ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Current Status of Fecal Microbiota Transplantation for Inflammatory Bowel Disease Management

Jessica R. Allegretti, MD, MPH
Director, Crohn's and Colitis Center
Director, Fecal Microbiota Transplant Program
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

G&H Based on the research to date, does fecal microbiota transplantation show promise for the treatment of ulcerative colitis?

JA Yes, although there is still a lot of work to be done. Several, albeit small, clinical trials were initially performed, mostly through academic institutions. A number of these trials were positive for their primary endpoints of achieving clinical remission and, even in some, endoscopic remission. However, there were several limitations with many of those studies. Their small sample sizes were not necessarily powered to those outcomes. The trials were performed differently in terms of whether concurrent biologics were allowed. The fecal microbiota transplantation (FMT) material was administered differently in the trials—via capsule, colonoscopy, or enema. The preparation of the material differed in terms of aerobic vs anaerobic preparation. The studies used different dosing strategies, some of which were high intensity and some of which were lower intensity. Efficacy differences between dosing strategies have not necessarily been seen yet. Thus, comparing across trials has been challenging, but there certainly have been signals to suggest that there may be a subset of patients who will respond to a microbiome therapeutic. In recent years, companies have started to try to elucidate this issue, although mixed signals have been seen, especially with regard to a milder population. It is still unclear which subset of ulcerative colitis patients is going to benefit from this therapeutic approach and how those patients can be identified.

G&H Is there any evidence yet for the use of FMT in the management of Crohn's disease?

JA The data in Crohn's disease are extremely limited because of the heterogeneic nature of the disease. Many of the studies have focused on ulcerative colitis, although there have been case series and small cohorts showing positive signals in Crohn's disease. Professor Harry Sokol's group performed a sham, randomized controlled trial that showed some positive signal, but this was a very small study (less than 20 patients in total). A lot of work still needs to be performed in Crohn's disease before any inferences can be made one way or the other.

G&H What has research thus far shown regarding the long-term outcomes of using this therapeutic approach in patients with inflammatory bowel disease?

JA A lot of data, much of which come from my colleagues and I, are available on the use of FMT to treat *Clostridioides difficile* in patients with inflammatory bowel disease (IBD), so we know that this therapy is safe and well tolerated in that population. We have not seen worsening of the underlying IBD, which was an initial concern in some of the early retrospective studies. However, looking at the studies that specifically used FMT to treat ulcerative colitis in the absence of *C difficile*, most were induction-only. Thus, very little work has been performed to date on maintenance. It is not known whether FMT is going to

work best as an induction therapy, potentially as a corticosteroid-sparing agent, or whether there is a role for it as a long-term maintenance therapy. There are also other questions: what is FMT's effect after induction? How long does it last? How long do the engraftment patterns last? A lot of work still needs to be done on FMT's long-term effects to understand whether this is something that patients have to undergo only a single time, once a month, or even every day.

Because the data are so limited, it is difficult to know whether FMT needs to be administered via colonoscopy with mucosal assessment or whether a capsule is adequate.

G&H Could you discuss research that has looked at different routes of administration for FMT in the setting of IBD?

JA Because the data are so limited, it is difficult to know whether FMT needs to be administered via colonoscopy with mucosal assessment or whether a capsule is adequate. Most of the clinical trials that have been performed have involved a colonoscopic component because obtaining mucosal assessment and delivering FMT right to the source does appear to be helpful; on the other hand, presumably, it is preferable to avoid needing to administer FMT via colonoscopy for long-term use. Therefore, administration via capsule is certainly promising, and various capsule formulations involve colonic release. In many ways, this mimics colonoscopic administration because the capsules do not necessarily open until they enter the colon. For longer-term use (anything beyond a single administration), I think a capsule is the way to go. The question is whether there is utility in the induction dose being administered via colonoscopy. The trials I have participated in followed this approach, but is it absolutely necessary or could capsules be used exclusively? The latter would certainly be more patient-friendly. This issue still needs to be sorted out.

G&H Is there any consensus yet regarding FMT donor selection or screening?

JA Most of the data that are available come from *C difficile* patients using OpenBiome, which was the largest stool bank in the United States but is no longer actively operating. In the *C difficile* population, no specific phenotype of donor criteria—including sex, age, Bristol stool scale, microbiome analysis, metabolomic profile, and diet—appeared to work best with regard to efficacy as long as the donor was healthy and passed all of the health safety screening checks. In the setting of chronic diseases such as IBD, more rational donor selection is frequently brought up as well as how to select specific donors for disease-specific criteria. Several key lessons were learned about the microbial pathogenesis of diseases such as IBD from some of the earlier trials. For example, it is known that there is often a decrease in alpha diversity and short-chain fatty acid–producing bacteria in IBD. Should donors enriched with those specific bacteria be selected? We do not have the answer yet. I do not like the term *superdonor* because what does it mean and is it disease- or person-specific? The question is whether to phenotype each individual, figuring out what they are deficient in and then creating a cocktail or donor profile that matches them, or whether to tailor donor selection on a disease level. There is also movement away from using whole stool FMT, even for *C difficile*. That has been shut down functionally in the United States. We are moving toward more defined, synthetic, or laboratory grown products for *C difficile*. I think that is ultimately where we are heading in IBD as well.

G&H Do there appear to be any safety issues with using FMT in the setting of IBD?

JA Generally speaking, FMT is thought to be safe, but a few cases have brought safety concerns to the forefront. In the summer of 2009, *Escherichia coli* was transferred from a donor to 2 different patients in the setting of FMT. Both occurred in clinical trials, one for hepatic encephalopathy and the other for graft-versus-host disease. Unfortunately, one of the patients died from this infection, raising concerns around meticulous attention to donor screening and the need for standardization. However, looking at the totality of the current data, safety signals are not being seen in a lot of the IBD studies. What is typically being reported, if anything, is not infection transmission but worsening of IBD, which is fairly typical of any IBD trial studying a therapeutic. There has been extensive study of the use of FMT in patients with IBD who are being treated for *C difficile,* and safety signals have not been seen in that population. I genuinely believe in the safety of this therapeutic if screened appropriately.

G&H Currently, what are the main challenges of studying FMT in patients with IBD?

JA The main challenge is performing clinical trials. FMT essentially feels impossible right now because many investigators in this space used to partner with OpenBiome to obtain source material, and an Investigational New Drug application is required to be able to perform trials. To perform a clinical trial in this space, investigators either would need to source and screen their own donors, which is extremely cumbersome and time-consuming, or would need to partner with Seres Therapeutics, Nestlé Health Science, or Ferring, who have US Food and Drug Administration–approved FMT products in Vowst (fecal microbiota spores, live-brpk) and Rebyota (fecal microbiota, live-jslm) to see if these companies would be willing to support an investigator-initiated study for a specific disease. It has become very challenging for small academicians with limited budgets to perform clinical trials in this area anymore, whereas previously we were able to perform them fairly readily.

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G&H What further research is needed?

JA Even though positive signals are being seen in ulcerative colitis, a lot of work still needs to be done in several aspects, as already mentioned. The dosing strategy and duration of dosing still remain relatively unknown. Is FMT meant to be purely an induction-based strategy, or is there utility for a maintenance approach in ulcerative colitis? Also, should FMT be aimed at mild to moderate patients or moderate to severe patients, which is the population that most of the studies have focused on? Questions also remain around pretreatment antibiotics and/or bowel preparation to essentially prepare the gut. It is still not known whether those are absolutely necessary, and how much of an efficacy increase is yielded by utilizing one or both of those strategies. Additionally, can FMT be performed exclusively with capsules or is some form of rectal administration or mucosal assessment critical? I do not think any experts in the field feel that whole stool FMT seems to be the answer. Research is also needed on combining microbiome therapeutics with more traditional advanced therapeutic options in IBD. To me, this is an exciting opportunity for new combination therapy. Finally, the state of FMT in the United States is rapidly changing without the presence of OpenBiome. A lot of the robust investigation that was occurring in earlier days when prescreened material was available has gone by the wayside. How investigators are going to continue to do this type of work continues to evolve.

G&H Would you like to highlight any ongoing or upcoming studies in this area?

JA My colleagues and I just finished a very small pilot trial in patients with moderate to severe ulcerative colitis looking at different dosing strategies to try to understand dosing differences. Also, the University of Minnesota is leading an effort looking at different capsule preparations in patients with Crohn's disease, so we are going to obtain some more robust Crohn's disease data soon, which is very exciting.

Disclosures

Dr Allegretti has served as a consultant for Seres Therapeutics, Ferring, and Merck.

Suggested Reading

Allegretti JR, Feuerstadt P, Knapple WL, et al. Safety and efficacy of fecal microbiota, live-jslm (REBYOTA®), for the prevention of recurrent *Clostridioides difficile* infection in participants with inflammatory bowel disease in PUNCH CD3-OLS [published online January 25, 2025]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izae291.

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