding fecal transmission of infectious agents from donor to recipient. Reported cases of Norovirus inoculation with a colonoscopy have been reported in three patients with Crohn's disease along with a reported case of Cytomegalovirus inoculation in a patient with ulcerative colitis [58,59]. Bacterial infections due to donor samples with *Escherichia coli, Proteus mirabilis, Citrobacter koseri, Enterococcus faecium* and 4 cases of unknown infections have been reported [60,61]. Thus, screening donors is paramount and stringent guidelines are needed for donors. About 1 in 3 patients will experience excessive bloating, excessive flatulence, abdominal pain, fever and/or worsening diarrhea [62]. It is believed that FMT may have immune modulating effects on some patient with IBD that may lead to worsening of IBD disease activity. Severe adverse effects (SAEs) and systemic infections are rare but reported with FMT. In some trials, emergent surgical colectomy was required after fecal microbiota transplantation [36,63,64]. Three patients with ulcerative colitis also underwent colectomy after FMT [38,41,65,66]. Due to limited study design and lack of control groups, it is not clear if the patients required surgery due to natural disease progression, adverse effects of FMT treatment, or other factors. A meta-analysis of 514 pooled total patients with IBD found that 14.9% of IBD patients reported worsening symptoms. Another randomized controlled study reported 4.6% of the patients reporting worsening symptoms [67]. Regarding patient safety, the Food and Drug Administration has classified donor stool as a biological product and is regulated by the government [68]. Furthermore, the Food and Drug Administration has only approved FMT treatment for colitis due to *Clostridium Difficile* infections that are refractory to antibiotics. Research using FMT, especially in IBD with severe disease, should be used with extreme caution until the full safety profile of FMT treatment is available.

Fecal Microbiota Transplant in Pouchitis

Pouchitis is characterized by inflammation of the ileal pouch reservoir. Data is still limited on FMT as a treatment option for pouchitis. 3 cohort studies have been done in order to evaluate

the effects of FMT on pouchitis. 1 case report has also been published. Landy et al did a study on 8 participants with chronic pouchitis who had a Perianal Disease Activity Index (PDAI) greater than 7. After transplanting stool using a nasogastric tube, he was able to demonstrate a change in stool microbiota, but no clinical remission was induced. 2 of the 8 patients did show a reduction in their PDAI after 4 weeks[69]. El-Nachef et al also did a cohort study with 7 patients to assess safety of FMT in pouchitis. After transplanting via pouchoscopy, there was a decrease in abdominal pain and number of bowel movements. No escalation of treatment was noted[70]. Fang et al was able to demonstrate an improvement of symptoms and quality of life for a patient with chronic antibiotic refractory pouchitis [71]. A third cohort study done by Stallmach et al showed clinical remission in 4/5 patients after multiple transplants. The 5th patient also had an improvement of symptoms [72]. These small studies show that FMT may be an option to help treat pouchitis but more information and data is needed. This also begs the question; are multiple transplants better than a single transplant and what is the optimal route of administration of the microbiota. Multiple clinical trials are currently underway.

Fecal Microbiota Transplant to treat Extraintestinal Manifestations of IBD

There is emerging interest in FMT as a therapy for Extraintestinal Manifestations of IBD. Altered microbiome plays a role in primary sclerosing cholangitis and Heath et al hypothesize that FMT may play a role treating this disease [73]. Borody et al mentions a case of Ulcerative colitis with abnormal liver biochemical tests characteristic of sclerosing cholangitis. After 100 FMTs over the course of 12 months, liver biochemical tests normalized [74]. Recently, Allegretti et al, at Brigham and Women's, enrolled 10 patients with primary sclerosing cholangitis (9 had concurrent Ulcerative Colitis and 1 had Crohn's Disease) who underwent FMT. 3/10 patients saw their ALP values drop by more than 50% and 7/10 saw a 30% drop in one of their liver biochemical markers [75]. FMT may have benefit with other extraintestinal manifestations, as well. Cui et al demonstrated remission in 8 out 11 patients who had skin manifestations. Remission was achieved within 2 weeks following FMT [76]. However, Teich et al present a case where erythema nodosum developed 3 days after a fecal transplant [77]. More information needs to be gathered with regards to FMT as a potential treatment for extraintestinal manifestations of IBD.

FMT as an adjunct to Biologic Therapy

FMT has been done in patients both as a primary therapy and adjunctive therapy [78]. However, from our research, no study was identified that that compared FMT as an adjunct to biologic therapy vs. FMT as a primary therapy. Further studies are still needed to determine protocols for using FMT.

Conclusion

Current available treatments options for IBD come with potential side effects that may harm the patient. New treatment strategies are needed for IBD. FMT represents one such novel treatment option. Multiple clinical trials have shown that FMT is the most effective treatment for *Clostridium Difficile* colitis [79,80]. Although promising, the results of FMT for the treatment of IBD

are not as impressive as efficacy in treating *Clostridium Difficile* Infection. A survey by Khan et al showed 46% of patients who failed first line treatment for IBD would consider FMT as the next option to avoid immunosuppressants. This study also showed that 36% of ulcerative colitis patients without active disease would opt for FMT as a future treatment [81]. If FMT is to be accepted as one of the accepted treatments for IBD, more research in long-term efficacy, safety, and maintenance regimens are necessary. Sustainability is another concern in FMT, specifically whether a patient should undergo transplant and how often the patient should undergo repeat transplantation for maintenance of IBD remission [82,83]. Until these barriers are overcome, FMT remains experimental and should be limited to the research setting.

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