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Review Article

Faecal Microbiota Transplantation as a Treatment to Combat Ulcerative Colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the mucosa and submucosa of the colon causing several symptoms. The aetiology is unknown, but it is thought to arise from a deregulation of the immune response against the colonic microbiome. This autoimmune response could be produced by several environmental factors in genetically susceptible individuals. When an IBD happens, the balance of the bacterial population is lost, producing a dysbiosis. Standard treatments are not ineffective at all but a more effective and a less-side-effects treatment is required. Faecal microbiota transplant (FMT) has emerged as a novel approach to regulate the colonic microbiota. The present work is aimed to review and identify the efficacy and safety of FMT and see the different strategies undertaken currently. Several current studies have been collected in order to find different strategies performed. After these studies have been compared, it is possible to see that the efficacy of this treatment reaches approximately a 30%, which is not as promising as expected. That means further studies are required in order to increase the efficacy of FMT for UC and long-term studies remain to be done.

Keywords: *Faecal Microbiota Transplantation; Ulcerative Colitis; Microbiota; Dysbiosis*

Abbreviations

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; FMT: Faecal Microbiota Transplant; GI: Gastrointestinal; FDA: Food and Drug Administration

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the mucosa and submucosa of the colon causing several symptoms such as diarrhoea, bloody-small stools, weight loss, abdominal pain, fatigue and rarely fever [1]. It has an unpredictable course, with one of five possible scenarios including a single episode of disease, chronic relapsing disease, chronic unremitting disease, severe colitis with need of a colectomy and death. The most common is chronic relapsing disease [2].

This disease has a continuous location and it is classified according to the affected area: proctitis known as the inflammation confined to the rectum, with fewer complications; proctosigmoiditis, which is the inflammation in the rectum and the rectosigmoid colon; left-sided colitis that affects extends from the rectum proximally to a bend in the colon near the spleen called the splenic flexure; extensive colitis, that affects until the hepatic flexure [3] and pancolitis which involves the entire colon.

The aetiology of the disease is unknown, but it is thought to arise from an aberrant immune response, probably against the colonic microbiome causing an imbalance of the percentage of the bacterial population which promotes dysbiosis [4,5]. This auto-immune response could be triggered by several environmental factors in genetically susceptible individuals. Factors such as a diet based on arachidonic acid (component of a like egg yolk and meat), antibiotics usage, non-steroidal anti-inflammatory drug (NSAID) inadequate consume or urban lifestyle increase the risk for these individuals of having UC. Whereas, omega-3 fatty acid based diet (found in salmon, tuna orwalnuts), appendectomy and cigarette smoking are factors that reduce the risk of developing UC [6-8].

The gut microbiome is very different both in diversity and in richness depending on which part is studied. Bacteria increase in concentration and complexity from the proximal gastric and duodenal population of 10^2-10^3 aerobic microorganisms per gramto 1011-1012 predominantly anaerobic bacteria per gram in the colon [5].

Greater than 99% of a healthy colonic microbiome is composed of species within four bacterial divisions: Firmicutes (64% attached colonic species) composed by the *Clostridium* XIV and IV groups, Bacteroidetes (23% of resident species), Proteobacteria (8%), and Actinobacteria (3%) [9].

When an IBD happens, such as ulcerative colitis, the balance of the bacterial population is lost and the percentages change, producing a dysbiosis, which is the quantitative and qualitative microbial imbalance in the gut between commensal and pathogenic microorganisms [2,4,5]. This fact causes the perpetuation of the colonic inflammation and loss of the barrier function of the epithelial cells of the intestine [10]. This microbial change has been shown by several authors [5,12]. They determined the decrease of Bacteroidetes, Clostridiales (with important significance of *Faecalibacter prausnitzii* and *Roseburia hominis* and their anti-inflammatory role by producing butyrate and other short-fatty acids) [1,11] and the increase of *Bacillus*, and the phyla Proteobacteria and Actinobacteria [5,12] (Figure 1).

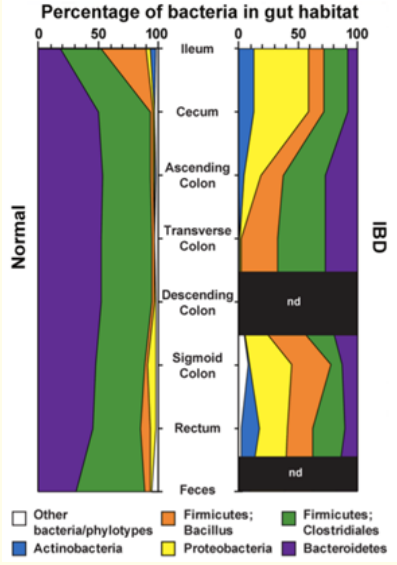

Figure 1: *Bacterial phyla identified in the human gut microbiota.*

Distribution of predominant bacterial phenotypes in the human intestinal tract. Phylogenetic classifications were made by parsimony insertion of aligned sequences from healthy young adults and samples from patients with either Crohn's disease or ulcerative colitis. Abbreviations: n.d., not done. Taken from Peterson DA., et al

Several treatments have been used to treat UC such as anti-inflammatory drugs (5-amino-salicylates or corticoids), immune-suppressive drugs (Azathioprine, Cyclos-porine, Infliximab, Vedolizumab), antibiotics, prebiotics and probiotics. Although some of them are effective [13-15], it is described that long term treatment may not be acceptable to many patients and can cause some side effects like kidney and pancreas problems or surgical need as colectomy or some types of cancers [16].

In the case of prebiotics and probiotics some promising studies are underway, but it is still far to be introduced in the daily clinical [17].

Thus, an alternative treatment was required in order to find an effective therapy with fewer side effects. It is described that faecal material transplant (FMT) has emerged as a novel approach to regulate the colonic microbiota. It has been successful for treating antibiotic

resistant *Clostriudium difficile* infection (CDI) [1,18,19]. FMT is focused on the correction of the colonic microbiota, as this is altered in patients with a gastrointestinal disorder compared with healthy individuals. In order to reach this goal, a transplantation of faecal matter from a healthy patient with a normal colonic microbiota is transferred into the intestines of a patient with the disease.

The application of FMT in UC was first published as a case report by Justin Bennet in 1989, who achieved both clinical and histological remission after administration of donor microbiota via faecal enemas [20]. Apart from this route of administration, other strategies have been performed afterwards such as the ones undertaken through the upper GI tract (endoscopy) or the lower GI tract (colonoscopy).

The aim of this review is to collect several clinical trials in humans in which FMT has been undertaken in patients with UC and examine their results in order to see the efficacy of this treatment and its safety. In addition, different FMT strategies carried out in the trials will be compared as well.

Methodology

To write this review, an electronic search in MEDLINE database (PubMed) was done in order to find some free-full-text reviews and clinical trials with the following searching tools:

("faeces"[MeSH Terms] OR "faeces"[All Fields] OR "faecal"[All Fields]) AND ("transplantation"[Subheading] OR "transplantation"[All Fields] AND ("colitis, ulcerative"[MeSH Terms] OR ("colitis"[All Fields] AND "ulcerative"[All Fields]) OR "ulcerative colitis"[All Fields].

Once some reviews have been found, references in those reviews made possible the screening of clinical trials.

Those studies that were published before 2006 were dismissed in order to have recent information excepting reference 16 which is the article that corresponds to the first experiment about treating the ulcerative colitis (1989) mentioned above.

Results

For clinical trials, a total of 9 articles were found in the search. Six were potentially eligible for this review following the publication date criteria established in methodology. Two randomized-controlled clinical trials published their study head-to-head in Gastroenterology [23,24], a paediatric trial was undertaken [22] and four of them analysed microbial diversity of the participants [21,23,24,26]. All the patients from the trials had received current medications that were not working at all for them. Some of them continued with the medications during the trial [26]. These drugs can help to improve the healing of the mucosa but do not assure a total recover. That is why these six authors and their teams aimed to find a treatment that induces a long-term remission.

Kump KP., *et al*. reported a FMT approach via colonoscopy in six patients with ulcerative colitis (Table 1). The recipients received the FMT from four healthy donors. All the patients experienced a clinical improvement the first two weeks and two of them (33.3%) improved up to the third month. However, none of them achieved clinical remission [21]. FMT was associated with a temporal increase in species richness in faecal and mucosal samples of the patients but, this trend failed to reach statistical significance.

In other study, ten children were evaluated with mild-to-moderate UC administrating via faecal from healthy donors (Table 1), as seen in Kunde S., *et al.* 78% of the subjects showed clinical response within one week and 67% maintained it at one month. 33% of the subjects achieved clinical remission at one week after FMT and were able to maintain it by four weeks after FMT [22].

Moayyedi P., *et al.* studied the safety and efficacy of FMT in patients with an active UC without diarrhoea (Table 1). This study included a placebo-controlled randomized trial in 75 participants (38 for FTM and 37 for placebo). Faecal microbiota was recruited from 6 anonymous donors. This faecal material or water (for controls) was administrated via enema once per week for six weeks. Seventy patients completed the trial. 24% of FMT and 5% of placebo patients were in remission at week seven without any differences in adverse events. Microbial diversity was higher at the end of the trial for those patients who received FMT [23].

Study	Number of patients	Age, y	Male sex, n	Previous treatment	Route	Follow up
Kump K.P. *et al.*	6	>18	3	5-ASA Prednisolon Infliximab Adalimumab Azathioprine	colonoscopy	12 weeks
Kunde S. *et al.*	10	from 7 to 21	6	5-ASA Steroids 6-MP anti-TNFα methotrexate	enema	4 weeks
Moayyedi P. *et al.*	75	>18	44	Mesalamine Glucocorticoids Immunosuppressants anti-TNFα	enema	7 weeks
Rossen N.G. *et al.*	50	>18	22	Mesalamine Immunosuppressants corticosteroids Loperamide anti-TNFα	nasoduodenal	12 weeks
Yao Wei *et al.*	14	>16	6	Mesalamine Gentamicina Norfloxacin SASP Gatofloxacin	colonoscopy	4 weeks
Bota Cui *et al.*	15	from 11 to 48	10	Mesalamine 5-ASA Traditional China medicine	esophagogastroduodenoscope	3-18 months

*Treatments: 5-ASA: 5-aminosalicylic acid preparations ; 6-MP: 6-mercaptopurine; anti-TNF-α: antitumor necrosis factor-α; SASP: salicylazosulfapyridine

Table 1: *Baseline characteristics of patients in the trials.*

To assess the efficacy and safety of FMT, Rossen NG., *et al.* selected 50 patients with UC (Table 1) and divided them in two groups: autologous FMT (FMT-A; control) and donor's FMT (FMT-D; 15 healthy partners, relatives or volunteers > 18 years of age). The transplant was undertaken by nasoduodenal endoscopy. At week six, 26.1% of patients from FMT-D and 32% from FMT-A achieved clinical remission. Plus, at week 12, the percentage of FMT-D reached 30.4% whereas it remained at 32% for FMT-A [24]. No statistical significance in the results was found. The increase in diversity at week 12 could be attributed to an increase in both richness and evenness in all responders. Diversity in non-responders did not change over time.

In order to determine the effect in FMT in 14 patients (3 for Crohn's disease and 11 for UC), Yao Wei., *et al*. performed a study by treating them with FMT (Table 1). It was administrated via colonoscopy from a single healthy female donor. All the patients had a remission of the symptoms after four weeks [25].

Finally, Bota Cui., *et al*. wanted to evaluate the efficacy and safety of FMT in 15 steroid-dependent UC patients using healthy children as donors (Table 1). This was administrated via an esophagogastroduodenoscope. 57.1% of patients achieved clinical improvement and a 28.6% of the total responded a long-time remission (3 - 18 months) [26]. The bacterial diversity after FMT increased in three of the four patients with screened microbiota (the other patient did not have an increase of bacterial diversity due to taking antibiotics).

Discussion

Ulcerative colitis can be defined as an autoimmune disease knowing the fact that the microbiome is considered a proper organ of our organism. The steps followed by the several authors in their studies to perform FMT differ in many aspects. It would be useful for the future to find a defined methodology that achieves the highest efficacy and safety for patients. Despite this, it is impossible to achieve a standard methodology of the treatment without a higher number of studies.

Patients

In total, a number of 167 UC patients have been exposed to the treatment in these trials. The characteristics of those patients were different from the patients of the several trials in this review (Table 1). The range of ages was wide (7 to 80); the number of patients in each study vary (having some trials with less than 15 patients [21,22,25,26] others with more than 50 [22,23]), severity of the illness also changes and medication before the trials well.

Two other studies treated mild-to-moderate UC [22,23].

Donor

It is important that the faecal material from the donors lacks of any factor for transmissible diseases or any issues that can alter the composition. To be sure about this, it is common to provide a questionnaire approval to the donors as seen in some clinical trials [22-24]. All the studies in this review screened the donor's stools to avoid transmission of other diseases.

In some studies, patients identified their own donors [22,24,26] but then some institutions offered the option of receiving from anonymous donors [21,23-25]. Some authors claim the difference of results from similar patients in the same study to the fact that there are differences in donors' stool samples.

In the study of Moayyedi., *et al*. a remarkable part was the variation of the microbiome in donors' stools and the influence of the respective donor on the clinical outcome. One donor (donor B) was associated with a higher rate of induction of remission. Rossen., *et al*. talks about "superdonor" and "poor donor" according to the percentage of patients with remission from their stool sample.

However, Professor Peer Bork explained to The Scientist that some patients whose FMT received from the same donor showed different responses, suggesting that a universal faecal "superdonor" does not exist [27].

Thus, the success of the transplant appears to depend on the compatibility between the donor and the recipient. He remarked that a "one-stool-fits-all" model, currently supported by standardized donor stool banks, may not be clinically appropriate [28].

Therefore, there are not established characteristics for the samples and this could lead an interesting path of new studies in order to improve the efficacy and assure a better result from the treatment.

Material Preparation

The stools are usually diluted, generally with normal saline and homogenized. However, water and other diluents (eg. milk), can also be used [29,30]. A filtration is undertaken in order to remove particulate matter to facilitate administration. It is possible to store them mixed with a cryoprotectant and frozen them at a temperature of -20^{0}C and/or -80^{0}C [23,26] but most institutions use them fresh [21,22,24,25].

It has been shown that the efficacy of both options have equivalent clinical efficacy. That means that in the future, the treatment would probably be used with frozen material, due to the comfort for the donor to donate without any dependence of the recipient.

Rout of administration

The way of administration is different depending on the trial but the results do not seem to be conditioned by this factor at all.

Two studies from this review [24,26] used the upper GI tract as a way to administrate the microbiota into the intestinal track but some previous literature explained that some patients may not find it "palatable" [29]. Thus, smaller volumes are used in order to avoid problems with the comfort of patients. Two other studies [25,26] performed a colonoscopy, which is useful for allowing direct assessment of the colonic mucosa. It is also a quick route, convenient, inexpensive, and technically simple. Moreover, it is known that the enema is effective, cheap, safe, easy to administer and can be infused in the comfort of a patient's home. However, some patients have reported an aversion to handling stool, which obviously might interfere with the acceptability of faecal enemas [30]. This method was used in two trials [22,23].

Clinical response and remission

The efficacy of FMT in these studies differs in clinical response, having more than 39% of improvement in a short-term analysis (less than a month after FMT). For clinical remission the percentage of patients decays (24 - 33%) and in some cases it was not achieved [25].

All the clinical trials but one [26] lasted a maximum of 12 weeks which could not be enough for a long-term study. Only Bota Cui., *et al*. achieved 28.6% of the patients responding a remission at 3 - 18 months. It cannot be compared to other studies because of their lack of analysis at that time. However, it would be interesting to do so, in order to know if this study became efficient due to the use of children as faecal donors or it is just the lack of information from other studies in long-term that enhance to propose that result.

Microbial Diversity

Four studies were undertaken a microbial analysis to see the population change in the gut of the patients and donors within the study.

In general, all the patients with UC suffer a decrease of the phylum Bacteroidetes and order Clostridiales (Firmicutes) and the increase of the genus of *Bacillus* (Firmicutes) and the phyla Proteobacteria and Actinobacteria [18,19]. When patients responded to the treatment, their colonic microbiota diversity started to restore significantly taking similarities to the microbiota of their donors.

The diversity of the microbiota increases in all the recipients of the faecal transplant as compared to non responders [21,23,24,26]. Phyla Bacteroidetes was increased in two of four studies [21,26] as well as Firmicutes, with an important increase of Clostridium IV, XIVa, XVIII in Rossen NG., *et al*. All the studies but one [23] showed a Proteobacteria decreased. Moayyedi., *et al.* Only talk about the similarity of the recipients versus donors' profiles. However, a study failed to achieve statistical significance [26].

Plus, these studies emphasize that is yet to be defined a microbial composition that might carry a higher therapeutic potential.

Adverse events

Some literature suggests that adverse events of FMT for *C. difficile* are rare, which can probably be extrapolated to Ulcerative Colitis [31,32].

However, the majority of the patients from all the studies of this review experienced mild adverse events. That events might be abdominal pain [25], fever, increase of diarrhoea frequency [24,26], cramping, fullness, flatulence, bloating, and blood in stool [22] and act during or shortly after treatment. Those side-effects, though, had a spontaneous recovery.

Moreover, some patients had some complications like inflammation of the colon and also rectal abscess formation, resolved with antibiotic therapy [23], abdominal discomfort tested positive for C. difficile toxin [23] and intolerance with FMT [22,24]. The patient with the C. difficile toxin and the intolerance patients had to decline to participate in the studies.

Legislation

The US Food and Drug Administration, under pressure from patients and clinicians, has recognized FMT as an investigational drug (IND) so, nowadays, it can only be used in clinical trials, not in daily routine. That also means that when using this treatment in patients has the responsibility of the fails falls on the clinicians because no good long-term data or registries yet exist [33].

The FDA has also found it difficult to standardize and regulate the FMT administration, identifying it as an inherently variable, metabolically active, and ubiquitously available [34].

Future Approaches

It would be interesting for the future to do a long-term study to know how the restored microbiota develops after a remission, in cases where patients achieved it. Those long-term studies could help to better understand how this reconstituted microbiota behaves after remission.

Plus, advancements in transplant method are also underway. For instance, oral FMT administration through the use of lyophilized, encapsulated, and enteric-coated capsules are starting to be in progress. Perhaps there will come a time when oral FMT will be routinely given along with antibiotics in efforts to preserve the gut microbiota [29].

According to faecal material from donors, outcomes varied across donor-recipient pairs. That indicates that microbiota compatibility (the likelihood that donor's bacteria are able to coexist or replace microbial strains in the recipient) is a factor that could provide a rationale for more targeted microbiota-based therapies [28].

Conclusion

A total efficacy of approximately 30% of the treatment has been found in the reviewed studies. This efficacy cannot be considered as promising, so further studies have to be performed in order to increase it and accept it as a reasonable treatment.

The trials reviewed have duration of the follow up in the short-term. That information is insufficient to assess the efficacy of the treatment.

Moreover, these trials have a great variation of the initial parameters such as illness severity, number of patients or administration route and time. Thus, it is difficult to compare them due to the quantity of different parameters that change in all the cases.

The term "superdonor" is not yet accepted although some papers of this review talk about it. Microbiota compatibility between donor and recipient is another current model to have consideration with.

The route of administration does not seem to have differences in the efficacy of the treatment.

Further studies are required in order to increase the efficacy of FMT for UC and long-term studies remain to be done.

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