ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Update on Fecal Microbiota Transplantation in Patients With Inflammatory Bowel Disease

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G&H What is the rationale for using fecal microbiota transplantation to try to treat disease, particularly inflammatory bowel disease?

PM The concept of using fecal microbiota transplantation (FMT) for the treatment of disease has possibly been around for over 2000 years in Chinese literature and since the 1950s in Western literature. The thinking is that if a person has a disordered microbiome in the colon, order can be restored by administering microbes from a healthy volunteer so that the healthy organisms overrun the organisms causing the disease. This has been borne out in clinical practice with antibiotic-resistant *Clostridium difficile* infection, in which administering just 1 FMT can cure *C difficile*–associated diarrhea. (However, sometimes more than 1 FMT is needed to bring the patient to lasting remission.) A large amount of observational case-series data support this claim, with an approximately 90% cure rate; however, such research usually overestimates benefit. In addition, randomized, controlled trials have shown that this treatment works better than antibiotics in antibiotic-resistant *C difficile* infection.

In the past, inflammatory bowel disease (IBD) was thought to be an autoimmune disease, but the current thinking is that it is actually an immune disease mediated by an antigen, presumably a microbial antigen to which the immune system is reacting. Current therapies are directed at dampening the autoimmune response, but it may be more sensible to just change what is driving this immune reaction in the first place. Given the success of FMT in *C difficile*–associated diarrhea, it is possible that such an approach may be effective if IBD is driven by a disordered microbiome. A small amount of observational case-series data, as well as several randomized, controlled trials (including one conducted by my colleagues and I), suggest that FMT may work in the setting of ulcerative colitis. There is less evidence that FMT works in patients with Crohn's disease, but the same principle applies.

> To me, these findings constitute reasonably persuasive evidence that, ultimately, the microbiome may change disease, at least in ulcerative colitis.

G&H What are the most recent data on the use of FMT in patients with IBD?

PM Last year, my colleagues and I published the results of a systematic review of FMT in patients with ulcerative colitis. Four randomized, controlled trials were included, one of which was published by us in 2015. Three trials (ours and 2 Australian trials) had positive findings, whereas

one (a Dutch trial) had negative findings. However, the results of the Dutch trial were in a similar direction as the other trials, and the numbers in that trial were smaller. In addition, patients in the Dutch trial underwent 2 FMTs via the nasogastric route, whereas patients in the other studies, including ours, received FMTs rectally or via enema at least once a week for 6 weeks (up to 5 times a week for 8 weeks in an Australian study). Overall in these 4 studies, 277 participants were randomized to FMT or placebo, and there was a significant difference in the remission rate between the FMT group and that of the placebo group, with a number needed to treat of 5. The effect size was fairly similar to that of biologic therapy. Essentially, there was an approximately 5% remission rate in the placebo group and an approximately 25% remission rate at 6 to 8 weeks in the FMT group. To me, these findings constitute reasonably persuasive evidence that, ultimately, the microbiome may change disease, at least in ulcerative colitis.

In Crohn's disease, there has been no randomized, placebo-controlled trial evidence to date involving FMT. There are only observational data, which showed that approximately two-thirds of people went into remission with FMT. However, as previously mentioned, case series are typically small and overestimate success. Randomized, placebo-controlled trials of FMT in Crohn's disease are currently ongoing.

G&H How long did the effects of FMT last in the ulcerative colitis studies?

PM Our study reported effects up to a year, but that was in 2015. We now have 4-year data. All 9 patients who went into remission have now relapsed. All but 1 patient chose to undergo FMT again and remission was induced in all but 1 of these patients. Most patients have elected to continue undergoing FMT anywhere between once every 2 weeks to once a month, and most are still in remission with this approach. However, it is important to note that the number of patients involved is now small because not all of the patients who originally achieved remission have continued with FMT for one reason or another. For example, some patients moved to a place where they could not easily undergo FMT, and one elected to switch to biologic therapy.

G&H Is it possible yet to determine which IBD subgroups respond best to FMT?

PM There are not enough data to determine with confidence whether there are predictors of FMT success. Each study has reported that a certain subgroup might respond better, but none of these findings have been the same. For example, an Australian group has suggested that certain microbiome profiles may predict success, but our group has not reported the same finding. In contrast, we found that patients with early onset of disease (ie, disease that has been present for a year or less) responded better than patients with disease that has been present for longer. However, this was not confirmed by the Australian group.

G&H Has there been any research on which FMT delivery methods or preparation processes might be most effective in the setting of IBD?

PM Trials have used different approaches, but all have reported similar efficacies. The Australian groups have tended to use stool that was pooled from various donors. My colleagues and I have used stool from only a few heavily screened donors for the entire study population (although we principally relied on 2 donors and used only 1 donor for individual patients whenever possible). Stool from one donor appeared to do much better than from the others, suggesting that, unlike in *C difficile* infection, there may be a donor-specific effect. The Australian studies cannot confirm or refute our finding because they use a mixture of many different people's stool, making it impossible to know whether there is a particular stool that is working well. The Dutch study used stool from a relative or friend of each study participant; thus, because different donors were used in every case, it was not possible to determine whether there was a donor-dependent effect.

In terms of delivery, for patients with ulcerative colitis, the FMT must be administered to the colon, whereas for patients with Crohn's disease, the FMT can be administered via tablets or the nasogastric route, as these patients usually have terminal ileal disease. My colleagues and I used rectal administration in our trial of ulcerative colitis patients, whereas the Australian groups first used colonoscopic and then rectal administration, and the Dutch group used nasogastric administration. The Dutch study is the only one with negative findings, so it seems that rectal administration is the best delivery method for ulcerative colitis, which makes sense given the location of the disease. I do not think that colonoscopic administration is necessarily required in these patients; in my opinion, rectal administration is good enough.

As for the frequency of FMT administration, once a week seemed to work in our study. The efficacy was similar in the Australian studies, in which FMT was performed 5 times a week for 8 weeks. Therefore, I think that FMT definitely needs to be given more than once, probably repeatedly over at least 6 weeks, unlike with *C difficile* infection.

Finally, my colleagues and I used both fresh and frozen stool in our study, and both types seemed to work. As for the other studies, the Australian studies used frozen FMT and the Dutch study used fresh.

G&H What have studies recently reported regarding the use of FMT for the treatment of *C difficile* infection in IBD patients?

PM There is no reason to suspect that FMT differs in efficacy when performed in patients who have both *C difficile* infection and IBD compared to patients who have a flare of IBD without *C difficile* alone, but this has not been studied in randomized, placebo-controlled trials. The challenge is determining whether the patient's diarrhea is due to *C difficile* infection or to ulcerative colitis or Crohn's disease.

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G&H Has there been any recent research on FMT in children with IBD?

PM Observational data suggest that FMT works in children with IBD. There have been no completed randomized, placebo-controlled trials as of yet, although one is currently being conducted by Dr Nikhil Pai at McMaster University in children with ulcerative colitis.

G&H According to the most recent research, how safe is FMT? Are there any significant safety concerns?

PM There have not been any safety concerns reported from the large amount of data on FMT in *C difficile* infection. However, in this setting, patients underwent FMT only once or maybe twice, not repeatedly. In the aforementioned systematic review of 277 IBD patients enrolled in randomized, controlled trials of FMT, no safety signals of concern were found, although this review was on a much smaller scale than the *C difficile* data. My colleagues and I have now followed a small number of IBD patients undergoing FMT over 4 years, and no safety concerns have been found. Having said that, it is important to keep in mind that FMT is an experimental therapy. Essentially, a soup of bacteria is being administered, and it is not possible to know specifically what those bacteria are.

Rectal FMT has not caused problems across several randomized, placebo-controlled trials and smaller observational studies. However, with nasogastric administration of FMT, particularly when involving the jejunum, some patients develop a high fever and feel unwell for several days. Thus, the nasogastric route is not recommended for ulcerative colitis.

G&H Are there any regulatory or ethical issues associated with FMT in IBD patients?

PM The main ethical issue is that it is not possible to control exactly what is being given to the patient or if there is a donor-specific effect. Thus, FMT will be difficult to use in clinical practice. In my opinion, there is not enough evidence yet to suggest that FMT can be used in clinical practice for IBD; at the moment, it should only be used in the context of a clinical study. Scaling up could prove challenging even if subsequent data suggest that FMT could be used in clinical practice for IBD. In a very controlled setting, such as the one in which my colleagues and I are using FMT, the risk to the patient taking part in the study is minimal. However, expanding FMT nationally or internationally may lead to less-effective donor screening.

In addition, several companies have been trying to create synthetic stool, but I think FMT needs to be better understood before moving to this approach, at least for IBD. Having said that, synthetic stool may be the way to make FMT more accessible, although more research will be required.

G&H Thus far, how receptive have IBD patients and doctors been to FMT?

PM Doctors are fairly resistant. Most doctors who conduct trials and have expertise in IBD dismiss FMT. On the other hand, patients are very interested. My colleagues and I have received much interest in our studies from all over Canada and even the United States (although we cannot treat patients from the United States). FMT resonates with patients; there are many people who think that FMT makes sense as a way of treating their disease.

However, it is important to emphasize to patients that FMT is not a miracle for everyone; no treatment for IBD is. FMT may bring patients into remission, as other therapies can, but it does not cure IBD. Patients also need

to understand that FMT is not necessarily completely safe. As previously mentioned, harm signals have not yet been seen with FMT, but this does not mean that the procedure is completely safe; there are always risks with every treatment, and patients have to understand that. Nevertheless, I think that this therapeutic approach may one day lead to a cure of ulcerative colitis, and perhaps Crohn's disease, in a more meaningful way than therapies that address the immune system.

G&H What are the next steps in research?

PM My colleagues and I are currently conducting a trial to determine whether administering antibiotics before performing FMT improves the efficacy of the procedure. The thinking is that the antimicrobial combination may better suppress the organism(s) driving the disease, which may allow FMT to work better.

In addition, larger-scale randomized trials are needed to examine what is happening to the microbiome with FMT. My colleagues and I have studied this issue, as have Australian and Dutch groups, but the patient populations have been too small. Some of the groups are trying to combine data to see whether adding the microbial signature in all of the studies provides answers. However, each study has used a different methodology and different types of donors. In my opinion, we need to use a small number of donors and a large number of patients all evaluated the same way. I am the principal investigator of the IMAGINE Network (imaginespor.com), which is funded by the Canadian Institutes of Health Research and other partners and is looking at the microbiome in IBD patients, irritable bowel syndrome patients, and healthy volunteers to try to unravel what is causing the disease.

Another area of future research is determining whether FMT affects the mind in a positive way. Patients with IBD are known to have a higher level of anxiety and depression and other psychological and cognitive disturbances compared to the general population and even some people with other chronic diseases. Other doctors at McMaster University have found that the microbiome in the gut may play a part in anxiety and depression, but more research is needed.

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Suggested Reading

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