ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Recent Research on Fecal Microbiota Transplantation in Inflammatory Bowel Disease

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G&H What is the current understanding of the role that the gut microbiome plays in inflammatory bowel disease?

MF It is thought that bacterial and fungal antigens may play a role in activating immune cells and therefore contribute to the ongoing inflammation in patients with inflammatory bowel disease (IBD). Antibodies produced against certain components of bacteria and fungi have been found in the blood of patients with Crohn's disease and ulcerative colitis. It has been known for several years now that IBD patients have a unique microbial flora that is less diverse than that of healthy individuals. Certain potentially pathogenic bacteria, such as *Escherichia coli* and Enterobacteriaceae, are more abundant in patients with ulcerative colitis and Crohn's disease. On the other hand, beneficial bacteria that are important for health, such as certain *Clostridium* clusters, *Akkermansia muciniphila*, *Ruminococcus*, and *Faecalibacterium prausnitzii*, are decreased in IBD patients.

IBD patients have significant alterations in their bacterial flora. It is unclear whether these alterations are the product or the cause (or both) of chronic inflammation—in other words, whether the chronic inflammatory milieu in Crohn's disease or ulcerative colitis preselects for the abnormal microbes, or the abnormal flora elicits and/or maintains the mucosal inflammation (the chicken or the egg causality dilemma). The genetic alleles associated with the development of Crohn's disease and ulcerative colitis are also known to be associated with abnormal response to bacterial elimination or processing in the mucosa. Thus, individuals who are predisposed to IBD have abnormal bacterial and fungal processing in the gut, causing the bacteria and fungi in the gut microbiota to have improper contact with immune cells.

G&H Why is fecal microbiota transplantation being studied as a possible treatment option for IBD?

MF Because the microbiota may have a pathogenic role in the development of IBD, it is thought that restoring healthy microbiota in an IBD patient may stop inflammation by blocking antigen stimulation of the immune system. Previous experience in IBD patients has shown that antibiotics that kill harmful bacteria can be helpful in certain complications and in postoperative prevention of Crohn's disease, while probiotics have been shown to be useful in patients with pouchitis and some patients with mild to moderately severe ulcerative colitis. Therefore, microbiome modulation in IBD is not a new idea. With fecal microbiota transplantation (FMT), doctors usually transplant a full-spectrum gut microbiota–based product obtained from a healthy individual.

G&H Based on the research that has been conducted to date, does FMT appear to be effective for treating IBD?

MF FMT appears to be very promising for the treatment or induction of remission of ulcerative colitis, according to the meta-analyses or complete data of 3 of the 4 randomized, controlled trials (RCTs) that have been published to date.

On the other hand, the data on FMT in Crohn's disease are very limited. To my knowledge, no RCTs have been finished or published; there are only case series or cohort studies, which do not provide high-quality evidence. Therefore, it is unclear whether FMT has a role in patients with Crohn's disease. It is more difficult to study this disease because of its heterogeneity.

G&H What were the remission rates in the RCTs of ulcerative colitis patients who underwent FMT?

MF These RCTs are usually referred to simply by their first author or location: Rossen (Europe), Moayyedi (Canada), Paramsothy (Australia), and Costello (also Australia). Overall, these studies enrolled 277 patients randomized to FMT or placebo. Each RCT had a different study design, length of follow-up, and stool preparation. The European study had negative findings, whereas the other 3 studies had positive results. The overall clinical remission rate at the end of the trials (which ranged from 6-12 weeks) was 28% for FMT compared to 9% for placebo. The remission rate for FMT is impressive because medical therapies for IBD have reported rates from 17% to 38%. Notably, overall endoscopic remission was also significantly higher in the FMT groups compared to the placebo groups (14% vs 5%, respectively).

G&H How did the RCTs compare in terms of delivery methods, donors, and stool preparations?

MF The FMT delivery methods varied. The European study used a nasoduodenal tube, which may be why the study produced negative results. The other studies delivered stool via a lower route: either weekly enemas (in the Canadian study) or an initial colonoscopy to the cecum followed by multiple enemas (in the Australian studies). The Paramsothy study used 5 enemas per week for the duration of the study, but the Costello study was able to achieve a better clinical remission rate with fewer procedures (a single colonoscopy FMT followed by 2 enemas later on that week).

There were also differences in the stool donors. The European and Canadian studies used a single donor per patient, but the Australian studies used pooled stool from multiple donors (3-7) for each patient. This is an important issue because it is currently unclear what constitutes the optimal donor for FMT in IBD patients. We know that it does not matter who the stool donor is for FMT when it is performed to cure *Clostridium difficile* as long as the donor is healthy. Thus far, it looks like the characteristics of the donor stool do matter in IBD. In the Canadian study, this observation became known as the "donor B" or "super donor" phenomenon. This trial was actually closed early to enrollment because the interim analysis showed no superiority of FMT compared with placebo. The patients who were already enrolled were able to finish the trial. For the remainder of the trial, donor B was used because donor A became sick. All of the patients who used donor B achieved remission. When the researchers evaluated the differences among the donors, they found that donor B, whose stool was associated with the highest remission rate, had more *Ruminococcus* and Lachnospiraceae than the other donor.

As for the preparation of the stool, some of the RCTs used fresh stool, whereas others used frozen stool. Interestingly, the Costello study, which achieved the highest remission rate, used stool that was prepared under anaerobic circumstances (ie, oxygen could not touch or interfere with the bacteria). It has been speculated that this process better preserves the beneficial bacteria. It should be noted that autologous stool was used as the comparator in the Rossen and Costello trials, whereas the Moayyedi and Paramsothy trials used colored (and scented) water in the placebo arm.

Another interesting difference was that the studies that applied a so-called low-intensity approach (the Moayyedi study only used 8.3 g of stool × 6 weeks, and the Costello study used 100 g within 1 week) achieved similarly high remission rates as the trials that used a high-intensity approach (the Paramsothy study administered 40 enemas over 8 weeks using 187.5 g of stool per week). Thus, more stool is not necessarily better. It may be more important to find the right (most efficacious) single donor.

G&H What else was learned from these RCTs?

MF The Moayyedi study suggested that patients with a shorter disease duration (ie, less than 1 year) have mild mucosal inflammation and are more likely to respond. As an IBD specialist, I agree that this is likely. We have seen this occur with other therapies. They work better when initiated early in the disease course or in recently diagnosed IBD patients who have rather mild inflammation. Thus, restoring the microbiota at an early stage of disease and in patients with mild symptoms likely improves the chance for achieving remission.

We also learned that FMT is safe in ulcerative colitis patients. There were no significant differences in terms of serious adverse events in the FMT arm vs the placebo arm in all of the RCTs. Nearly equal numbers of patients in the FMT and placebo arms (79% vs 75%, respectively) reported transient side effects, similar to the rate seen after FMT is administered to patients with *C difficile*. The most common side effects are usually nausea, bloating, increased number of bowel movements, and low-grade

fever. These side effects usually do not require treatment, and normally go away after a week.

G&H What questions remain after the RCTs?

MF Several questions remain. One is whether upper or lower delivery of FMT is better. I think it will end up being lower delivery, but more data are needed. Another question is whether an aerobic or anaerobic preparation is optimal. It may be that an anaerobic preparation is more helpful because it can preserve more beneficial bacteria, but more research should be conducted. It is also unknown whether a single donor should be used or whether stool from several donors should be pooled together and then administered.

In addition, because the RCTs were short (only 6-12 weeks), it is unknown how long remission will last and, thus, how often FMT should be administered to maintain remission. Likewise, the long-term safety of this treatment approach is unclear.

G&H Is it known if the administration of antibiotics improves the efficacy of FMT in IBD patients?

MF The patients in the RCTs were not treated with antibiotics prior to administering FMT, unlike in trials of *C difficile* patients. Antibiotics have been shown to be effective in the treatment of Crohn's disease, but can induce flares in patients with ulcerative colitis.

To my knowledge, antibiotic pretreatment in IBD patients receiving a microbiome-based therapy has only been examined in a recent multicenter study of ulcerative colitis patients who received SER-287 (Seres Therapeutics), a microbiome-based therapy composed of a consortium of bacterial spores. Initially, the trial used vancomycin pretreatment, but the researchers found that it did not improve the results.

G&H What has the most recent research reported regarding whether FMT can cause IBD or a flare in disease activity?

MF It is unclear whether FMT can cause IBD. At least 2 studies in sterile mice found that terminal ileal inflammation can be induced by transferring the microbiota from mice with Crohn's disease or terminal ileal inflammation to healthy mice. No human experiments have been conducted. However, my colleagues and I published a report on one of my universal FMT donors, who donated to 31 patients within a 6-month period, developed diarrhea, and was diagnosed with ileocolonic Crohn's disease within 1 week of the last donation. Fortunately, none of the recipients have developed new IBD or experienced worsening of their existing IBD to date.

Retrospective studies and meta-analyses of reported cases have estimated that approximately 14% of patients with *C difficile* and IBD who underwent FMT will have either a flare or worsening of their clinical course. A study by Dr Alexander Khoruts and colleagues reported flares in 25% of IBD patients overall and even higher rates in patients with underlying extensive colonic disease. The question is whether these patients would have experienced these events even if they had not undergone FMT. That is what my colleagues and I are trying to determine in a prospective, single-arm, multicenter study (ICON). In this study, which is being led by Dr Jessica Allegretti, we are examining the effects of FMT in patients with underlying IBD (mostly colonic disease) and recurring *C difficile* (at least 2 episodes), and are analyzing clinical outcomes, biologic markers, and safety. The first results will be presented at the upcoming Digestive Disease Week meeting. The next phase of the study will examine whether using bezlotoxumab (Zinplava, Merck), an immunoglobulin that captures *C difficile* toxin B, given in combination with FMT improves outcomes.

G&H Based on the research that has been conducted so far, are there any other safety concerns or risks associated with FMT in IBD patients?

MF No, at least not in the short term. Long-term safety is still unknown, which is why the American Gastroenterological Association (led by Dr Colleen Kelly) is establishing an FMT registry that includes IBD patients. The goal is to follow 4000 patients over 10 years.

Because universal donors, especially through stool banks, are frequently being used now for FMT, the stool of a single individual may end up being given to thousands of patients. Therefore, it is essential to carefully screen donors to avoid transmitting diseases. Years ago, blood transfusions transmitted many diseases because doctors were not aware of them or did not know that they could be transmitted via blood. These unforeseen potential risks are one of the reasons that the US Food and Drug Administration (FDA) is hesitant to allow FMT for indications other than refractory *C difficile* that is not responding to the currently available antimicrobial therapies. FMT is difficult to regulate, and each stool is different.

G&H Is FMT allowed at all yet in IBD patients outside of clinical trials?

MF Absolutely not. FMT in IBD patients is still restricted to clinical trials and is strictly regulated by the FDA. Any

doctor who wants to perform FMT for IBD, even for a single patient, needs to obtain an investigational new drug license from the FDA. A doctor could lose his or her license by providing FMT to IBD patients who do not have recurrent *C difficile*.

G&H Do you foresee FMT becoming more widespread in the future?

MF Yes, especially because various encapsulated stool formulations are being developed and are currently undergoing clinical trials. The ultimate goal is to perform FMT by swallowing a capsule instead of undergoing a series of colonoscopies and/or enemas. Having a capsule that patients can easily swallow and take every day if needed would change the paradigm of FMT and IBD treatment, as well as reduce costs.

In addition, patients and doctors have become more comfortable with the concept of using stool for treatment. My IBD patients would rather use a natural treatment by swallowing a stool capsule rather than take a drug that suppresses the immune system and potentially causes significant risks.

G&H Has there been any recent research on the use of FMT in the pediatric IBD population?

MF No RCTs have been completed in the pediatric IBD population to date. There have been case series, although only a limited number. However, I am aware of 2 RCTs that are in progress. Dr Stacy Kahn is finishing a trial on FMT in 10 pediatric ulcerative colitis patients. The study results are not yet available. There is also an RCT currently being conducted in pediatric ulcerative colitis patients in Canada.

Dr Fischer is on the advisory board for OpenBiome and is a consultant for Finch Therapeutics.

Suggested Reading

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