ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Update on Fecal Microbiota Transplantation for the Treatment of Inflammatory Bowel Disease

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G&H What is the role of the gut microbiome in the pathogenesis of inflammatory bowel disease?

JA It is now understood that the gut microbiome is one piece of the multifactorial puzzle that leads to the pathogenesis of inflammatory bowel disease (IBD). The exact microbial factors are still relatively unknown, but through the use of fecal microbiota transplantation (FMT) and other microbial therapeutics, we are starting to obtain a better understanding of which families of bacteria are important and which are considered protective or more proinflammatory. However, quite a bit of work remains in this area.

G&H What is the rationale for using FMT for the treatment of IBD?

JA Several health conditions, including IBD, have been linked to a dysbiotic state. Cross-sectionally, when the microbiomes of patients with IBD have been assessed, overall there is a decrease in certain types of bacteria, specifically *Bacteroides* and Firmicutes, which are thought to be anti-inflammatory. These patients have also been shown to have decreased amounts of bacteria that make short-chain fatty acids, which are important for anti-inflammatory response. Based on these findings, it was clear that therapeutic manipulations of the microbiome in IBD were worth exploring.

In Crohn's disease specifically, diversions of the fecal stream have been known to be effective, as well as the use of antibiotics in certain subsets of patients with Crohn's disease, and also total parenteral nutrition (TPN) and bowel rest, which augments the gut microbiome. In ulcerative colitis, the role of microbial manipulation appears to be less clear; diversion has not been found to be effective, nor has there been a clear role for antibiotics or TPN and bowel rest. However, there are some data on the use of probiotics in patients with mild ulcerative colitis.

Putting all of this information together, the next step was to explore FMT, which is currently the most commonly utilized method of restoring the composition and functionality of the gut microbiome.

G&H What is the most recent research on FMT for the treatment of ulcerative colitis patients?

JA Four randomized, controlled trials have been published on the treatment of ulcerative colitis using FMT. Overall, they are fairly difficult to compare with regard to study design, but 3 of the 4 trials were ultimately positive for their primary outcome of clinical remission. These positive trials show that there is promise in using FMT in ulcerative colitis and that it is worth continuing this research.

G&H How did the trials differ?

JA One of the trials delivered material via nasoduodenal tube, 1 used a weekly enema preparation, and 2 used a combination of colonoscopy and enema. One of the studies used fresh fecal material, whereas the others used frozen material or a combination of fresh and frozen material. Three of the studies prepared the material aerobically, whereas 1 used an anaerobic preparation. Notably, the studies were not equivalent with regard to the number of donors used. Two of the studies had a single donor, whereas the other studies used a pooled donor process in which each patient received material from multiple donors. With all of these differences, it is quite difficult to compare the trials.

My opinion is that FMT is more likely to work in patients with mild to moderate disease early on in their disease course (eg, patients who are mesalamine failures, perhaps before they are escalated to a biologic).

Nevertheless, 3 of the 4 trials ultimately showed that treatment with FMT yielded a significant result with regard to induction of remission compared to placebo. Interestingly, when pooling together data from these 4 trials, FMT had an overall remission rate of approximately 28% compared with approximately 9% for the placebo arms. FMT's remission rate might not seem impressive overall, but pivotal clinical trials for biologics in IBD have shown remission rates of 17% and 19%, with the highest rates being 27% to 38% in ACT I and II, putting FMT on par with other IBD therapies.

G&H Were there any safety issues with FMT in these trials?

JA Generally speaking, no. There were no short-term safety signals. Many of the serious adverse events were related to the underlying IBD and were not thought to be related to the therapy. For example, one patient required a colectomy owing to worsening of underlying IBD, but, not surprisingly, this occurred more often in patients who received placebo. The most common adverse events seen in these trials, and in FMT studies generally, are mild transient gastrointestinal symptoms such as mild diarrhea, gas, and bloating.

G&H How long were these patients followed?

JA Follow-up varied among the studies. Generally speaking, the primary outcomes have been between 8 and 12 weeks, which is fairly typical with other IBD therapies. There have not been many robust long-term follow-up data yet, although some preliminary data out of the Australian study show that the results were sustained over several months. Long-term follow-up is actively underway.

G&H Based on the research conducted thus far, does it seem that certain ulcerative colitis patients might respond better to FMT?

JA This is still unclear. The patient populations differed; for example, not all of the studies allowed concurrent biologics, and not all used corticosteroid tapers. FMT has been studied in patients whose disease has failed to respond to multiple therapies, but I am not convinced that this is the right patient population for this type of therapy. My opinion is that FMT is more likely to work in patients with mild to moderate disease early on in their disease course (eg, patients who are mesalamine failures, perhaps before they are escalated to a biologic). However, FMT has not been extensively studied yet in that patient population.

G&H What has been the most recent research regarding FMT in Crohn's disease patients?

JA There are limited data on FMT in Crohn's disease patients. Until fairly recently, there have only been cohort studies and small case series; there have not been any randomized, controlled trials. A group of researchers in Paris is actively studying FMT in Crohn's disease, so additional data may be available soon. However, based on the current lack of randomized, controlled trials and the small number of studies that have been conducted to date, it is difficult to recommend FMT for patients with Crohn's disease.

What has been challenging about Crohn's disease is that it is much more heterogeneous than ulcerative colitis, and I think there has been a struggle deciding which Crohn's disease phenotype may be most appropriate. For example, Dr Alan Moss and I have worked on a study on FMT for the prevention of postoperative recurrence of Crohn's disease (ie, a patient population starting in remission as opposed to one with moderate to severe IBD,

which is the patient population most commonly studied in FMT trials). The studies to date on Crohn's disease are difficult to compare based on disease phenotype, which may be why there are limited data in Crohn's disease, but I am hopeful that higher-quality data will be available in the future.

G&H Could you discuss the most recent research regarding FMT for *Clostridioides difficile* infection in patients who also have IBD?

JA This is an important area of research, as patients with IBD are disproportionately affected by *Clostridioides difficile* infection. In fact, they have a 10% overall lifetime risk of developing a *C difficile* infection, and then once that occurs, they have nearly a 5-fold higher risk of recurrence. *C difficile* infection in patients with IBD results in many sequela, including exacerbations of IBD, increased hospitalizations, escalation of IBD therapy, and occasionally colectomy. Diagnosis can be extremely complicated, as *C difficile* infection and IBD often have many similar features (eg, diarrhea, abdominal pain, and fever).

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Some initial retrospective data reported reasonable efficacy of FMT in this patient population, but there was a concern for IBD flare. However, an IBD flare in this context had variable definitions depending on the study, making it difficult to assess this issue retrospectively. My group conducted a meta-analysis to try to understand where this signal was coming from. Looking just at studies that used FMT specifically for the treatment of IBD, there was no signal for IBD worsening or flare; studies where FMT was being performed in patients with *C difficile* infection and IBD were driving the signal. We felt that there was a knowledge gap and that we needed to understand FMT in this vulnerable patient population because of concern that providers may be withholding the therapy from patients with IBD. Thus, my group performed the first prospective trial of the use of FMT for the treatment of recurrent *C difficile* infection in patients with IBD. This was a multicenter study performed at 4 sites around the United States that enrolled patients with a confirmed diagnosis of IBD as well as 2 or more confirmed episodes of *C difficile* infection. We assessed patients at baseline, performed a single FMT via colonoscopy, and then followed patients through 12 weeks, testing their stool at multiple intervals for both *C difficile* infection as well as for fecal calprotectin to look at inflammatory markers. We were assessing the efficacy of this therapy in patients with IBD and *C difficile* infection and also wanted to look at IBD outcomes to determine whether there was any merit to the concern of IBD worsening.

Fifty patients were enrolled in the study, and all did extremely well. The overall failure rate for FMT was only 8%, which is lower than the failure rates that have been previously reported. The vast majority of patients either had no change or had an improvement in their IBD disease scores, with only 1 patient in the ulcerative colitis group meeting the definition set at baseline for a de novo flare. Thus, we feel confident that this study helped debunk some of the initial concerns in the retrospective data and helped show that FMT is safe in patients with *C difficile* infection and IBD, is effective, and does not lead to IBD worsening. We are continuing this work and are conducting an even larger study to further assess this patient population.

G&H What is the current status of the use of FMT in IBD patients in clinical practice?

JA FMT has not been approved by the US Food and Drug Administration (FDA) for any indication, including *C difficile* infection or IBD. Clinicians are only allowed to perform FMT for recurrent and refractory *C difficile* infection under the FDA's enforcement discretion policy, which states that they are allowed to use this therapy for clinical care without applying for an investigational new drug license from the FDA as long as they state that it is an investigational therapy and review its real and theoretical risks in detail with patients. That is the only indication for clinical care for which FMT can currently be used. For any other indication, including IBD, an investigational new drug license from the FDA is needed and FMT can only be used in the setting of a clinical trial.

G&H Has research in this area been affected by the coronavirus disease 2019 pandemic?

JA When the pandemic started, the FDA mandated that only material produced before December 1, 2019 could be used, and FMT was still being utilized in clinical trials, of which I was conducting several. However, as of July 23, 2020, all clinical trials and clinical care of FMT essentially has been halted, specifically for investigators who use stool-banked material, which applies to the vast majority of centers in the United States, until a valid stool test has been developed for severe acute respiratory syndrome coronavirus 2.

Disclosures

Dr Allegretti serves as a consultant for Takeda, Janssen, Pfizer, Pandion, Servatus, Finch Therapeutics, Iterative Scopes, and Artugen, and has received grant support from Merck.

Suggested Reading

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