ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Microbiologic Approaches to Treating Inflammatory Bowel Disease

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G&H Why might a microbiologic approach represent a promising treatment strategy for inflammatory bowel disease?

MF The bacterial microbiota of patients with inflammatory bowel disease (IBD) has been extensively studied worldwide for several decades, and an imbalance in composition compared with healthy controls has been well described and replicated in several studies. The so-called dysbiosis, or lack of eubiosis or normal state, in IBD is characterized by a reduction in biodiversity, including decreased abundance of Firmicutes, as well as an increase in Proteobacteria. More recent publications have also highlighted alterations in the gut virome and fungome, with the latter showing a decreased proportion of *Saccharomyces cerevisiae* and an increased proportion of *Candida albicans*.

An enticing hypothesis is that the correction of this dysbiosis may lead to cure of the disease. However, it is not known at this time whether the microbiota alterations observed in patients with IBD are the cause or the consequence of the chronic inflammatory process of the disease, or perhaps both. This is currently the most important question in this area. A twin study recently published in *Gastroenterology* illustrated this dilemma well. This study, which included both mono- and dizygotic twins, examined the gut bacterial microbiota signatures of patients with an established diagnosis of IBD and their discordant or healthy twins who did not exhibit any signs of IBD, and compared them with unrelated patients with IBD and healthy controls. The findings were surprising. The microbiota patterns in the healthy twins were similar to the patterns in their IBD twins and were more similar to the patterns in unrelated patients with IBD than to the patterns in healthy controls. The authors concluded that these IBD-like microbiome signatures might precede the onset of IBD. However, other twin studies have shown that even among homozygotic twins, there is only a 20% to 65% concordance in the development of IBD; thus, sharing the same genetic material does not always lead to IBD through a lifetime. In other words, a good portion of healthy individuals whose twins have IBD may never develop IBD themselves despite having abnormal IBD-like microbiota signatures. This suggests that an individual's microbiota is genetically predetermined and may not be sufficient for someone to develop IBD. Longitudinal follow-up studies are needed to infer a causal relationship between microbiota and disease. Determining whether abnormal microbiota is a cause or consequence of IBD (or perhaps both) is a crucial step before microbiology-based approaches can be applied as treatment for the disease.

G&H Which bacteria and metabolites appear to be protective against IBD?

MF A number of metabolites and the bacteria that produce them are thought to exert an anti-inflammatory effect and have been found to be decreased in patients with IBD. Short-chain fatty acids, secondary bile acids, tryptophan metabolites, certain polysaccharides, and sphingolipids are known to decrease inflammation and improve the barrier function of the mucosa. For example, *Faecalibacterium prausnitzii* increases secretion of anti-inflammatory cytokines that help maintain the integrity

of the mucosal barrier function. In addition, *Roseburia hominis* and *intestinalis* are involved in the metabolism of short-chain fatty acids, whereas *Roseburia* and certain *Clostridium* strains (among others) are involved in bile acid metabolism. *Bacteroides fragilis* has been shown to produce polysaccharides and sphingolipids, which are involved in anti-inflammatory functions of regulatory T cells and in homeostasis of host intestinal natural killer cells, respectively.

G&H Which microbiologic approaches are currently being studied for the treatment of IBD?

MF The current focus has been on fecal microbiota transplantation (FMT) and the development of live biotherapeutic products. Results from studies on probiotics in patients with IBD have been mixed and disappointing overall. Current guidelines do not recommend the use of probiotics in Crohn's disease at all. There may still be a role for certain probiotic mixtures for the maintenance of remission in pouchitis and in mild forms of ulcerative colitis. As for prebiotics, there has been interest surrounding dietary interventions (eg, the Mediterranean diet, Specific Carbohydrate Diet, Crohn's Disease Exclusion Diet) for both Crohn's disease and ulcerative colitis.

G&H What have studies found regarding the use of FMT in patients with IBD?

MF The success of FMT for treating recurrent *Clostridioides difficile* infection generated tremendous interest in trying to use this treatment method for other diseases, including IBD. As of the beginning of this past April, ClinicalTrials.gov listed 19 ongoing registered FMT intervention trials for ulcerative colitis, 8 for Crohn's disease, and 4 for pouchitis. There have been 4 published randomized controlled trials (RCTs) in ulcerative colitis; in addition, there have been numerous case series, cohort studies, and uncontrolled studies in this setting as well as in Crohn's disease and pouchitis. There has been only 1 RCT in Crohn's disease, which failed to meet the primary endpoint, and 1 randomized placebo-controlled trial in pouchitis, which also failed to meet its primary endpoint and was stopped prematurely.

A Cochrane review of all 4 of the RCTs in ulcerative colitis (total of 277 patients) found low overall heterogenicity. At 8 weeks, 37% of patients in the treatment arms achieved clinical remission vs 18% of control patients; 48% vs 28%, respectively, achieved clinical response; and 30% vs 10%, respectively, achieved endoscopic remission. These are better rates than those reported from clinical trials of biologic agents. However, the authors of this review noted that the quality of the evidence is still low and that the serious adverse event rates are uncertain. Therefore, it is not possible to draw solid conclusions, and there is still a need for further high-quality studies before FMT can be used in clinical practice for the treatment of ulcerative colitis. Problematically, the RCTs were heterogeneous in terms of the stool (including route of administration, frequency, volume, and preparation), donor type, and patient type/disease severity.

G&H What has this research shown specifically regarding the safety of FMT in this setting?

MF Overall, FMT has been shown to be very safe. No significant difference in adverse events was found between the treatment groups and the placebo groups in the 4 RCTs. Initial retrospective studies suggested that a significant minority of patients with *C difficile* infection and underlying IBD might flare or have worsening disease activity after receiving FMT. However, this was not confirmed in prospective studies such as the ICON study. Thus, in my opinion, there are no concerning safety signals; however, the authors of the Cochrane review voiced concerns about the unknown rates of rare but possibly serious adverse events.

G&H In the RCTs, which types of FMT were most effective?

MF Of the 4 RCTs, the only one that failed to meet its primary endpoint was the one that administered the fecal transplant via nasoduodenal tube. Thus, the consensus is that, for ulcerative colitis, if FMT is in a liquid form, it should be delivered via colonoscopy or a lower route.

However, these studies were published several years ago, and there have been tremendous advances in the area of FMT. There are currently several ongoing studies of freeze-dried capsules and lyophilized, encapsulated formulations of fecal material. Being able to administer FMT via capsule will be a paradigm-changer because it can then be given every day for a long time and would be much more acceptable to patients in such a formulation.

G&H Have any data been released yet on these capsules?

MF Results from the only study thus far using a capsule formulation in ulcerative colitis were recently released online ahead of print publication in *Gastroenterology*. Dr Paul Moayyedi's group studied the use of lyophilized oral FMT capsules in pediatric patients with ulcerative colitis. However, the study did not meet its primary endpoint,

which the authors attributed to extremely slow enrollment. The study ended up consisting of only 25 patients who were randomized to FMT or placebo.

G&H What are the main benefits of using microbiologic therapies compared with traditional IBD treatments?

MF The main benefits are safety, durability, and cost. The immunosuppressive agents that are currently being used for the treatment of IBD suppress different functions of the adaptive immune response and are associated with a number of risks such as an increase in infections, bone marrow suppression, liver injury, malignancy, lupus-like autoimmunity, demyelination of the central nervous system, hypersensitive reactions, and the development of neutralizing antibodies. Even in the best-case scenario, only approximately half of patients respond to a certain mechanism of action in immunosuppressive drugs, and these agents often do not work very long. They are also very expensive, placing a financial burden not just on the patient but on the health care system.

G&H What are the main limitations of using microbiologic approaches?

MF Currently, most of the data are based on stool-derived, full-spectrum microbiota therapy, which is FMT. No matter how much it is processed, it still includes the entire microbiota—bacteria, viruses, fungi, and even some components that we do not know are there. We are trying to give everything in a normal microbiota to a patient with IBD in order to change or normalize his or her microbiota imbalance. Although data have accumulated showing that FMT is very safe overall, some publications have noted a risk of transmissible infections, even though donors are typically screened carefully. There have been transmissions of organisms that did not cause disease in an immunocompetent donor, but caused disease, sepsis, and even death in an immunocompromised individual. Thus, risk of infection is still a major limitation, as is the transmission of other diseases, such as metabolic syndrome and diabetes, as well as weight gain and antibiotic-resistant organisms. The development of live biotherapeutic products with well-characterized, reproducible, cultured bacterial products (meaning that all of the contents are well known) aims to eliminate or reduce these concerns.

G&H What are the latest developments with live biotherapeutic products?

MF Seres Therapeutics has developed 2 live biotherapeutic products that are currently being studied in ulcerative colitis trials (SER 287 in phase 2 and SER 301 in phase 1). Finch Therapeutics has 2 capsules currently in preclinical development (FIN 524 for ulcerative colitis and FIN 525 for Crohn's disease).

Of these products, the only data that have been published thus far are from the phase 1b safety study of SER 287, which is a spore-based microbiome therapeutic for active mild to moderate ulcerative colitis. The results were published in January of this year in *Gastroenterology*. The 8-week, placebo-controlled study enrolled 58 patients, some of whom received vancomycin conditioning prior to treatment to make sure that most of the other bacteria were eliminated and in the hope of improving engraftment. Although this was merely a small phase 1b study, the remission rate in the treatment group was 40% at 8 weeks compared with 0% in the placebo group. These results are impressive. Enrollment recently ended for this agent's phase 2 trial, and the results of this study will hopefully be published within the year. I think that SER 287 might be one of the first live biotherapeutic products approved by the US Food and Drug Administration for the treatment of mild to moderate ulcerative colitis.

G&H Have microbial-derived immunotherapies shown any promise for the treatment of IBD?

MF We have known for some time that patients with IBD are genetically immunocompromised and have a defective innate immune system. Most of the gene alleles that have been shown to be associated with IBD are related to diminished response to bacterial invasion. There is a compensatory upregulation of the adaptive immune system, which results in a response that is out of proportion to commensal bacteria and causes chronic inflammation, ultimately leading to the structural damage associated with IBD. With such microbial immunotherapy, investigators are using an inactivated gastrointestinal pathogen to activate certain functions in the innate immune response that are diminished in patients with IBD. This makes sense, but investigators of the novel microbial immunotherapy QBECO (Qu Biologics) did not find any difference between the treatment and placebo groups in a phase 1 and 2 proof-of-concept study. I am not certain whether this immunotherapy will undergo further study.

G&H What other microbial-based treatment approaches are currently under investigation?

MF A recent study led by Dr Fabio Cominelli examined autologous fecal transplant for the treatment of IBD, which I think is a fascinating approach. Normally, FMT studies try to find the perfect donor whose microbiota

will correct the dysbiosis in patients with IBD; however, as mentioned, this might cause problems because antigens from the donor are being introduced that can passively trigger an immune response, and there are risks (eg, of infections). With autologous fecal transplant, stool would instead be harvested from the IBD patient when in remission. It has been well described that when patients with IBD are in remission, their microbiota can be very similar to those of healthy controls. Dr Cominelli's group is studying stool in mice to determine whether it has anti-inflammatory or pro-inflammatory effects. If the stool has anti-inflammatory effects, then the researchers could preserve the stool and give it back to the IBD patient during a flare. The group has published about this concept and is currently conducting a trial. I am interested to see what they find.

G&H What are the next steps in research involving microbiologic approaches for treating IBD?

MF We need to continue to develop live biotherapeutic products and fine-tune therapeutic approaches using full-spectrum microbiota (FMT). I believe that live biotherapeutic products are the future.

Disclosures

Dr Fischer has served as a site investigator for Seres Therapeutics and Finch Therapeutics as well as on the Data and Safety Monitoring Board for Rebiotix/Ferring.

Suggested Reading

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